Ministry of Public Health of Ukraine
Poltava State Medical University
Department of biological and bioorganic chemistry

Biochemical functions of the liver. Biochemistry of jaundices. Biotransformation of foreign compounds in the liver.

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Lecture plan

- Functions of liver.

✓Carbohydrate (glycogenic) function of the liver.

✓Lipid metabolism.

✓Protein and amino acids metabolism

✓Bile formation function of the liver. Biochemical composition of bile.

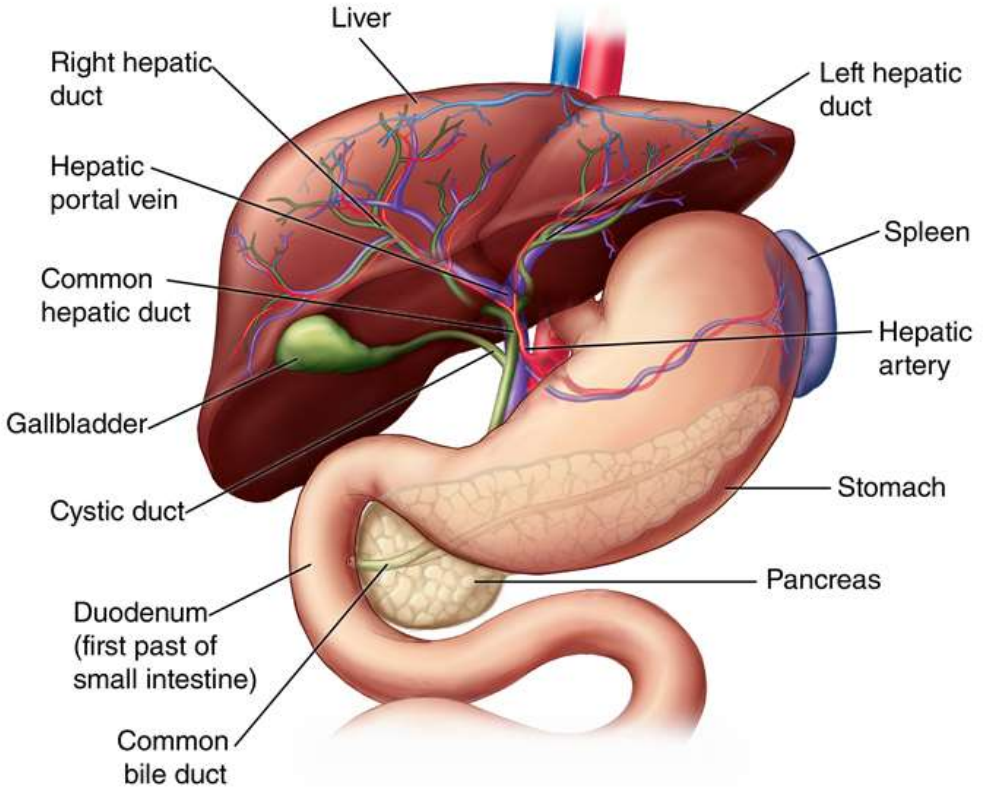
✓Role of the liver in metabolism of bile pigments. Catabolism of hemoglobin.

✓Pathochemistry of jaundices.

✓Detoxification function of the liver.

Liver

- The liver is located in the upper right-hand portion of the abdominal cavity, beneath the diaphragm, and on top of the stomach, right kidney, and intestines.
- Shaped like a cone, the liver is a dark reddish-brown organ that weighs about 3 pounds.
- There are 2 distinct sources that supply blood to the liver, including the following:
- Oxygenated blood flows in from the hepatic artery
- Nutrient-rich blood flows in from the hepatic portal vein
- The liver holds about the 13% of the body's blood supply at any given moment. The liver consists of 2 main lobes. Both are made up of 8 segments that consist of 1,000 lobules (small lobes). These lobules are connected to small ducts (tubes) that connect with larger ducts to form the common hepatic duct. The common hepatic duct transports the bile made by the liver cells to the gallbladder and duodenum (the first part of the small intestine) via the common bile duct.



https://www.hopkinsmedicine.org/health/conditions-and-diseases/liver-anatomy-and-functions

Functions of liver.

