МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ
БЕЛОРУССКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ
КАФЕДРА ПАТОЛОГИЧЕСКОЙ ФИЗИОЛОГИИ

**С. А. Жадан, Ф. И. Висмонт**

# ПАТОЛОГИЧЕСКАЯ ФИЗИОЛОГИЯ ПЕЧЕНИ

# PATHOLOGICAL PHYSIOLOGY OF THE LIVER

Учебно-методическое пособие

Минск БГМУ 2018

Репозиторий БГМУ

УДК 616-002-092(075.8)-054.6
ББК 52.5я73
Ж15

Рекомендовано Научно-методическим советом университета в качестве учебно-методического пособия 21.03.2018 г., протокол № 7

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Ж15 Патологическая физиология печени = Pathological Physiology of the Liver: учебно-методическое пособие / С. А. Жадан, Ф. И. Висмонт. – Минск: БГМУ, 2018. – 34 с.

ISBN 978-985-21-0176-9.

Рассматриваются основные вопросы патофизиологии печени: клинические признаки, этиология и патогенез нарушений функции печени, основные синдромы и исходы патологии.

Предназначено для студентов 2–3-го курсов медицинского факультета иностранных учащихся, обучающихся на английском языке.

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**ББК 52.5я73**

**ISBN 978-985-21-0176-9**

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## MOTIVATIONAL CHARACTERISTIC OF THE TOPIC

The teaching manual is designed to optimize the learning process and is offered to prepare students for the laboratory lesson on the topic.

**Purpose of the Lesson**: to study the causes and the mechanisms of basic syndromes occurring in liver pathology. To characterize the typical forms of liver functional impairments and form the ability of students to analyze the clinical situations related to liver pathology, to solve professional problems of the doctor.

**Objective of the Lesson**: the student should:

**1. Know**:

– the definition of the notions: «liver failure», «jaundice», «cholestasis syndrome», «portal hypertension», «ascites», «acholia»; «hypercholia» «cholemia»;

– causes and mechanisms of liver pathology;

– the signs of liver metabolic disorders;

– the main clinical syndromes at liver pathology;

– the characteristic and types of jaundice syndromes;

– the characteristic of malnutrition syndrome at liver pathology;

– the characteristic of hemorrhagic syndrome at liver pathology;

– the characteristic of cholestasis syndrome at liver pathology;

– the pathogenesis of liver pathology complications;

– the definition, types and characteristic of hepatic coma.

**2. To be able:**

– to interpret the main existing theories of liver diseases pathogenesis;

– to interpret the clinical-biochemical parameters of blood and specify the type of jaundice;

– to solve professional problems based on analysis of clinical and pathophysiological model situations related to the liver pathology development.

**3. To be familiar with:**

– clinical manifestations and basic signs of liver pathology;

– clinical-biochemical and clinical-pathophysiological syndromes of liver pathology.

**Requirements for the initial level of knowledge.** For complete mastering of the theme the student must go over the notions from Biochemistry, Histology and Normal Physiology including: «bilirubin exchange», «hemolysis of erythrocytes», «functions of liver».

**Control questions from related disciplines**:

1. The liver. Morphofunctional characteristics. Features of liver blood circulation. The structure of the classical hepatic lobule. The concept of portal lobule and acinus. Regeneration. Age features.

Liver: structural basis of bile formation and biliary excretion. Histophysiology of hepatocytes, lipocytes, hepatic macrophages. Sinusoidal hemocapillaries, perisinusoidal space. Ways of bile outflow. Gallbladder: structure and function.

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2. Antitoxic functions of the liver. Neutralization of toxins, normal metabolites, drugs in the liver.

3. The role of the liver in protein, carbohydrate and lipid metabolism.

4. Synthesis and decay of blood pigments. The role of the liver in bile pigments formation. Metabolism of bile pigments.

5. Jaundice, origin, methods of jaundice diagnosis.

6. Biochemical methods of liver damage diagnosis.

**Control questions**:

1. Experimental methods for studying the liver functions (N. V. Ekk, E. S. London, I. P. Pavlov). Changes in the body occuring during these interventions.

2. Basic etiological factors of hepatic damage. The basic syndromes of liver and bile ducts pathology.

3. The definition of the notion, etiology and pathogenesis of hemolytic, parenchymatous and mechanical forms of jaundice. Bilirubin exchange at various forms of jaundice.

4. The definitions of cholemia, acholia and hypercholia syndromes. Basic manifestations.

5. The portal hypertension syndrome. The definition, forms, clinical symptoms.

6. Pathogenetic characteristic of collateral and portocoval blood circulation at portal hypertension.

7. Pathogenesis of ascites at portal hypertension.

8. Hepatic failure. The definition, etiology, pathogenesis, laboratory and clinical manifestations.

9. Hepatic coma. The definition, forms (bypass, hepatic-cellular). Pathogenesis.

## GENERAL CHARACTERISTICS OF THE LIVER

The liver is the most important organ ensuring the constancy of the organism internal environment, its compensatory-adaptive reactions. The main liver structural and functional unit that determines specific functions of the organ is a hepatic lobule which consists of hepatocytes — parenchymal cells with a wide functional and metabolic profile. The main features of hepatocytes are their ability to participate in various types of metabolism (anabolism, catabolism, detoxication, biotransformation, etc.) of different plastic, energy and regulatory substances. The liver participates in cellular and humoral specific and nonspecific immunity regulation due to the presence of a large number of macrophages (Kupffer cells), lymphocytes, etc. in it.

Liver pathology includes a variety of clinical forms and syndromes characterized by numerous homeostatic functions decreasing, namely:

– protective-barrier (detoxification, phagocytic, endotoxin-eliminating);

– participation in digestion process (bile formation);



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– participation in metabolism (protein, carbohydrate, lipid, pigment, mineral, vitamin);

– participation in cellular and humoral immunity reactions;

– participation in acid-base balance and hemostasis maintenance;

– participation in normal hemodynamics maintenance;

– participation in hormone metabolism.

Pathogenic factors can act *directly* on the various cellular structures which are responsible for providing a variety of metabolic processes as well as for blood and lymph circulation in the liver. In addition, pathogenic factors can act *indirectly* through changes in the executive (blood circulation, breathing, excretion, etc.) and regulatory (nervous, endocrine, immune) systems.

Various pathogenic agents enter the liver in three main ways: 1) through the portal vein (intestinal toxins, alcohol, microorganisms); 2) through the common bile duct; 3) through the hepatic artery (drugs).

The action of pathogenic factors leads to a disruption of the liver functions aimed at maintaining homeostasis. Such disorders manifest themselves both as independent liver diseases (for example, viral hepatitis) or in the form of hepatic syndromes that determine the clinic of specific nosological form of liver disease or the accompanying diseases of other organs and systems.

There are different criteria to classify liver violations:

– ***by origin***: hereditary (primary) and acquired (secondary);

– ***by the extent of the damage***: focal and diffuse;

– ***by leading clinical syndrome severity***: jaundice, portal hypertension, ascites, epithelial cell insufficiency (hepatic coma);

– ***by clinical course***: acute and chronic;

– ***by compensation degree of impaired functions***: compensated and uncompensated;

– ***by severity degree***: light, moderate, severe;

– ***depending on pathology reversibility***: reversible and irreversible;

– ***by function change***: hypofunction, hyperfunction and disfunction;

– ***by predominant violation of structural elements***: damage of hepatocytes, endothelial cells, macrophages, etc.;

– ***by character and severity of liver pathological process***: in the form of inflammation, dystrophy, cholestasis, cytolysis, hepatocellular insufficiency or mixed.

## THE ETIOLOGY OF LIVER PATHOLOGY

Liver pathology is caused by a variety of etiological factors. Among the causes and factors causing disorders of multifunctional liver activity, the most significant are: *biological agents* (viruses, bacteria, fungi, parasites, etc.); *chemicals with hepatotropic action* (exo- and endogenous origin); *physical factors* (ionizing radiation, mechanical trauma); *alimentary factors* (quantitatively and qualitatively

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defective food, starvation); *allergens* (exogenous and auto-allergens (in response to hepatocytes injury autoimmune liver damage develops due to autoantigens appearance and humoral and cellular autoimmune reactions development)); *local and general circulatory disorders; endocrine and metabolic disorders* in the body; *tumors* (primary and metastases from other organs); *genetically determined metabolic defects* (enzymopathy) and malformations.

## THE PATHOGENESIS OF LIVER PATHOLOGY

Such typical pathological processes as injury, inflammation, peripheral circulation and microcirculation disorders, hypoxia, tumors, etc. most commonly form the basis of liver pathology.

The effect of etiological factors on liver cells leads to:

– the damage of hepatocytes membranes;
– the activation of free radical reactions and lipid peroxidation processes;
– the activation of membrane enzyme systems and lysosomal hydrolases;
– the activation of immuno-pathological processes;
– the development of inflammation.

These mechanisms induce liver cells damage and promote the releasing of various hydrolytic enzymes into interstitium. It in turn additionally potentiates inflammatory, immunopathological and free radical reactions. With massive damage of organ cells a liver metabolic insufficiency (or *liver failure*) can develop. This state is characterized by partial or complete violation of basic liver functions.

## LIVER FAILURE

***Liver failure*** (*or hepatic insufficiency*) is a complex of homeostatic disorders caused by impaired liver functions and manifested by intellectual, mental and motor-vegetative activity disorders. This state is characterized by a decrease in one, several or all of the liver functions below the level which is necessary to ensure normal vital activity of the body.

In liver failure the following functions are mainly violated: metabolic, protective (phagocytic and antitoxic), excretory, hemodynamic.

### CLASSIFICATIONS OF LIVER FAILURE

There are several classifications of liver failure (depending on the criteria taken as a basis):

1) ***depending on origin:*** *hereditary and acquired*;
2) ***depending on reason:*** *relative and absolute*.

*Relative* liver failure occurs due to primary load increase on the organ, when the body's requirements for maintaining homeostasis exceed the organ's functionality. The relative insufficiency of liver can eventually become absolute.

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*Absolute* hepatic insufficiency develops as a result of primary damage of liver tissue (cells, vessels, bile ducts etc.).

3) ***depending on damaged functions volume:*** partial (violation of some liver functions) and total (violation of all the liver functions);

4) ***depending on disease duration and rate of main symptoms development:***

– *acute liver failure* — a clinical syndrome characterized by rapidly developing liver failure (during a day) as a result of massive liver cells necrosis;

– *chronic liver failure* — a syndrome that is formed over several months or years and usually is typical for the late stages of liver cirrhosis or arises due to vascular shunting;

5) ***depending on the mechanism of development (pathogenesis):***

– hepatic-cell;

– cholestatic;

– vascular liver failure.

*Hepatic-cell failure* is a result of primary damage of hepatocytes and their inadequate functions; it develops at dystrophic and necrotic lesions of significant amounts of hepatocytes. As a result all the liver functions are violated to varying degrees.

*Cholestatic (excretory) liver failure* is caused by prolonged violation of bile excretory function of the liver, outflow of bile and its regurgitation. In this case there is a violation of the intake of bile in the intestine. The defeat of the liver in such cases is associated with the retrograde pressure of bile accumulated in the bile ducts which leads to their rupture and direct toxic effects of bile. Excretory form of hepatic insufficiency is modeled by the ligation of the bile ducts and more often of the common bile duct.

*Vascular liver failure* occurs with insufficient blood flow and often is accompanied by intoxication of the body with metabolic products as well as exogenous substances normally disinfected by liver cells. The most common causes of hepatic-vascular insufficiency are portal hypertension, ischemia and venous plethora of the liver.

## EXPERIMENTAL METHODS FOR LIVER FUNCTIONS STUDY

The vascular form of liver failure is modeled by the imposition of Eck's and Eck-Pavlov's fistula and ligation of the hepatic artery, portal and hepatic veins.

The purpose of this operation is to study liver functions in different conditions of nutritional load and determining its detoxication role in the body.

***Direct Eck's fistula*** (anastamosis) is applied between the portal and inferior vena cava with subsequent tying of the portal vein above the anastomosis.

Normally the blood from the portal vein collects the blood from the gastrointestinal tract, passes through the liver, where it is «purified» from toxins and flows into the lower hollow vein and eventually to the brain vessels. In order to reduce portal hypertension and abdominal ascites, N. V. Eck directly connected

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the portal vein to lower hollow vein (side-to side or end-to side), directing all blood into the brain and bypassing the liver (a).

As a result of fistula imposition a blood supply through the vessels of the portal vein system stops and all the liver functions disrupt (fig. 1, *a*).

When ***Eck-Pavlov's back fistula*** is applied, unlike Ekk's fistula, the portal vein is not ligated, and the lower hollow is ligated above the anastomosis. In this case, the liver receives blood from the digestive tract through the portal vein and from the posterior half of the trunk. As a result, only a part of "unpurified" blood bypasses the liver and penetrates into the central bloodstream, which prolongs animal survival time (fig. 1, *b*).

Natural liver shunt is depicted on the fig. 1, *c*. It may appear in the cirrhotic state as an adaptive response to a portal vein hypertension.

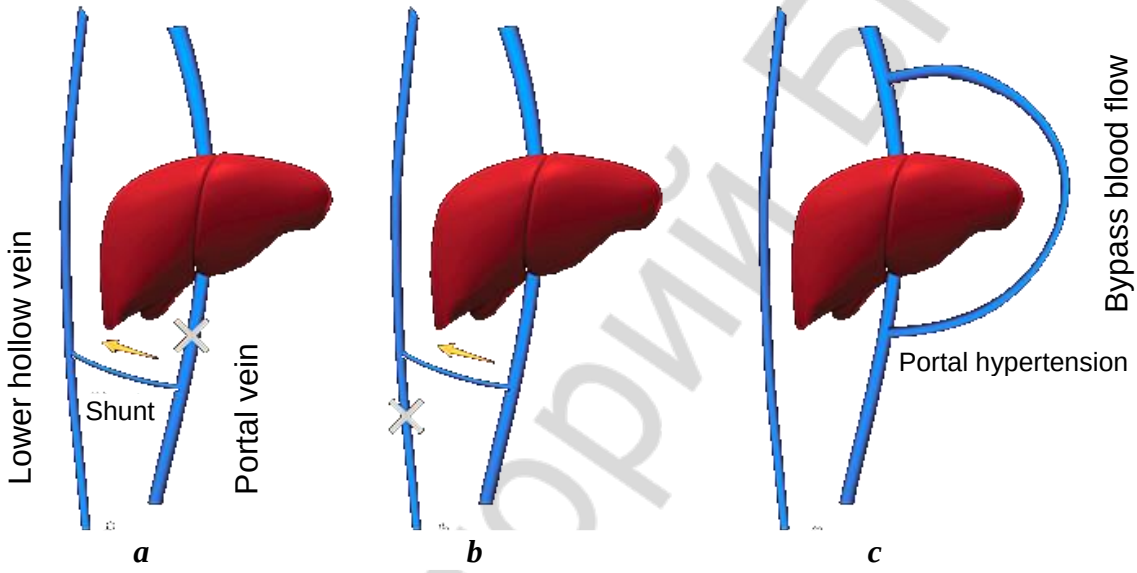


*Fig.1.* Experimental methods for liver functions study.
*a* — Direct Eck's fistula; *b* — Eck-Pavlov's back fistula; *c* — natural liver shunt

After the hepatic artery ligation a liver infarction can develop. It creates conditions for infection of liver tissue with the intestinal microflora and the progression of liver failure. The ligation of all afferent vessels (liver devascularization) leads to the development of fulminant hepatic insufficiency and subsequent death of an organism. It should be noted that clamping of all liver afferent vessels used in clinic during organ operations to reduce blood loss should not exceed the critical period of liver ischemia –1 hour.

Hepatic failure can develop due to:

– ***pathological processes localized in a liver and bile ducts:*** hepatitis, dystrophy, cirrhosis, tumors, parasitic lesions, genetic defects of hepatocytes, cholelithiasis with cholestasis;

– ***extrahepatic pathological processes:*** shock, cardiac insufficiency, hypoxia, renal failure, protein starvation, hypovitaminosis, endocrinopathy.

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All substances entering the body undergo the adaptive biotransformation in the liver. It has several defense mechanisms to protect the organism from permanent «threat» of damage by any of metabolites.

*The first (fast) mechanism* of hemodynamic protection consists of reflex reduction of blood flow in portal system which in turn leads to decrease of substances absorption from the digestive tract.

*Second (slow) metabolic mechanism* is based on change of hepatocyte biochemical activity (substrate or hormonal adaptation).

If protection mechanisms do not work then either inflammation (hepatitis) or inflammatory-dystrophic processes (cirrhosis) take place. In both cases liver failure develops. It is manifested by metabolism violations, bile-forming disorders, detoxication function abnormalities, coagulopathies, endocrinopathies, etc.

## METABOLIC DISORDERS AND LIVER FUNCTIONS CHANGES AT LIVER FAILURE

Hepatic insufficiency is characterized by metabolic disorders (change of protein, lipid, carbohydrate, mineral substances levels; vitamin exchange) and liver functions violation. Next states are related with liver pathology:

***Hepatitis*** (from the Greek «Hepar» — the liver, «itis» — suffix meaning inflammation) — inflammation of liver parenchyma. There are:

– *acute hepatitis* is inflammatory disease usually occuring as a result of a viral infection (hepatotrophic hepatitis viruses) or intoxication;

– *chronic hepatitis* is diffuse liver damage accompanied by progressive destructive-dystrophic disorders caused not only by damage of the parenchymal cells but also mesenchymal structures and usually develops as a result of untreated or poorly treated acute hepatitis.

***Hepatosis*** (from the Greek «Hepar» — liver, «osis» — suffix meaning suffering, disease) — a chronic disease accompanied by dystrophic changes in liver parenchyma and most often developing under the influence of hepatotropic chemicals (drugs, alcohol, industrial poisons).

***Cirrhosis*** (from the Greek «Cirroz» — orange or tan) is a chronic pathological process in the liver characterized by progressive damage and death of hepatocytes, proliferation of connective tissue (fibrosis) replacing the parenchyma which leads to blood flow violation and liver failure (fig. 2).

***Cholecystitis*** (from the Greek «Chole» — bile, «systis» — a bubble, «itis» — a suffix meaning inflammation) is inflammation of the mucous membrane of the gallbladder.

***Cholangitis*** (from the Greek «Chole» — bile, «angion» — vessel) — bacterial infection of the extra-hepatic biliary system often accompanying cholecystitis.

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***a*** ***b***

*Fig. 2.* Liver at cirrhosis:
*a* — healthy; *b* — cirrhosis

***Gallstone disease*** is a disease characterized by stone (concrement) formation in gallbladder or (and) in ducts (fig. 3). According to the chemical composition three types of gallstones are distinguished: *cholesterol* (cholesterol content 79 % and higher), *black pigment* and *brown pigment*. Cholesterol and black pigmented stones are formed mainly in the gallbladder, brown — in the bile ducts.