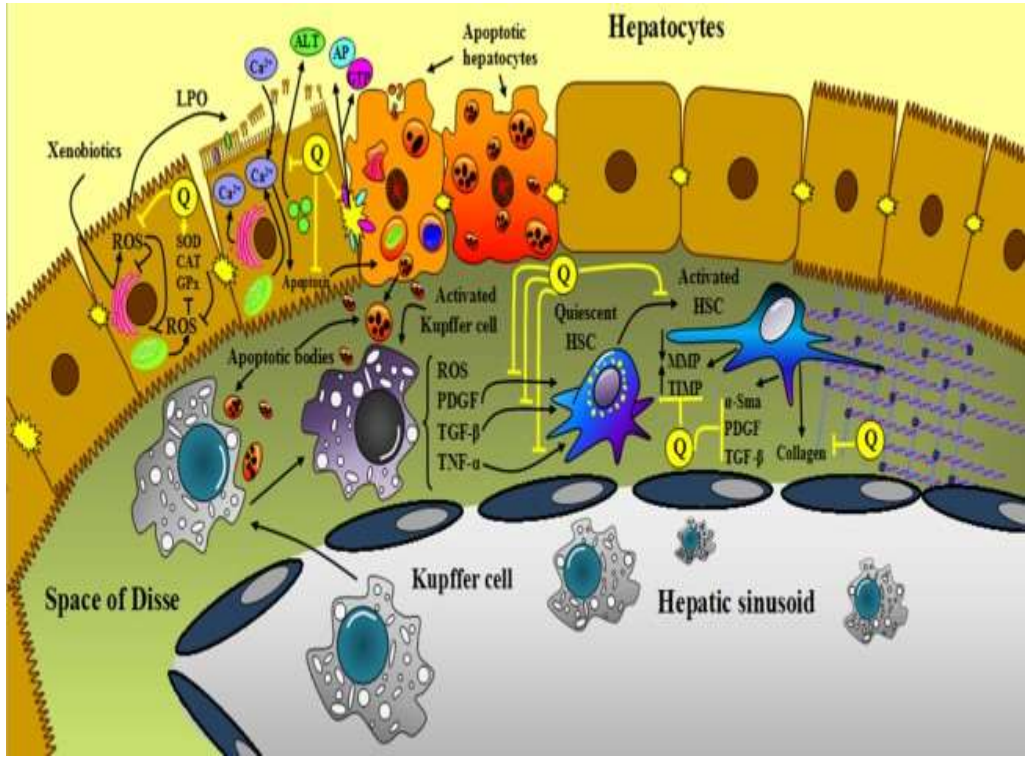
- More than 500 vital functions have been identified with the liver. Some of the more well-known functions include the following:

✓ Accepts and distributes substances that enter the body from the digestive tract, which are brought with blood through the portal vein. These substances penetrate into hepatocytes, undergo chemical transformations and, in the form of intermediate or final metabolites, enter the bloodstream and are carried to other organs and tissues.

✓ Serves as a place for the formation of bile.

✓ Synthesizes substances that are used in other tissues.

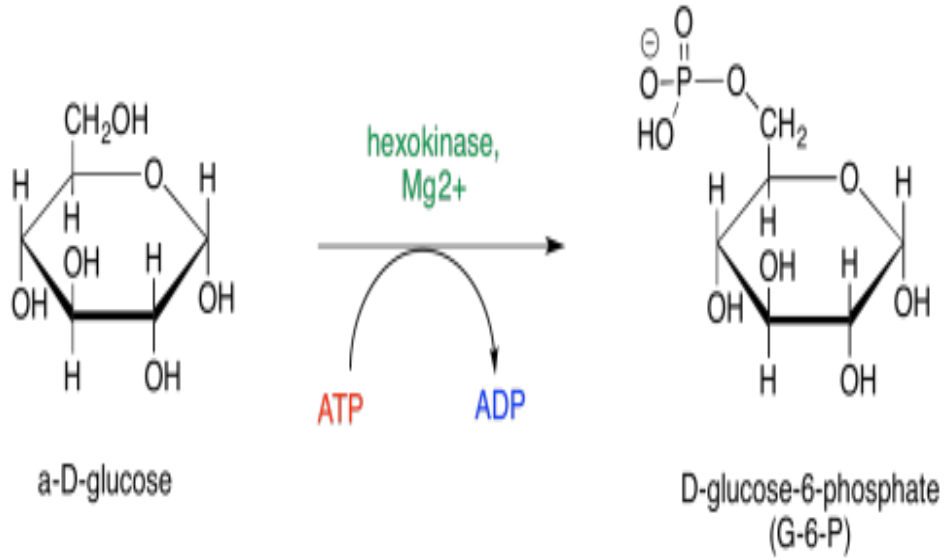
✓ Inactivates exogenous and endogenous toxic substances, as well as hormones.



http://scitechconnect.elsevier.com/morphology-physiology-biochemistry-liver-diseases/

Metabolism of carboxydrates

- The main role of the liver in carbohydrate metabolism is to maintain a blood glucose concentration.
- **Processes in the liver with hyperglycemia:**
- After a meal, the concentration of glucose in the portal vein increases sharply: within the same limits, its intrahepatic concentration also increases. An increase in the concentration of glucose in the liver causes a significant the uptake of glucose by the liver.
- Glucose must necessarily be phosphorylated in the cell (phosphorylated monosaccharides do not pass through the cell membrane and are utilized directly by the cell). For this, all cells use hexokinase. Hepatocytes use an additional isoform of hexokinase - **glucokinase.**
- **Glucokinase,** like **hexokinase**, catalyzes the phosphorylation of glucose with the formation of glucose-6-phosphate, while the activity of glucokinase in the liver is almost 10 times higher than that of hexokinase. This allows glucose to be rapidly absorbed from the blood. An important difference between the two enzymes is that glucokinase, in contrast to hexokinase, has a high CM for glucose and is not inhibited by glucose-6-phosphate.