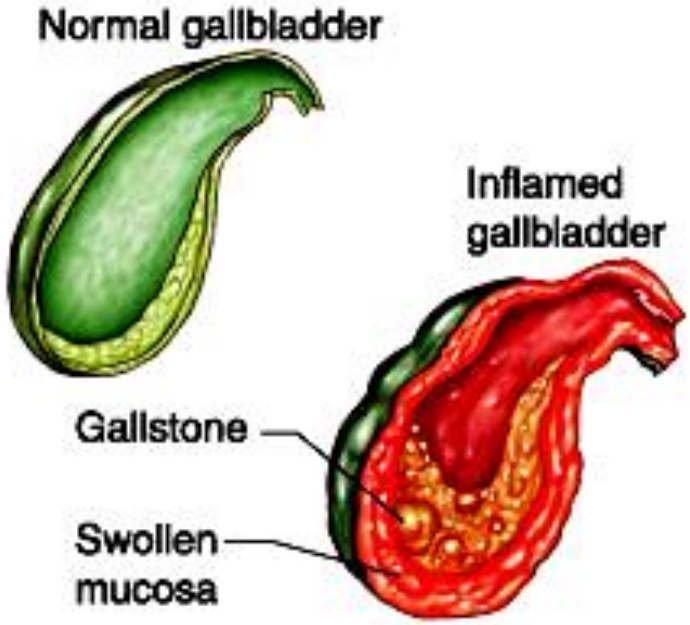


*Fig. 3.* Gallstone disease

Gallstone disease as a rule does not have specific symptoms. The cause of the disease is mechanical irritation of the gallbladder wall and bile ducts with a stone, their hyperextension.

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## THE MAIN CLINICAL SYNDROMES OF LIVER PATHOLOGY

Diseases accompanied by liver failure are characterized by the following clinical syndromes (tabl. 1).

*Table 1*

**Main clinical syndromes of liver failure**

| Clinical-pathophysiological syndromes | Clinical-biochemical laboratory syndromes |
|---|---|
| Jaundice | Immune-inflammatory |
| Cholestasis | Cholestasis (excretory-biliary) |
| Cholemic | Cytolysis |
| Malnutrition | Hepatic-cellular insufficiency |
| Hemorrhagic | – |
| Portal hypertension | – |
| Edematous-ascitic | – |
| Hepato-cerebral insufficiency | – |
| Hepato-endocrine | – |
| Hepato-renal | – |

## CLINICAL-PATHOPHYSIOLOGICAL SYNDROMES

### THE JAUNDICE'S SYNDROME

***Jaundice*** (from the Latin «Icterus») is a symptom characterized by the yellow staining of the skin and mucous membranes as a result of bile pigments deposition and associated with increased bilirubin content in blood (over 35 μmol/l). It is believed that for visible jaundice appearance the level of blood bilirubin should exceed twice the normal one.

The occurrence of jaundice is always due to a bilirubin metabolism disruption. The last one is formed as a result of erythrocyte hemoglobin breakdown and heme destruction. Bilirubin exchange in norm is carried out in several stages (fig. 4):

1) *formation of indirect (free) bilirubin in cells of reticuloendothelial system* (80 % from erythrocytes, 20 % from myoglobin and cytochromes). Every day 1 % of erythrocytes is destroyed and 100–250 mg of unconjugated (*indirect)* bilirubin is formed. This bilirubin presents in blood in a complex with transport albumin;

2) *capture of unconjugated bilirubin by hepatocytes, separation it from transport albumin, diffusion of bilirubin through the hepatocyte membrane and intracellular movement of indirect bilirubin to an endoplasmic reticulum*;

3) *conjugation of indirect bilirubin with glucuronic acid, formation of direct (bound) bilirubin;* 15 % of all direct bilirubin is formed in kidneys, brain tissue, intestinal mucosa (*extrahepatic conjugation of bilirubin*);

4) *excretion of direct bilirubin by hepatocytes to the bile ducts*.

The most of bilirubin is extracted through bile into intestine and 10% of bilirubin in the urobilinogen form is absorbed back and returned to the liver.

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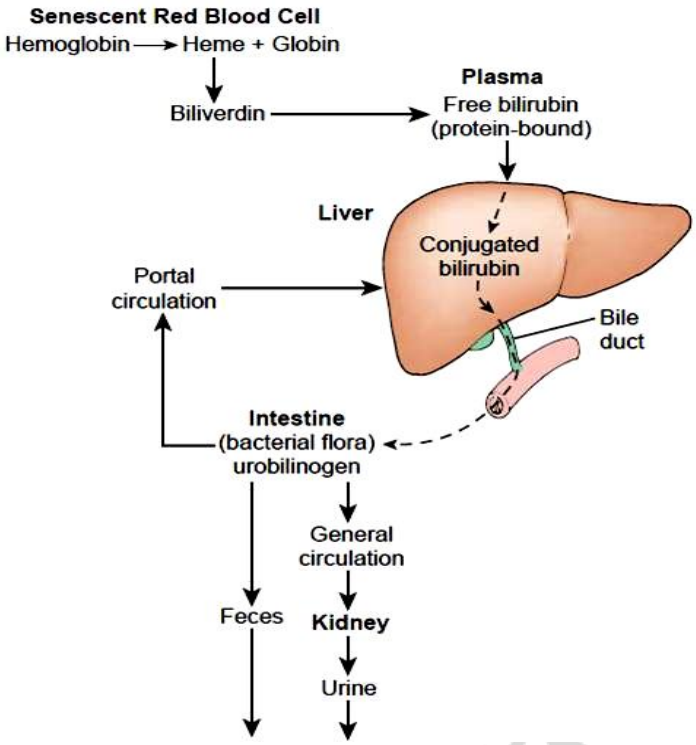


*Fig. 4.* The process of bilirubin formation, circulation and elimination

For the development of jaundice syndrome the main factors are: 1) excessive formation of bilirubin; 2) disruption of its capture and transport; 3) its accumulation in hepatocytes; 4) violations of bilirubin excretion in bile.

Depending on origin, localization of pathological process and mechanisms of development there are three main types of jaundice:

– ***superhepatic*** («hemolytic»);
– ***hepatic***: parenchymal (hepatic cell), enzymatic and cholestatic;
– ***sub-hepatic*** («mechanical»).

## SUPERHEPATIC (HEMOLYTIC) JAUNDICE

*Hemolytic jaundice* occurs as a result of erythrocyte increased hemolysis and bilirubin metabolism violation and is not associated with liver damage. It is characterized by increased formation of bilirubin. Hemolytic poisons (phenylhydrosine, arsenic hydrogen, snake venom, etc.), congenital and hereditary erythrocyte and hemoglobin abnormalities, damage of erythrocytes by various toxins and microorganisms, autoimmune damage of erythrocytes after transfusion of incompatible with group membership and Rh-factor blood can lead to this jaundice.

Hemoglobin released during hemolysis is converted to *indirect* bilirubin, which is formed in such a large amount that it does not have time to be metabolized and stand out by the liver (fig. 5).

However superhepatic jaundice cannot be caused by increased formation of indirect bilirubin only. For its occurrence a decrease of liver secretory capacity is necessary. It is known that indirect bilirubin is a toxic substance. Its accumulation

in high quantities in blood can cause damage of liver cells and thereby reduce the secretory bile-forming ability of the organ.

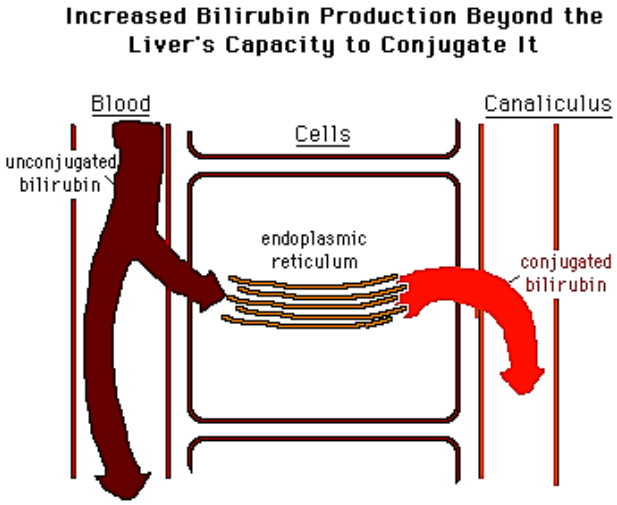


*Fig. 5.* Superhepatic jaundice

Hemolytic jaundice is characterized by accumulation of a large amount of indirect (unconjugated) bilirubin in blood because of inability of the liver to convert it completely into a bound (direct, conjugated) bilirubin. Direct bilirubin is secreted into the intestine. As a result more urobilinogen (appears in the urine) as well as stercobilin is formed. At hemolytic jaundice there is no accumulation of bile acids and cholesterol in blood. The jaundice of newborns (physiological and pathological) is referred to the group of hemolytic jaundice as well (fig. 6).

There are several variants of superhepatic jaundice with various pathogenetic links:

*Fig. 6.* The jaundice of newborns

1) hemolysis due to an increased decay of erythrocytes;

2) shunt hyperbilirubinemia — at increasing formation of the so-called shunt bilirubin from hemoglobin of immature forms of erythrocytes (for example, at inefficient hematopoiesis with $B_{12}$-deficient anemia) or from the heme proteins such as myoglobin, cytochromes, catalase, with extensive hematomas and infarcts;

3) when plasma transport of bilirubin is disrupted — at bond destruction between bilirubin and albumin by certain drugs or as a result of violation of bilirubin-albumin complex formation due to albumin level decrease in a blood.

## INTRAHEPATIC (HEPATOCELLULAR) JAUNDICE

*Intrahepatic or hepatocellular jaundice* is caused by disorders that directly affect the ability of the liver to remove bilirubin from blood or conjugate it. As a result bilirubin can not be eliminated with bile.

Liver diseases such as hepatitis and cirrhosis are the most common causes of intrahepatic jaundice.

Hepatocellular (parenchymatous) and enzymopathic varieties of jaundices are related to hepatogenous jaundice.

***Parenchymatous jaundice*** appears as a result of direct lesion of hepatic tissue by infection agents — parasitogenic (viruses, bacteria and their toxins, malaria plasmodiums and others) and non-infectious origin (organic and inorganic poisons (tetrachloride hydrocarbon), high doses of alcohol; hepatotrophic antibodies and sensitized lymphocytes; tumors and others). A type and manifestation of hepatic functions disturbances depend on a degree of hepatocytes damage and their mass. Damage beginning from the change of cellular membranes structure and/or enzymes activity suppression is increasing and may be completed by hepatic cells destruction in many cases. Bile-synthetic and bile-secretory functions of hepatocytes are disturbed in lesion zone at any liver damage. However, definite peculiarities of pigment metabolism disturbance are typical for various stages of pathologic process. Early specific signs of hepatocyte lesion in the *first (preicteric) stage* are: 1) the appearance of urobilinogen in blood and urine (due to enzyme mechanisms damage and/or violation of pigment catching and oxidation); 2) high level of hepatic transaminases in a blood (alanine, aminotranspherase, aspartataminotranspherase and others) which penetrate easily through the damaged cellular membrane.