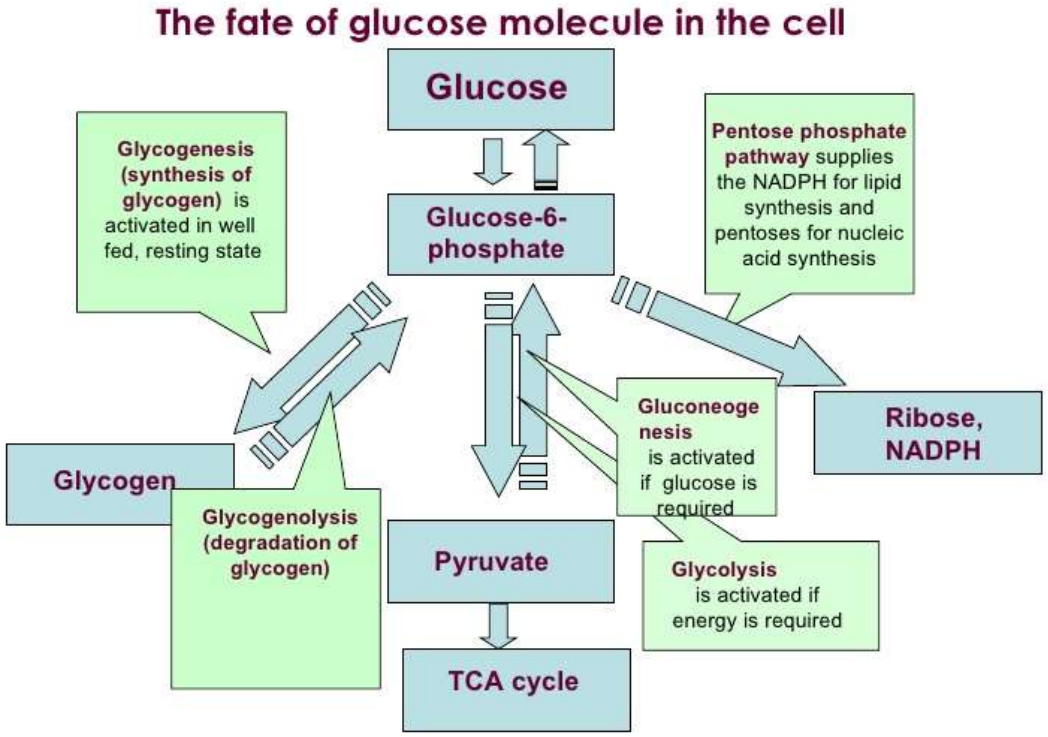
Metabolism of carboxydrates

- ✓ From the total amount of glucose coming from the intestine, the liver extracts most of it and spends: 10-15% of this amount for the synthesis of **glycogen, 60% for aerobic energy oxidation, 30% for the synthesis of fatty acids and triglycerides.**
- ✓ *In addition, the following processes of glucose metabolism occur in the liver:*
- ✓ **Pentose phosphate pathway.** In the reactions of this process, NADPH is formed in the liver, which is used for reducing reactions in the synthesis of fatty acids, cholesterol and other steroids; it is also necessary for reactions to neutralize toxins using microsomal oxidation. In addition, this results in the formation of pentoses necessary for the synthesis of nucleotides.
- ✓ **Glucuronic acid pathway – synthesise of UDP-glucuronic acid.** UDP-glucuronate participates in the detoxification of xenobiotics (phase II) by conjugation with the formation of glucuronides and important for synthesise of glycosaminoglycans, like heparin.
- ✓ **Nonessential amino acids** are synthesized from glucose.

- **Processes in the liver with hyperglycemia:**

- ✓ **Glycogen breakdown** - **glycogenolysis** is used to increase the blood glucose concentration (enough to maintain glucose during 8-12 hours of fasting) to free glucose (via glucose-6-phosphatase).
- ✓ **Gluconeogenesis** - the process of glucose synthesis from non-carbohydrate metabolites such as pyruvate, lactate, amino acids, glycerol - is a very powerful process that allows you to increase glucose levels for a long time.

- In addition to glucose metabolism, in the liver, **fructose** and **galactose** are actively metabolized. (Details and metabolic disorders are described in lecture on carbohydrate metabolism 1)



https://www.slideshare.net/senchiy/biochemistry-of-livermuscles

Metabolism of lipids

- Liver enzyme systems are capable of catalyzing all reactions or the vast majority of lipid metabolism reactions. This is like the ***synthesis of higher fatty acids, triglycerides, phospholipids, cholesterol and its esters, as well as triglyceride lipolysis, fatty acid oxidation, formation of acetone (ketone) bodies, etc.***
- The reactions for the **synthesis of triglycerides** in the liver and adipose tissue are similar. Thus, long-chain CoA derivatives of fatty acids react with glycerol-3-phosphate to form phosphatidic acid, which is then hydrolyzed to diglyceride. Which is further used to synthesize either **triglycerides or phospholipids**.
- Triglyceride synthesis is enhanced by high plasma fatty acid or glucose levels.
- Triglycerides synthesized in the liver either remain in the liver or are secreted in the form of **lipoproteins. very low density**.
- In addition to VLDL, the liver also synthesizes **high-density lipoproteins - HDL**.
- The liver synthesizes **ketone bodies** (acetoacetate, beta-hydroxybutyrate and acetone) from acetyl-CoA. These compounds are used to provide energy to the cells of the body. It is an important source of energy for the heart muscle and neurons (when there is little or no glucose in the diet).
- The concentration of ketone bodies increases during fasting and fasting, insulin-dependent diabetes mellitus, high lipid and low carbohydrate intake.
- В печени происходит **интенсивный распад фосфолипидов, а также их синтез**. Помимо глицерина и жирных кислот, которые входят в состав нейтральных жиров, для синтеза фосфолипидов необходимы неорганические фосфаты и азотистые соединения, в частности холин, для синтеза фосфатидхолина.
- With insufficient formation or insufficient intake of choline in the liver, the synthesis of phospholipids from the components of neutral fat becomes either impossible, or decreases sharply and neutral fat is deposited in the liver - liver steatosis develops ("fatty liver"). The synthesis of phospholipids is limited by the number of nitrogenous bases, i.e. for the synthesis of phosphoglycerides, either choline is required, or compounds that can be donors of methyl groups and participate in the formation of choline (for example, methionine, vitamins of B6, B12, Bc). Such compounds are called lipotropic factors.
- The liver synthesizes 75-80% of all **cholesterol** from acetyl-CoA. The biosynthesis of cholesterol in the liver is suppressed by exogenous cholesterol - the principle of negative feedback. The more cholesterol comes from food, the less it is synthesized in the liver, and vice versa.
- Part of the cholesterol synthesized in the liver is excreted from the body along with bile, the other part is converted into bile acids and is used in other organs for the synthesis of steroid hormones and other compounds.
- In the liver, cholesterol can interact with fatty acids (in the form of acyl-CoA) to form cholesterol esters.

Metabolism of proteins and amino acids

- The liver plays a central role in protein metabolism. Plasma proteins are synthesized in it:
- All albumins, 75–90% of α-globulins and 50% of β-globulins are synthesized by hepatocytes. Some γ-globulins are synthesized by Kupffer cells. The liver is the only organ where such important proteins as prothrombin, fibrinogen, proconvertin and proaccelerin are synthesized.
- Pathological processes in hepatocytes sharply reduce their synthetic capabilities. As a result, the content of albumin in the blood plasma drops sharply, which can lead to a decrease in the oncotic pressure of blood plasma, the development of edema, and ascite. It is noted that in liver cirrhosis occurring with symptoms of ascites, the content of albumin in the blood serum is 20% than in cirrhosis without ascites.
- Violation of a number of protein factors of the blood coagulation system in severe liver diseases can lead to hemorrhages.
- Amino acid metabolism reactions in the liver: direct oxidative deamination, transamination, indirect deamination, synthesis of creatine, porphyrins, glutathione, purine and pyrimidine nucleotides, as well as their catabolism, glucose synthesis from amino acids, synthesise of vitamin PP from tryptophan, etc.

Metabolism of vitamins and microelements

- Fat-soluble vitamins are deposited in the liver, as well as some water-soluble vitamins B12.
- Active forms of vitamins are formed in hepatocytes, for example, cholecalciferol is hydroxylated to form 25 hydroxycholecalciferol. Water-soluble vitamins are converted into coenzymes: a) by phosphorylation; for example: vitamin B1 - into thiamine diphosphate (TDF); B6 - to pyridoxal phosphate (FP); b) being incorporated into nucleotides: vitamin PP in NAD +, NAD + F; riboflavin in FMN, FAD; pantothenic acid into acylation coenzyme (HS-CoA), etc.
- The liver is responsible for the synthesis of specific proteins that transport vitamins in the blood plasma to the target organs.
- The catabolism of many vitamins is completed in the liver. Biotransformation products of lipovitamins, B12, are excreted from the body in the bile through the gastrointestinal tract.
- The liver deposits a large amount of various micro elements, for example, iron, copper, zinc, etc.