A process of conjugation of unconjugated bilirubin with glucuronic acid is disturbed in the *second stage (icteric*) because of glucoronyl transferase activity decrease. As a result a quantity of forming bilirubin diglucuronide (conjugated bilirubin) is decreased. Damaged hepatocytes start to secret bile not only into bile capillaries, but also in blood capillaries. It causes free bile acids appearance and total bilirubin level increase in blood, and also conjugated bilirubin appearance in urine. Besides crashing of bile capillaries by damaged edematic hepatocytes hamper the evacuation of bile from them and create the conditions for an increase of its resorption in blood capillaries of the liver. Bile excretion into the intestines is disturbed.

Total decrease of hepatocyte ability to catch and transform the unconjugated bilirubin into conjugated one occurs in case of serious liver lesion (*stage of precoma*). In this case a level of unconjugated bilirubin in blood starts to increase, the content of conjugated bilirubin decreases and urobilinogen disappears as a rule. The disturbance of barrier and other liver functions, appearance of toxic forms of bilirubin and other metabolites in blood lead to essential disturbance of homeostasis and a threat of hepatic coma development.

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***Enzymopathic jaundices*** are conditioned by intrahepatic bilirubin metabolism disturbances due to synthesis violation of some enzymes taking part in this process. By origin these jaundices are mainly hereditary. At the same time some forms occur after several liver diseases. Jaundice forms are distinguished depending on the mechanisms of development.

Intrahepatic or hepatocellular jaundice usually interferes with all phases of bilirubin metabolism — uptake, conjugation, and excretion. Herewith the level of conjugated and unconjugated bilirubin in blood rises, urine becomes dark because of bilirubin presence in it and an alkaline phosphatase level is slightly increased.

***Gilbert's syndrome***. This jaundice is based on the disturbance of active catching and transport of unconjugated bilirubin from blood into hepatic cells (fig. 7). The cause of syndrome is a genetic defect of proper enzime synthesis.An increase of total bilirubin level in blood is conditioned by an increase of unconjugated bilirubin content.

***Crigler-Nagar syndrome***. This variant of enzymopathic jaundice develops as a result of glucoronyltransferase deficiency — a key enzime participating in free bilirubin transformation into the conjugated one. As a result unconjugated bilirubin accumulates in blood (fig. 8).

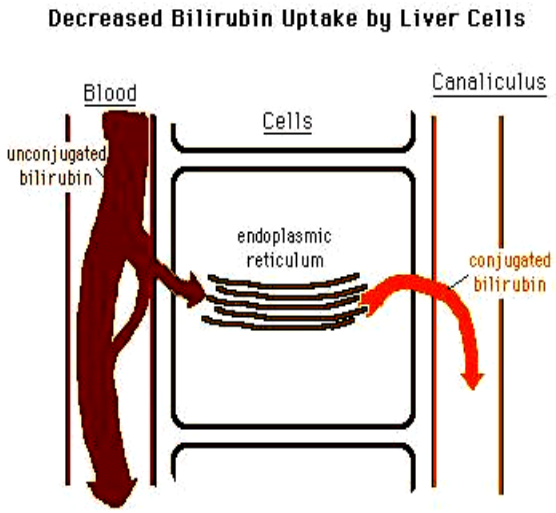


*Fig. 7.* Gilbert's syndrome

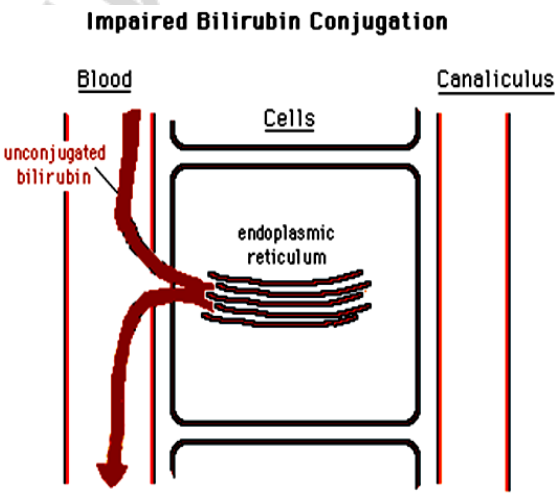


*Fig. 8.* Crigler-Nagar syndrome

***Dubin-Johnson syndrome.*** This variant of jaundice appears due to a *defect of enzymes which participate in bilirubinglucuronide (*conjugated bilirubin*) excretion through hepatic cells membrane to the bile capillaries*. As a result, direct bilirubin comes not only into the bile capillaries, but also in blood (fig. 9).

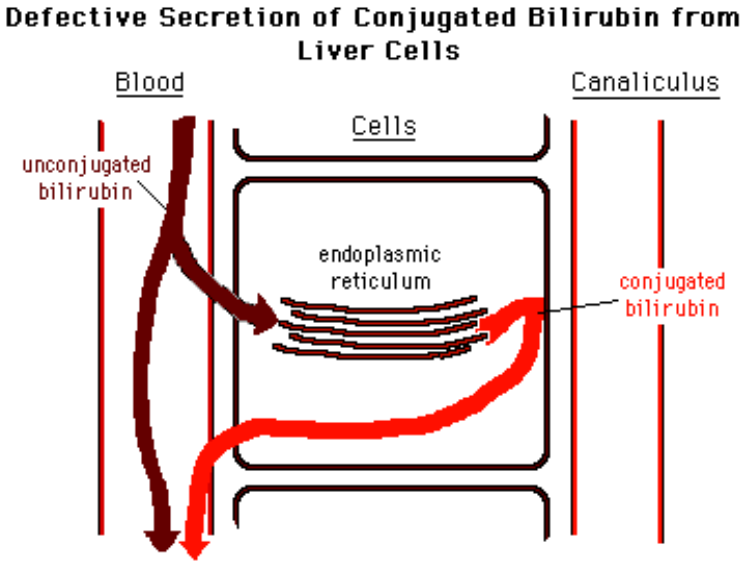


*Fig. 9.* Dubin-Johnson syndrome

Various liver diseases are mainly caused by such pathologic processes as inflammation, violation of peripheral blood circulation, metabolism and tumors. Inflammatory liver affection is called ***hepatitis***; primary changes in hepatocyte metabolism followed by dystrophy are called ***hepatosis;*** metabolic liver diseases and diffuse growth of connective tissue on the background of dystrophy or parenchyme necrosis is called ***cirrhosis*** of the liver.

## POSTHEPATIC (CHOLESTATIC) JAUNDICE

*Posthepatic or mechanical jaundice*, also called *cholestatic and obstructive* jaundice, occurs when bile flow is obstructed between the liver and the intestine. The jaundice develops due to disruption of the patency of bile ducts, as a result of their stenosis or obstruction or from external pressure (fig. 10).

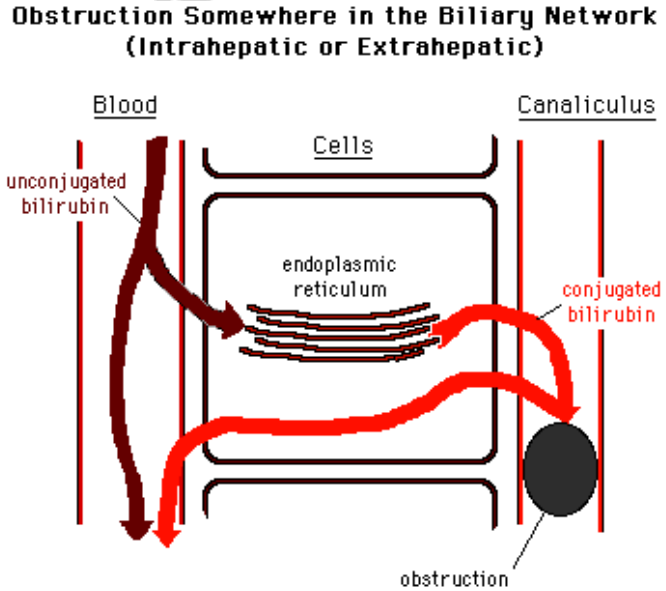


*Fig. 10.* Dubin-Johnson syndrome

The cause of its development is a steady disturbance of bilification from the bile capillaries, the gallbladder or its duct into duodenum lumen. It is stipulated by narrowing or total closing of their lumen (stones in the biliferous tracts; inflammatory process in them; presence of parasites in the gallbladder; biliferouse tracts dyskinesia; tumors). The disturbance of bile outflow is accompanied by an increase of pressure in the bile capillaries, their walls and reverse diffusion of many components of bile in the blood capillaries. The rupture of the bile capillaries is possible in cases of acute total obturation of the biliferous tracts. Bile, coming into contact with the hepatic tissue, provokes its damage and the development of the inflammatory process that is called *biliary hepatitis*. The development of two syndromes is typical for obstructive jaundice: *cholemia and acholia.*

*Cholemia* is a complex of disturbances which are conditioned by the appearance of bile components in blood and mainly of bile acids, glycocholic and taurocholic in particular. Yellow coloring of skin and skleras is provoked by an increase of conjugated bilirubin level in a blood. Conjugated bilirubin appears in urine in combination with bile acids (*cholaluria*) that gives a specific color to urine. The blood cholesterol level is high (*hypercholesterinemia*) and this leads to an appearance of xanthomas (frequently in the epidermis of eyelids skin).