Bile formation in the liver

- **Bile** is a yellowish-brown liquid secret, synthesized by hepatocytes. A person produces 500-700 ml of bile per day (10 ml per 1 kg of body weight). The composition of hepatic bile is (97–98)% water, 0.7%bile salts, 0.2% bilirubin, 0.51% fats (cholesterol, fatty acids, and lecithin), and inorganic salts. The two main pigments of bile are bilirubin, which is orange–yellow, and its oxidised form biliverdin, which is green.
- Bile formation occurs continuously, although the intensity of this process fluctuates sharply throughout the day. Outside of digestion, hepatic bile passes into the gallbladder, where it thickens as a result of the absorption of water and electrolytes.
- Bile formation begins with the active secretion of water, bile acids and bilirubin by hepatocytes, as a result of which the so-called primary bile appears in the bile tubules. The latter, passing through the bile ducts, comes into contact with blood plasma, as a result of which an equilibrium of electrolytes is established between bile and plasma, i.e. mainly two mechanisms are involved in the formation of bile - filtration and secretion.
- **In hepatic bile, two groups of substances can be distinguished.**

✓ The first group consists of substances that are present in bile in the same concentrations as in blood plasma (for example, Na +, K + ions, creatine, etc.).

✓ The second group is substances whose concentration in hepatic bile is many times higher than their content in blood plasma (bilirubin, bile acids, etc.), a number of enzymes are found in bile, one of the most active is alkaline phosphatase of hepatic origin. If the outflow of bile is disturbed, the activity of this enzyme in the blood serum increases.

- **Bile functions:**

✓ Emulsification. Bile salts have the ability to significantly reduce surface tension and emulsify fats in the intestine.

✓ Acid neutralization. Bile, which has a pH of just over 7.0, neutralizes the acidic chyme coming from the stomach, preparing it for digestion in the intestines.

✓ Absorption of the lipids.

✓ Excretion. Bile is an important carrier of excreted bile acids and cholesterol. In addition, it removes from the body many drugs, toxins, bile pigments and various inorganic substances such as copper, zinc and mercury.

✓ Stimulation of intestinal motility.

Cholelithiasis

- **Cholelithiasis** is the presence of one or more calculi (gallstones) in the gallbladder. Gallstones tend to be asymptomatic. The most common symptom is biliary colic; gallstones do not cause dyspepsia or fatty food intolerance. More serious complications include cholecystitis; biliary tract obstruction (by stones in the bile ducts (choledocholithiasis), sometimes with infection (cholangitis); and gallstone pancreatitis.
- **There are several types of gallstones.**
- **Cholesterol stones** account for > 85% of gallstones in the Western world. For cholesterol gallstones to form, the following is required:

✓ Bile must be supersaturated with cholesterol. Normally, water-insoluble cholesterol is made water soluble by combining with bile salts and lecithin to form mixed micelles. Supersaturation of bile with cholesterol most commonly results from excessive cholesterol secretion (as occurs in obesity or diabetes) but may result from a decrease in bile salt secretion (eg, in cystic fibrosis because of bile salt malabsorption) or in lecithin secretion (eg, in a rare genetic disorder that causes a form of progressive intrahepatic familial cholestasis).

✓ The excess cholesterol must precipitate from solution as solid microcrystals. Such precipitation in the gallbladder is accelerated by mucin, a glycoprotein, or other proteins in bile.

✓ The microcrystals must aggregate and grow. This process is facilitated by the binding effect of mucin forming a scaffold and by retention of microcrystals in the gallbladder with impaired contractility due to excess cholesterol in bile.

- **Pigment stones**

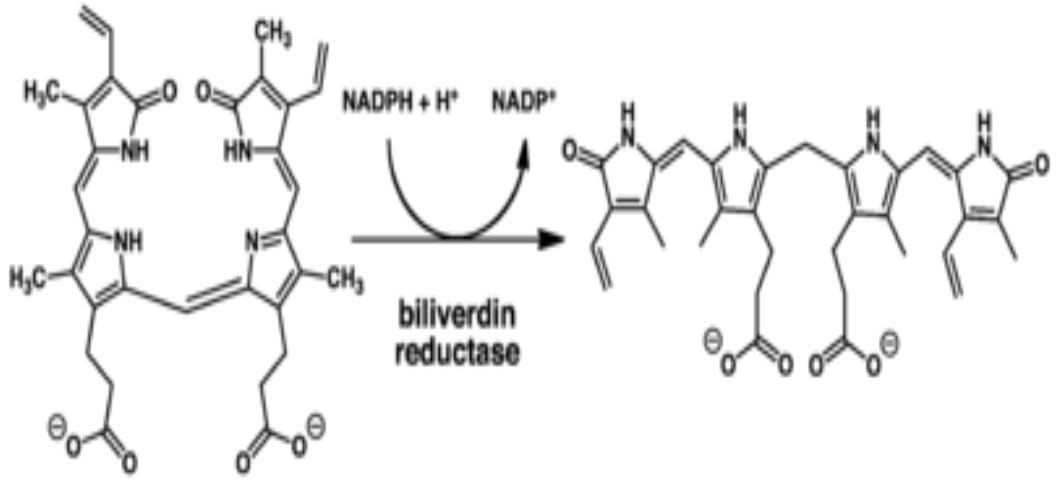
✓ Black pigment stones are small, hard gallstones composed of calcium (Ca) bilirubinate and inorganic Ca salts (eg, Ca carbonate, Ca phosphate). Factors that accelerate stone development include alcohol-related liver disease, chronic hemolysis, and older age.

✓ Brown pigment stones are soft and greasy, consisting of bilirubinate and fatty acids (Ca palmitate or stearate). They form during infection, inflammation, and parasitic infestation.

- **Mixed stones.**

Metabolism of bile pigments in the liver

- Bile pigments are biological pigments formed as a metabolic product of certain porphyrins. For the first time isolated from bile, which is given a characteristic color, from where they got their name; the color of various bile pigments - from yellow-orange to blue-green.
- In chemical terms, bile pigments are linear arrangements of four pyrrole rings (tetrapyrroles). In human metabolism, bilirubin is a breakdown product of heme.

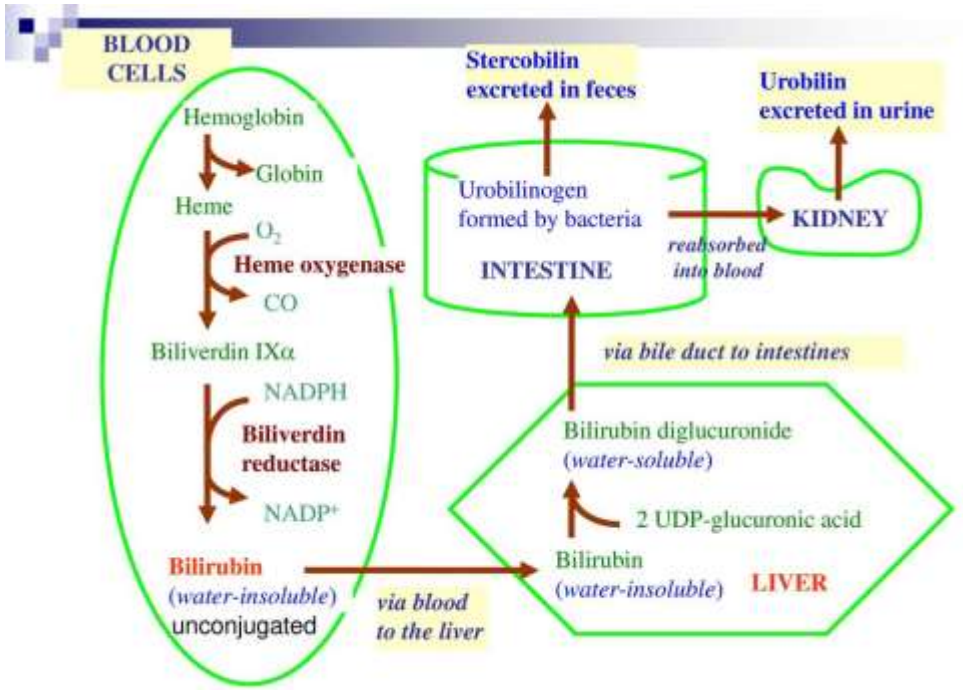


https://en.wikipedia.org/wiki/Biliverdin_reductase

Catabolism of hemoglobin

- Erythrocytes are continuously undergoing a hemolysis (breaking apart) process. The average life-time of a red blood cell is 120 days. As the red blood cells disintegrate, the hemoglobin is degraded or broken into globin, the protein part, iron (conserved for latter use), and heme. The heme initially breaks apart into biliverdin, a green pigment which is rapidly reduced to bilirubin, an orange-yellow pigment. These processes all occur in the reticuloendothelial cells of the liver, spleen, and bone marrow. The bilirubin is then transported to the liver where it reacts with a solubilizing sugar called glucuronic acid. This more soluble form of bilirubin (conjugated) is excreted into the bile.

- The bile goes through the gall bladder into the intestines where the bilirubin is changed into a variety of pigments. The most important ones are stercobilin, which is excreted in the feces, and urobilinogen, which is reabsorbed back into the blood. The blood transports the urobilinogen back to the liver where it is either re-excreted into the bile or into the blood for transport to the kidneys. Urobilinogen is finally excreted as a normal component of the urine.



Catabolism of hemoglobin

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Bilirubin

- **Bilirubin** (**BR**) is a yellow compound, consists of an open chain tetrapyrrole. It is formed by oxidative cleavage of a porphyrin in heme, which affords biliverdin. Biliverdin is reduced to bilirubin. After conjugation with glucuronic acid, bilirubin is excreted.