Skin pruritus which is provoked by irritation of nervous endings by bile acids is observed at *cholemia*. Cholemia is characterized by a decrease of inhibitory activity of cerebral cortex neurons that is accompanied by heightened irritability and excitability. Later the other centers of the brain and the spinal cord are inhibited. Depression, disturbance of daily rhythm of sleep and awaking, slight fatigability, a decrease of tendon reflex are observed.

*Acholia syndrome* arises as a result of bile absence in the intestines and characterized by:

1) disturbances of cavitary digestion;

2) disturbance of lypolysis and fat-soluble vitamins splitting;

3) presence of fat in feces (steatorrhea);

4) feces discoloration because of a stercobilinogen absence in it;

5) dysbacteriosis, which is combined with aggravation of putrefaction processes and fermentation in the intestines and, as a result, meteorism;

6) a decrease of the tone and depression of intestinal peristalsis, which leads to constipation, alternated with diarrheas;

7) hypovitaminosis of K;

8) disturbance of protein synthesis, including procoagulants;

9) an increase of microvascular walls permeability that stipulates the development of hemorrhagic syndrome in combination with hypocoagulation.

In this type of jaundice the conjugated bilirubin level is elevated; the feces are clay colored because of bilirubin lack in bile; urine is dark; the level of serum alkaline phosphatase is markedly elevated; and the aminotransferase level is slightly increased.

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One of the most important causes of mechanical jaundice is presence of gallstones within the gallbladder lumen (*cholelithiasis or gallstone disease*), whether symptoms occur or not.

More than 70 % are cholesterol stones; a remainder is a so-called brown pigment gallstone composed of $Ca^{2+}$ salts of bilirubin, carbonate, cholesterol and phosphate. The incidence of cholesterol stones among females is three times higher than among males.

## CHOLESTASIS SYNDROME

Cholestasis is understood as a violation of synthesis, secretion and outflow of bile, inadequate isolation of all or major components of bile. There are next kinds of cholestasis:

1) *functional* — when cholestasis is caused by violation of bile flow in the canalic ducts and decrease of water and organic anions (bilirubin, bile acids) excretion by the liver;

2) *morphological* — cholestasis is caused by accumulation of bile in hepatocytes and biliary tract;

3) *clinical* — when cholestasis is caused by a delay in blood of components normally excreted in bile.

There are *intrahepatic* cholestasis (or hepatic-tubular, intralobular) and duct (interlobular), as well as *extrahepatic* cholestasis (bile outflow disorders caused by mechanical factors).

In the pathogenesis of cholestasis a decrease in fluidity of hepatocyte membranes plays an important role. Reduction of capillary permeability and membrane fluidity is usually associated with an increased content of cholesterol and change in the ratio of phospholipids and cholesterol.

With intrahepatic cholestasis a decrease in fluidity of the membrane leads to a decrease in activity of the $Na^+/K^+$ — ATP-ase pump located on membranes of hepatocytes. This transport system can change under an influence of bacterial toxins. As a result the electrochemical potential of membranes changes and leads to a disruption of the sodium-dependent transport of bile acids.

In the development of intra-lobular cholestasis damage of microfilaments which form accumulations around capillary membranes plays a significant role. In addition intercellular contacts broke and this leads to reflux of bile into the sinusoids. Dysfunction of microtubules disrupts intracellular transport of bile acids.

Thus, there are following pathogenetic factors of cholestasis:

1) an increase of cholesterol content in hepatocytes membranes;

2) impairment of hepatocytes membranes fluidity and permeability;

3) decreased activity of Na+/K+-ATPase pump of hepatocytes membranes;

4) violation of sodium-dependent transport of bile acids;

5) damage of hepatocytes cytoskeleton elements.

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The main manifestations of cholestasis include following changes:

1) violation of cholesterol excretion with bile; development of hypercholesterolemia; violation of direct (conjugated) bilirubin excretion. It is manifested by jaundice;

2) violation of bile acids excretion. It is manifested by skin itching and leads to impaired absorption of fat-soluble vitamins (A, K, E, D) and the development of their deficiency with the corresponding clinical manifestations, in particular:

– hypovitaminosis A is manifested by «night blindness», hyperkeratosis;

– hypovitaminosis K — a decrease in the level of prothrombin, hemorrhagic diathesis;

– for hypovitaminosis E reproductive disorders and muscle weakness are typical;

– for hypovitaminosis D — osteomalacia, fractures.

In addition it has been established that cholestasis is the most important contributing factor to stone formation and development of cholelithiasis.

## MALNUTRITION SYNDROME

Metabolic disorders play a major role in the development of malnutrition syndrome. This syndrome is manifested by a worsening of appetite, nausea, abdominal pain, unstable stool, weight loss and anemia.

Hepatic failure is accompanied by various metabolism violations.

***Disorders of protein metabolism***. Liver pathology is manifested by changes of proteins synthesis and their splitting, deamination and decarboxylation, the formation of urea and creatinine (final products of protein metabolism). Disorders of final stages of protein metabolism lead to an increase in residual blood nitrogen (nitrogen urea, amino acids) and ammonia — the most important indicators of liver failure severity. Violation of albumin synthesis by hepatocytes is manifested by hypoalbuminemia and disproteinemia. Hypoalbuminemia promotes the development of edema and ascites formation (in condition of increased blood pressure in the vessels of portal vein).

The inhibition of protein synthesis of hemostasis system (fibrinogen, proconvertin, proaccelerin, prothrombin, factors of Kristmas and Stewart-Prower, anticoagulant proteins C and proteins S) leads to hypocoagulation, promotes hemorrhagic syndrome (hemorrhage in tissue, bleeding).

***Violations of carbohydrate metabolism*** are manifested by a decrease of glycogen synthesis and cleavage as well as gluconeogenesis which leads to the development of hepatogenic hypoglycemia. This may be a result of various enzymopathies caused by pathological processes in the liver or increased degradation of enzymes for example at protein starvation with a change in the neurohumoral regulation of enzyme processes.

Glycogen reduction leads to an inadequate production of glucuronic acid from it and as a consequence to a violation of liver detoxification function. On the contrary for many enzymopathies an increased deposition of glycogen in liver tis-

sue, proliferation of connective tissue, and formation of glycogenesis are characteristic.

Disorders of lipid metabolism due to pathology of bile formation and bile secretion are manifested by disorders of processes of synthesis, decomposition and absorption of fatty acids, phospholipids, cholesterol and its ethers in the intestine.

Decrease of phospholipids formation, weakening of oxidation of fatty acids and an increase of intake of endogenous lipids in the liver lead to liver fatty infiltration (fatty degeneration, fatty hepatosis) which is observed for example at poisoning with certain industrial poisons and drugs or alcohol. Pathology of the liver is also accompanied by enhanced ketone bodies formation.

Disturbance in liver cells of *low-density lipoprotein* (LDL) and *very low-density lipoprotein* (VLDLP) synthesis (possessing atherogenic properties), as well as *high-density lipoprotein* (HDL) (having an anti-atherogenic effect) may be accompanied by the development of lipid dystrophy of the liver (fatty hepatosis).

***Disturbances in metabolism of hormones and biological active substances*** at liver pathology are manifested by violation of hormones synthesis and their transport proteins and change of hormones and biological active substances inactivation (deactivation of serotonin and histamine). Thus the disruption of tyrosine formation from phenylalanine in the liver leads to a decrease in the production of iodine-containing hormones of the thyroid gland and catecholamines in the body. Pathological processes in the liver in which inactivation of hormones such as thyroxine, insulin, corticosteroids, sex hormones is violated, lead to shifts in their content in blood and the development of the corresponding endocrine pathology.

***Violations of water-electrolyte metabolism*** in liver pathology are associated with disorders of transport proteins (transferrin, ceruloplasmin) synthesis and processes of microelements depositing. In blood there is hyperkalemia, metabolic or mixed acidosis. In the body cells the sodium, calcium and hydrogen ions (intracellular acidosis) content increases.

## HEMORRHAGIC SYNDROME

Hemorrhagic syndrome is the appearance of hemorrhages and bruises on the skin and subcutaneous tissue, bleeding gums, nosebleeds, etc. In the basis of this syndrome pathogenesis the following factors are:

1) *a decrease of clotting factors synthesis* associated with the suppression of protein-synthetic liver function;

2) *increased consumption of clotting factors*. Releasing of thromboplastic substances by damaged cells of the liver into blood leads to the dessiminated intravascular coagulation of blood with fibrinolysis and the formation of thrombi. These processes require an increased number of clotting factors, resulting in the consumption coagulopathy development;

3) *a decrease of platelets number* most often associated with hypersplenism;

4) *increased vascular wall permeability* under toxic substances influence.

Disturbances of hemodynamics at liver pathology are associated with disorders of functions involved in maintaining normal blood circulation. It is known that the liver provides:

1) collector function (through the liver passes 30–35 % of blood minute volume, which is 1.5–1.8 l/min);

2) blood deposition (in the liver can be up to 700 ml of blood, temporarily turned off from the circulation);

3) participation in blood vessels tone maintenance (synthesis of angiotensinogen and other precursors of biological active substances).

Violation of liver hemodynamic functions can lead to arterial hypotension or portal hypertension syndrome development.

Development of hepatic hypotensive syndrome is caused by a decrease of angiotensinogen (a substrate for the formation of angiotensin II) synthesis by damaged hepatocytes, as well as by hypotensive effect of bile acids.

## PORTAL HYPERTENSION

Portal hypertension is a persistent increase of the portal system vessels pressure in excess of 250–300 mm. Normally a healthy person has a portal pressure of 4.5–10 mm Hg. The main link of portal hypertension pathogenesis is blood stasis in the portal vein system. Pressure in the portal vein is not a constant value. It increases with inspiration and decreases with exhalation, significantly increases with filling the stomach, etc.