Characteristics	Unconjugated ()Bilirubin	Conjugated Bilirubin
Structure	Bilirubin IXα	Bilirubin diglucuronide
Solubility	Alcohol soluble	Water-soluble
Type of compound	Non-polar	Polar
Vandenberg reaction	Indirect	Direct
Presence in urine with jaundice	Negative (tightly bound to albumin)	Positive (Loselybound to albumin)
Toxicity	Toxic	Non-toxic

- **Total bilirubin** = ***indirect (unconjugated) bilirubin*** + ***direct (conjugated) bilirubin*** - **8.5-20.5 mcmol/l**
- **Indirect (unconjugated) bilirubin - 1.7-17.0 mcmol/l**
- **Direct (conjugated) bilirubin – 1.0-5.0 mcmol/l**

Hyperbilirubinemia is a higher-than-normal level of bilirubin in the blood.

- **Causes of hyperbilirubinemia:**

✓ Hemolysis, Gilbert's syndrome, hepatitis, cirrhosis, cholelithiasis, neonatal hyperbilirubinemia, Crigler–Najjar syndrome,Dubin–Johnson syndrome.

- **Consequences of hyperbilirubinemia:**

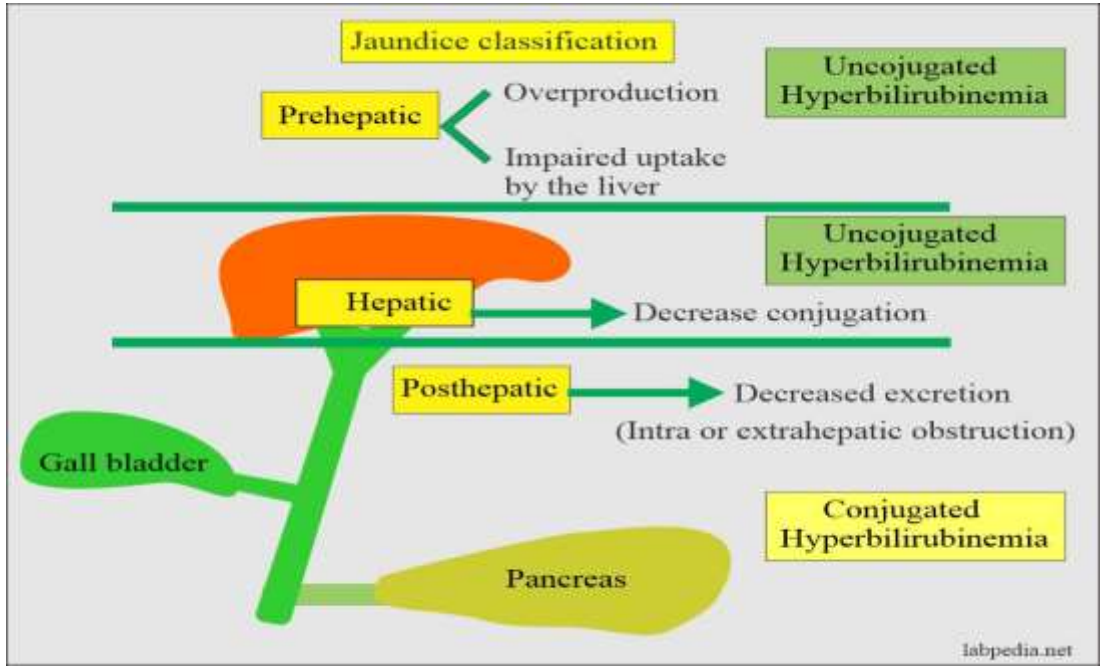
✓ Indirect bilirubin is highly lipophilic, so it can interact with phospholipids of cell membranes, especially brain cells, thereby penetrating the blood-brain barrier, where it uncouples oxidative phosphorylation processes and reduces ATP synthesis.

✓ This explains the toxicity of free bilirubin to the cells of the nervous system. This is most clearly manifested in newborn children. Bilirubin is able to stain the skin, visible mucous membranes - the development of **jaundice.**

✓ In addition, the accumulation of bilirubin can be the reason for the formation of pigment stones in the gallbladder.