There are many reasons for portal hypertension. Taking into account the localization of portal blood circulation, the following types of portal hypertension are distinguished: ***intrahepatic*** (the most common cause is cirrhosis of the liver, less often a tumor or fibrosis of the organ) and ***extrahepatic*** due to the difficulty of blood outflow through the hepatic veins. The latter, in turn, can be *over-* and *underhepatic*. The superhepatic form of portal hypertension develops with cardiac decompensation of the right ventricular or mixed type, Chiari's disease (thrombosis of the hepatic veins), Badda-Chiari syndrome (thrombosis of inferior vena cava at the hepatic veins level). The sub-hepatic form is associated with blockade of portal blood flow at the portal vein level.

The main reason for portal pressure increasing at liver cirrhosis is the obliteration of a significant part of liver small vessels, as well as the compression of these vessels with a proliferating connective tissue, and, as a consequence, the growth of vascular resistance, i. e. increased resistance of liver blood vessels.

Clinical manifestations of portal hypertension are: 1) *varicose veins of the anterior abdominal wall* («*caput meduzae*»); 2) *ascites;* 3) *splenomegaly*. Simultaneous their presence is not necessary, a complete triad occurs in approximately 9–12 % of cases.

The earliest compensatory-adaptive reaction aimed at unloading of the portal vein is *collateral circulation development* by expanding of pre-existing anastomoses and formation of new ones.



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Collateral circulation is an important feature of the porto-hepatic circulation at cirrhosis; it is carried out not only by intrahepatic shunts, but also by extrahepatic portocaval anastamoses. A significant part of blood passes through the liver, bypassing active parenchyma. «Useless bloodstream» through the liver can account for more than 50 % of blood received by the hepatic artery and portal vein. Circulation bypassing active parenchyma significantly impairs — metabolism of hepatic cells, leading to periodic bacteremia and endotoxinemia with febrile episodes, as well as to hepatic encephalopathy and coma.

Thus, along with compensatory-adaptive value (unloading the portal basin and preventing general hemodynamic disorders in the body), the functioning of this kind of anastomosis has negative consequences:

1) promotes the discharge of a large volume of untreated blood to the common bloodstream and the development of endogenous intoxication of the body, encephalopathy and coma;

2) creates a threat of esophageal bleeding;

3) as a result of blood flow shunting liver cells are partially turned off from functioning and do not perform a detoxification function, pathological regeneration (cirrhosis) goes on which aggravates structural and functional disorders of the organ.

Blood stagnation in the abdominal cavity organs leads to violations of their functions, disorders of general hemodynamics and is accompanied by accumulation of abdominal cavity fluid (development of ascites).

***Splenomegaly*** as a consequence of the splenic veins increased pressure is manifested by accelerated blood destruction, which leads to a shortening of blood elements lifespan, the development of anemia and thrombocytopenia.

## ASCITIC SYNDROME

***Ascitic syndrome*** (fig. 11) occurs with hepatic insufficiency progression. The pathogenesis of this syndrome is complex and depends on the interaction of several factors: 1) disorders of hormonal and neurohumoral regulation, caused by hemodynamic changes and disturbance of water-electrolyte equilibrium; 2) developing portal hypertension.

The main links of pathogenesis are the following:

1) hemodynamic — increased portal pressure which causes increased transudation through the liver sinusoids walls;

2) decrease in oncotic pressure due to hypoproteinemia (hypoalbuminemia) associated with impaired hepatic protein function;

3) increased lymph formation in the liver;

4) sodium and water retention in the body due to secondary hyperaldosteronism as a result of violation of aldosterone inactivation in the liver;

5) increased production of antidiuretic hormone (ADH) by the pituitary gland — as a result of plasma effective volume decrease;

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6) increased vascular permeability due to hypoxia and endogenous intoxication;

7) accumulation of histamine-like and other vasoactive substances (nitrogen monoxide, etc.) leads to vasodilation, swelling.

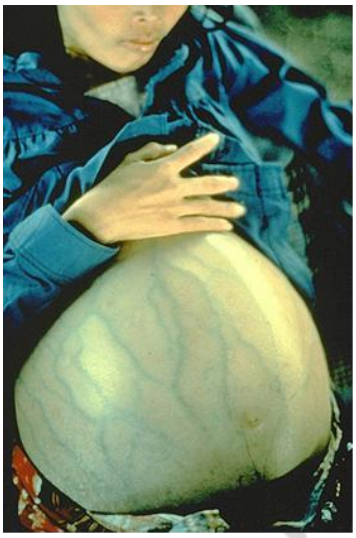

*Fig. 11.* Ascitic syndrome

The main links in the pathogenesis of liver failure complications are presented in table 2.

*Table 2*

**Complications of hepatic insufficiency (pathogenesis)**

| **Complications** | **Pathogenesis** |
|---|---|
| Azotemia | Decrease of blood volume. Acute tubular necrosis, hepatorenal syndrome |
| Cerebral edema | Impairment of vascular permeability, circulating toxins |
| Gastrointestinal bleedings | Erosive gastritis aggravated by coagulopathy and portal hypertension |
| Hypoxemia | Discharge of blood from the right to the left, non-cardiogenic pulmonary edema |
| Hypotension | Decrease of vascular resistance, sepsis, gastrointestinal bleedings |
| Acidosis | Decrease of tissue perfusion, decreased hepatic clearance of organic acids |
| Alkalosis | Hyperventilation (mainly of a central genesis) |
| Hypokalemia | Renal or gastrointestinal, loss of potassium |
| Hyponatremia | Reduced hepatic clearance of free water, taking liquids |
| Hypoglycemia | Reduced glycogenolysis and glyconeogenesis |

*Hematologic aspects of liver pathology*:

1) violation of erythropoiesis, development of anemia;

2) appearance of pathological forms of erythrocytes (hypochromic erythrocytes due to iron deficiency, echinocytes, acanthocytes, etc.);

3) increased hemolysis (shortened erythrocyte lifespan);

4) increase of plasma volume;

5) bone marrow insufficiency;

6) leukopenia and thrombocytopenia.



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## HEPATO-CEREBRAL, HEPATO-ENDOCRINE AND HEPATO-RENAL INSUFFICIENCY SYNDROME

*Syndrome of hepato-cerebral insufficiency* arises as a result of liver antitoxic function violations and concomitant hypoglycemia. The main manifestations are:

1) emotional — mental disorders: (alternation of euphoria and depression; insomnia at night, drowsiness during the day; headache; dizziness);

2) impairment of consciousness — development of stupor, confusion;

*Hepato-endocrine syndrome* (syndrome of endocrine disorders) is associated with impaired metabolism of a number of hormones (impaired inactivation of glucocorticoids, thyroxine, ADH, aldosterone, estrogens, insulin) and leads to decreased libido, infertility and gynecomastia, atrophy of the testicular, mammary glands and uterus, menstrual cycle violation. The appearance of diabetes and secondary aldosteronism is possible. The development of endocrine pathology can be caused by estrogens accumulation or a decrease in their inactivation, a violation of pituitary gland functions, the accumulation of vasoactive substances in the body.

*Hepato-renal syndrome* is manifested with severe liver damage and is associated with a secondary impairment of kidney function up to severe kidney failure. It is assumed that the following factors play a role in the pathogenesis of liver damage: 1) circulatory disorders in the kidneys (renal capillary spasm); 2) kidney hypoxia at liver diseases; 3) damage of the kidneys by endogenous toxins and xenobiotics uncleared by the liver; 4) arachidonic acid metabolism change (violation of the prostaglandins and thromboxane ratio).

## CLINICAL-BIOCHEMICAL HEPATIC SYNDROMES

1. **Cytolysis syndrome:** *an increase in blood serum:* 1) of АсАт, АлАт, total lactate dehydrogenase (LDH) and $LDH_{4-5}$, fructose-1-phosphate aldolase (P-1-P-aldolase), sorbitoldehydrogenase, ornitincarbamoiltransferase, glutamatdehydrogenase activity; 2) bilirubin (conjugated one mainly) level; 3) iron and vitamin $B_{12}$ content.

2. **Cholestase syndrome (excretory-biliary)**: *an increase in blood serum* of alkaline phosphatase, bilirubin and cholesterol activity.

3. **Hepatocellular insufficiency syndrome**: *a decrease in blood serum* of cholinesterase (butirilcholinesterase), prothrombin, cholesterol, albumin, glucose; *increase* of bilirubin.

4. **Syndrome of hepatic reticuloendothelium irritation** (mesenchymal-inflammatory syndrome): *an increase in blood serum*: of globulin (sometimes hyperproteinemia); modification of protein-sedimentary tests (a factor of the thymole test).

## HEPATIC COMA

***Hepatic coma*** — (from the Greek «Koma» — deep sleep) — the extreme degree of functional liver hepatic-cell and (or) vascular insufficiency, characterized by presence of hepatocerebral syndrome or consciousness disorders associat-

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ed with the accumulation of cerebro-toxic substances (ammonia, phenols, indole, amines, etc.), increasing metabolic acidosis, leading to direct damage of cells and tissue structures in various organs (liver, kidney, heart, especially the central nervous system).

There are two variants of hepatic coma pathogenesis:

1) *hepatic-cell* (*endogenous*) *coma* occurs with massive necrosis of liver parenchyma when it's homeostatic and barrier functions are significantly reduced;

2) *shunt (vascular, exogenous) type of coma* occurs as a consequence of severe sclerotic (cirrhotic) liver damage, accompanied by portal hypertension development, leading to the portocaval anastomoses development and «dropping» of blood bypassing the liver to total blood flow.

There are several interrelated mechanisms in a basis of hepatic coma: 1) hypoglycemia; 2) severe acidosis; 3) intoxication of the body by protein and lipid metabolism products; 4) amino acids and protein metabolism violations; 5) mixed hypoxia.

During hepatic insufficiency toxic substances (in particular ammonia and products of amino acids oxidation in an intestine (phenol, indole, amines, etc.), lactic and pyruvic acids (acetone) derivatives, low-molecular fatty acids (oily, caproic, etc.)) which have a direct damaging effect on the cell-tissue structure of the body accumulate in blood. Toxic factors, in addition, can indirectly enhance damage cell-tissue structures of various organs through generalized disorders of systemic and regional hemodynamics, microcirculation, external and internal respiration and hemostasis. Since a number of cerebro-toxic substances (low-molecular fatty acids, ammonia compounds with glutamic or alpha-ketoglutaric acids) are false neurotransmitters the accumulation of these substances can replace normal neurotransmitters of the nervous system or disrupt their formation from the predecessors and violate the synaptic transmission.

As a result various progressive neuropsychiatric disorders occur, opioid and unconditioned reflex activity is inhibited, convulsions, delusions, confusion and loss of consciousness occur, and a «hepatic» odor from the mouth appears. The hepatic coma may lead to the death.

## PRINCIPLES OF PREVENTION AND THERAPY OF LIVER PATHOLOGY

Prevention includes: 1) full balanced diet adequate to the body needs; 2) correct diet; 3) prevention of various pathogenic factors effect on the body in particular hepatotropic.

Therapy of liver pathology is based on etiotropic, pathogenetic and symptomatic principles.

*Etiotropic*. It is aimed at the causative factor eliminating (reducing the degree of pathogenic action). For this purpose, for example, antibacterial drugs (for cholecystitis, viral hepatitis) are used.

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*Pathogenetic*. It aims to break the pathogenesis links of liver pathology. In particular for autoimmune hepatitis the immunosuppressants and anti-inflammatory agents are indicated. The component of the pathogenetic principle is use of cholagogue, spasmolytic drugs, diet therapy (the exclusion of fatty foods, eating plant foods and drinking mineral water), parenteral administration of glucose, electrolytes, antioxidants, vitamins, the administration of hepatoprotectors, antihistamines, and glucocorticoids. With toxic liver damage detoxication measures (hemodialysis, hemosorption and other methods of detoxifycation) are carried out.

Along with conservative methods surgical treatment (cholecytectomy), lithotripsy (crushing stones by ultrasound) are used.

*Symptomatic*. It consists of elimination (or alleviation) of secondary suffering and the consequences caused by liver pathology (ascites, thrombohemorrhagic disorders, portal hypertension, skin itching, pain syndrome, etc.).

## SITUATIONAL TASKS

**Tasks 1.** The patient with insufficient secretion of bile into a small intestine and marked steatorrhea developed multiple hemorrhages.

**Question**: Explain the possible mechanisms of interrelations of the above pathologic processes.

**Tasks 2**. Patient K., 31 years old, was delivered to the clinic by an ambulance. On admission: passive, retarded, apathic, answers questions not always at once and adequately. The tongue is coated. The body temperature is 36.5 °C. Skin integuments and mucous membranes are of a yellowish color, there are teleangiectasias on the skin of the upper trunk, erythema of the palms is marked. The abdomen is enlarged due to ascites fluid that makes palpation of the liver difficult. Edemas of lower extremities are noted. The border of the left ventricle of the heart is slightly dilated. Blood pressure — 160/95 mm Hg, HR — 90 beats/min, the pulse is rhythmic.

The results of biochemical blood test: hyperbilirubinemia, hypoglycemia, hypoproteinemia, hypocholesterinemia, the urea content is decreased, the prothrombin index is reduced. The activity of AlAT and AsAT in blood is increased.

**Questions**: What are the developmental mechanisms of teleangiectasias and persistent erythema of the palms in the patient? What other symptoms are caused by the same effect?

Specify the basic developmental causes of portal hypertension and ascites? What is the role of ascites in secondary impairments of the organism function?

Are there any laboratory symptoms of hepatic insufficiency? If yes, then what is their development mechanism?

How can you assess the state of consciousness in this patient?

**Tasks 3.** Specify the type of jaundice and give the conclusion.

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*Table 4*

| | Factor | Content | Norm |
|---|---|---|---|
| Blood | Bilirubin: | | |
| | – indirect | 51.3 mcmol/l | 8.5–20.5 mcmol/l |
| | – direct | – | – |
| | Urobilin-(ogen) | ++ | – |
| | Stercobilin-(ogen) | +++ | + |
| | Cholesterol | 6.8 mcmol/l | 3.1–5.2 mmol/l |
| | Bile acids | – | – |
| Urine | Bilirubin: | – | – |
| | Urobilin-(ogen) | ++ | – |
| | Stercobilin-(ogen) | +++ | + |
| | Bile acids | –dark yellow | – |
| | Color | | straw-yellow |
| Faeces | Stercobilin | +++ | + |
| | Fatty acids | – | – |
| | Bile acids | + | ± |
| | Color | dark-brown | brown |

*Table 5*

| | Factor | Content | Norm |
|---|---|---|---|
| Blood | Bilirubin: | 342.3 mcmol/l | |
| | – indirect; | 20.1 mcmol/l | 8.5–20.5 mkmol/l |
| | – direct | 322.2 mcmol/l | – |
| | Urobilin-(ogen) | – | – |
| | Stercobilin-(ogen) | – | + |
| | Cholesterol | 14.2 mmol/l | 3.1–5.2 mmol/l |
| | Bile acids | +++ | – |
| Urine | Bilirubin: | +++ | – |
| | Urobilin-(ogen) | – | – |
| | Stercobilin-(ogen) | – | + |
| | Bile acids | +++ | – |
| | Color | dark beer | straw-yellow |
| Feces | Stercobilin | – | + |
| | Fatty acids | +++ | – |
| | Bile acids | – | ± |
| | Color | grey-white clay | brown |

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*Table 6*

| | Factor | Content | Norm |
|---|---|---|---|
| Blood | Bilirubin: | 150.7 mcmol/l | |
| | – indirect; | 20.5 mcmol/l | 8.5–20.5 mkmol/l |
| | – direct | 130.2 mcmol/l | – |
| | Urobilin-(ogen) | ++ | – |
| | Stercobilin-(ogen) | ++ | + |
| | Cholesterol | 10.2 mmol/l | 3.1–5.2 mmol/l |
| | Bile acids | ++ | – |
| Urine | Bilirubin: | + | – |
| | Urobilin-(ogen) | ++ | – |
| | Stercobilin-(ogen) | ++ | + |
| | Bile acids | + | – |
| | Color | dark beer | straw-yellow |
| Feces | Stercobilin | ± | + |
| | Fatty acids | + | – |
| | Bile acids | ± | ± |
| | Color | light-brown | brown |

**Tasks 4.** Patient I. at the age of 20 years old suffered serum hepatitis. After discharge from the hospital, he didn't go to doctor for a number of years. Periodically he was troubled by pains in the right hypochondrium, nausea, malaise. At the age of 28 years old his weakness increased. There appeared marked signs of «medusa's head» on the anterior abdominal wall, often he had diarrhea, hemorrhagic bleedings. Palpation revealed splenomegaly, the liver extending 2 cm from the costal arch, its edge being uneven.

**Question**: What syndrome developed in the patient? Name its form.

**Tasks 5.** What type of jaundice is characterized by bilirubinemia, cholacidemia, bilirubinuria, urobilirubinuria?

**Tasks 6.** After the symptoms of general malaise the patient developed yellowish coloring of sclera and the skin, itching; bilirubinuria, urobilirubinuria; the urine acquired the color of beer.

**Tasks 7.** What syndrome is characterized by a yellowish coloring of sclera and skin, bilirubinemia, bilirubinuria? Specify the possible causes of its development.

**Tasks 8.** Patient A. was delivered to the clinic by an ambulance with profuse epigastric bleeding. Three years ago he was diagnosed cirrhosis of the liver.

**Question**: The complication of what syndrome was epigastric bleeding?

**Tasks 9.** The abdomen of the patient with cardiac insufficiency of the right-ventricular type in the stage of decompensation enlarged. Abdominal puncture revealed the presence of ascites.

**Question**: What syndrome has developed in the patient? Specify its form.

**Tasks 10.** A yellowish coloring of the skin and sclera in the newborn has been persisting for 3 weeks. Urobilin is revealed in urine. Feces are intensely colored. Rh-incompatibility of the mother and the child is revealed.

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**Questions**: What is the development mechanism of jaundice in the child? What type is it referred to?

**Tasks 11.** Patient K. was admitted to the department of hepatology with symptoms of marked jaundice, psychomotor excitation and complaints of severe pains in the right hypochondrium, itching, nausea. Were revealed bilirubinemia, cholacidemia, bilirubinuria, acholic stool?

**Questions**:

1. What form of jaundice is in this patient?
2. What is the most probable cause of its development?

**Tasks 12.** There is a yellowish coloring of sclera and skin integuments, severe itching, general malaise, increased excitability in the patient; the urine is of a beer color, he has an acholic stool, bilirubinemia, cholacidemia, bilirubinuria.

**Question**: Give a full name of the syndrome developed in this patient.

**Tasks 13.** The patient suffering from cancer of the pancreas head of the developed a yellowish coloring of the skin and sclera, itching. The tests of blood and urine revealed hyperbilirubinemia, cholalemia (cholacedemia) and bilirubinuria.

**Question**: What form of jaundice developed in the patient?

**Tasks 14.** 7 months ago girl M., 6.5 years old, became listless, lost appetite, lost weight. Soon ascites developed and her legs swelled. Ascetic fluid was let out several times. The bilirubin content in the blood serum is increased. Multiple bruises, recurrent intestinal bleedings exist. The patient died at the 11 months since the beginning of the disease in the state of cachexia. Both her brothers suffered from hepato-cerebral dystrophy.

**Question**: What form of portal hypertension did the child have?

## ANSWERS TO SITUATIONAL TASKS

**Answers 1.** Under the conditions when fats are not absorbed in the small intestines, there will be also impairment of the absorption of fat-soluble vitamins, particularly of vitamin K, which is necessary for synthesis of so-called K-vitamin-dependent coagulating factors - prothrombin, proconvertin, factor of Stuart-Prauer, a plasmatic component of thromboplastin. Insufficient synthesis of these factors entails the impairment of the coagulation process and occurrence of hemorrhagic phenomena.

**Answers 2.** Erythema of the palms is due to changing of the wall structure of microvessels, including the dilation of capillaries, with adventitia thickening in the zone of venules and their dilation (teleangiectasia). Structural changes are caused, basically, by an excess of estrogens. Usually these symptoms appear in dystrophic lesions of the liver, as hepatic cells lose their ability to inactivate steroid hormones, including those of the adrenal origin.

The causal factors of a portal hypertension and ascites can be:

a) Long-term elevation of systemic venous pressure in the right-ventricular cardiac insufficiency. Venous plephora of the liver results in dystrophic changes there and destruction of microvessels due to the development of sclerosis (cirrhosis);

b) Thrombosis or embolism of the portal vein vessels;

c) Direct lesion of the parenchyma (viral, toxic, alcoholic) can end with destruction of a significant amount of hepatocytes and development of cirrhosis. It makes it impossible for normal passage of blood through hepatic capillaries that leads to the development of stagnant venous hyperemia of the intestines. The impairment of transcapillary exchange results in penetration of fluid from microvessels and its accumulation in the abdominal cavity — the development of ascites.

Secondary consequences: draining of a part of fluid from the total volume of circulating blood, mechanical squeezing of abdominal organs.

The laboratory parameters revealing the damage of hepatic cells and the presence of hepatic insufficiency:

– impairment of protein exchange (hypoalbuminemia, blood hypooncia, oncotic edemas);

– decrease of the prothrombin level (impairment of blood coagulation);

– decrease of the blood cholesterol level;

– a low blood urea level;

– increase of the blood bilirubin content;

– hyperfermentemia, characterized by transport of enzymes (AlAT and AsAт) into the blood from damaged hepatic cells.

Taking into account the clinical and laboratory data of a severe hepatic injury, it is possible to suggest a precomatous condition of consciousness.

**Answers 3**. A — suprahepatic; B — subhepatic; C — hepatic.

**Answers 4**. Parenchymatous (epithelial-cellular) jaundice.

**Answers 5**. The specified symptoms are characteristic of parenchymatous (epithelial-cellular) jaundice.

**Answers 6**. The patient has an intrahepatic form of portal hypertension.

**Answers 7**. For mechanical jaundice.

**Answers 8.** Epigastric bleeding was a complication of portal hypertension (its intrahepatic form).

**Answers 9.** The patient has a suprahepatic form of portal hypertension.

**Answers 10.** The child has hemolytic jaundice.

Its cause is an intensified hemolysis of erythrocytes due to formation of anti-bodies in the maternal organism to erythrocytes of the child.

**Answers 11.** The patient has mechanical (obturation, stagnant) jaundice.

Accounting the anemnesis, its most probable reason is the obstruction of a bile duct by a bile stone.

**Answers 12.** A mechanical (stagnant) jaundice.

**Answers 13.** A mechanical jaundice.

**Answers 14.** An intrahepatic form of portal hypertension.

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*Appendix*

*Table 1*

**Types of Primary (hereditary, enzymopathic) Jaundice**

| Type of pathology | Manifestations |
|---|---|
| Gilbert's syndrome | Mild decrease in UDP-glucuronide transferase activity and transport of unconjugated bilirubin into the liver cell; mild asymptomatic increase in the blood level of unconjugated bilirubin. |
| Crigler-Najar syndrome type I | Absence of UDP-glucuronide transferase activity in the liver cells; very high unconjugated bilirubin levels in the serum (340–770 umol/L); no conjugated bilirubin is formed — colorless bile; severe neurologic complications. |
| Crigler-Najar syndrome, Type II | Partial deficiency of UDP-glucuronide transferase; high unconjugated bilirubin levels in the serum (103–340 umol/L); neurologic complications are uncommon. |
| Dubin-Johnson syndrome | A defect in biliary excretion of bilirubin, cholephilic dyes, porphyrins; high bilirubin levels in the serum (51–257 umol/L), predominantly of the conjugated type; patients are asymptomatic or have vague constitutional or GI symptoms; liver cells contain dark pigment |
| Rotor syndrome | Similar to the Dubin-Johnson syndrome but the defect of biliary excretion of dyes is not as diffuse; high bilirubin levels in the serum, predominantly of the conjugated type; there is no dark pigment in the liver cells. |

*Table 2*

**Laboratory Diagnosis of Jaundice**

| Factors | **Norm** | | | **Jaundice** | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | **supra-hepatic** | | | **sub-hepatic** | | | **hepatocellular** | | | | | | | | |
| | | | | | | | | | | **1 stage** | | | **2 stage** | | | **3 stage** | | |
| | Blood | Urine | Feces | Blood | Urine | Feces | Blood | Urine | Feces | Blood | Urine | Feces | Blood | Urine | Feces | Blood | Urine | Feces |
| Indirect bilirubin | + | – | – | ↑ | – | – | N | – | – | N | – | – | N | – | – | ↑ | – | – |
| Direct bilirubin | – | – | – | N | – | – | | + | – | – | – | – | ↑ | + | – | – | – | – |
| Urobilin-(ogen) | – | – | – | + | + | – | – | – | – | + | + | – | + | + | – | – | – | – |
| stercobilin-(ogen) | + | + | + | ↑ | ↑ | ↑ | – | – | – | N | N | N | ↓ | ↓ | ↓ | – | – | – |
| Bile acids | – | – | – | – | – | – | ↑ | + | – | – | – | – | + | + | – | + | + | – |
| Hepatic enzymes | | | | | | | | | | | | | + | + | – | + | + | – |

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*Table 3*

**Biochemical factors of blood in norm**

| | |
|---|---|
| Total protein,g/l | 65–85 |
| Albumin, g/l | 35–50 |
| Globulins, g/l:<br>α1<br>α2<br>β<br>γ | <br>3–5<br>5–7<br>7–11<br>11–13 |
| Residual nitrogen, mmol/l | 14.3–28.5 |
| Nitrogen of amino acids, mmol/l | 3.6–5.7 |
| Urea, mmol/l | 2.5–8.3 |
| Uric acid, mmol/l | 0.8–0.48 |
| Creatinine, mcmol/l (male)<br>(female) | 44–150<br>44–97 |
| Ammonia, μmol/l | 19–43 |
| Glucose, mmol/l | 3.85–6.05 |
| Total lipids,g/l | 4.0–8.0 |
| Total cholesterol, mmol/l<br>Cholesterol LPHD, mmol /l<br>Cholesterol LPLD, mmol/l | 3.1–5.20<br>0.8–2.2<br>< 4,9 |
| LPHD, g/l | 2.57–4.56 |
| LPLD, g/l | 2.30–3.51 |
| Triglycerides, mmol/l | 0.50–2.10 |
| Bilirubin, total , mcmol/l | 8.5–20.5 |
| Calcium, mmol/l | 3.3–4.9 |
| Chlorine, mmol/l | 97–110 |
| Serum iron, mcmol/l (male)<br>(female) | 8.8–27<br>9.5–29 |
| Potassium, mmol/l | 3.8–4.7 |
| Sodium, mmol/l | 135–145 |

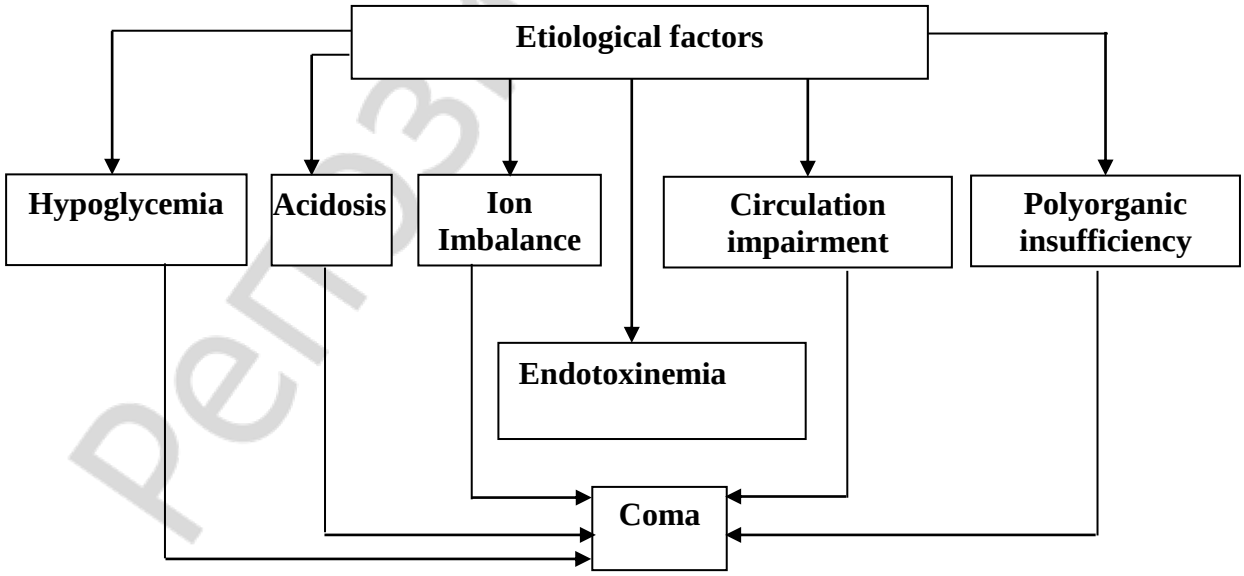


*Fig.* Major factors of hepatic coma pathogenesis

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**CONTENT**



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Учебно-методическое пособие

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Компьютерный набор С. А. Жадан
Компьютерная верстка А. В. Янушкевич

Подписано в печать 16.11.18. Формат 60×84/16. Бумага писчая «Xerox office».
Ризография. Гарнитура «Times».
Усл. печ. л. 2,09. Уч.-изд. л. 1,85. Тираж 170 экз. Заказ 750.

Издатель и полиграфическое исполнение: учреждение образования
«Белорусский государственный медицинский университет».
Свидетельство о государственной регистрации издателя, изготовителя,
распространителя печатных изданий № 1/187 от 18.02.2014.
Ул. Ленинградская, 6, 220006, Минск.

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