Types of jaundice

- **Prehepatic (hemolytic) jaundice.** Associated with increased hemolysis of erythrocytes.
- **Hepatic (hepatocellular) jaundice.** Associated with liver diseases such as hepatitis.
- **Post-hepatic jaundice (obstructive).** Associated with the secretion of bile, for example, in connection with gallstones, pancreatic cancer.



https://www.labpedia.net/bilirubin-part-1-total-bilirubin-direct-and-indirect-bilirubin-classification-of-jaundice-neonatal-jaundice/

Test	Pre-hepatic jaundice	Hepatic jaundice	Post-hepatic jaundice
Total serum bilirubin	Normal / increased	Increased	Increased
Conjugated bilirubin	Normal	Increased	Increased
Unconjugated bilirubin	Normal / increased	Increased	Normal
Urobilinogen	Normal / increased	Decreased	Decreased / negative
Urine color	Normal	Dark (urobilinogen, conjugated bilirubin)	Dark (conjugated bilirubin)
Stool color	Brown	Slightly pale	Pale, white
Alkaline phosphatase levels	Normal	Increased	Highly increased
Alanine transferase and aspartate transferase levels		Highly increased	Increased
Conjugated bilirubin in urine	Not present	Present	Present

Biochemical tests to diagnose liver disease

- A series of special blood tests can often determine whether or not the liver is functioning properly. These tests can also distinguish between acute and chronic liver disorders and between hepatitis and cholestasis.
- Serum bilirubin test: An elevated bilirubin level may indicate an impaired bile flow or a problem with the liver processing bile.
- Serum albumin test) - a decrease in albin levels indicates a violation of the protein-synthesizing function of the liver.
- Serum Alkaline Phosphatase Test: Alkaline phosphatase is found in many tissues, with the highest concentrations in the liver, biliary tract and bone. This test can be performed to evaluate liver function and to identify liver lesions that can cause obstruction of the biliary tract, such as tumors or abscesses. Serum aminotransferases (transaminases): This enzyme is released from damaged liver cells.
- Prothrombin time (PTT) test: The prothrombin time test measures how long it takes for blood to clot. Blood clotting requires vitamin K and a protein that is made by the liver. Prolonged clotting may indicate liver disease or other deficiencies in specific clotting factors.
- Alanine transaminase (ALT) test: This test measures the level of alanine aminotransferase (an enzyme found predominantly in the liver) that is released into the bloodstream after acute liver cell damage. This test may be performed to assess liver function, and/or to evaluate treatment of acute liver disease, such as hepatitis.
- Aspartate transaminase (AST) test: This test measures the level of aspartate transaminase (an enzyme that is found in the liver, kidneys, pancreas, heart, skeletal muscle, and red blood cells) that is released into the bloodstream after liver or heart problems.
- Gamma-glutamyl transpeptidase test: This test measures the level of gamma-glutamyl transpeptidase (an enzyme that is produced in the liver, pancreas, and biliary tract). This test is often performed to assess liver function, to provide information about liver diseases, and to detect alcohol ingestion.
- Lactic dehydrogenase test: This test can detect tissue damage and aides in the diagnosis of liver disease.
- 5'-nucleotidase test: This test measures the levels of 5'-nucleotidase (an enzyme specific to the liver). The 5'- nucleotidase level is elevated in persons with liver diseases, especially those diseases associated with cholestasis (disruption in the formation of, or obstruction in the flow of bile).
- Alpha-fetoprotein test: Alpha-fetoprotein (a specific blood protein) is produced by fetal tissue and by tumors. This test may be performed to monitor the effectiveness of therapy in certain cancers, such as hepatomas.
- Mitochondrial antibodies test: The presence of these antibodies can indicate primary biliary cirrhosis, chronic active hepatitis, and certain other autoimmune disorders.

Cytolysis syndrome

- Cytolysis syndrome (cytolytic syndrome, hepatocyte integrity disorder syndrome) is a non-specific reaction of liver cells to the action of damaging factors. The syndrome is based on a violation of the permeability of cell membranes, their organelles, which leads to the release of intracellular enzymes into the blood plasma. The cytolytic process can affect a small number of hepatocytes, but often he more common, captures a huge amount free cells.
- The following tests are indicators of cytolysis:

✓ alanine aminotransferase (ALT);

✓ aspartate aminotransferase (AST);

✓ γ-glutamyl transpeptidase (GGPT);

✓ lactate dehydrogenase - LDH (5th fraction);

✓ glutamate dehydrogenase (GDH);

✓ aldolase, etc.

- It should also be borne in mind that ALT, GGPT, LDH are cytoplasmic enzymes, GDH - mitochondrial, AST - cytoplasmic-mitochondrial enzyme. This is important to know for an indirect assessment of severity damage to hepatocytes.

Cholestasis syndrome

- Cholestasis syndrome (violation of excretory liver function)
- Cholestasis - reduction or complete cessation outflow of bile due to a violation of its formation, excretion and / or excretion. The pathological process can be localized anywhere from the sinusoidal membrane of the hepatocyte to the duodenal papilla.
- The following enzymes are biochemical markers of cholestasis:

✓ alkaline phosphatase (ALP);

✓ γ-glutamyl transpeptidase (GGPT);

✓ 5-nucleotidase;

✓ leucine aminopeptidase;

✓ cholesterol;

✓ LDL;

✓ phospholipids;

✓ direct (bound) bilirubin;

✓ bile acids.

Liver failure

- Liver failure can result from many liver diseases, including viral hepatitis (most commonly hepatitis B or C), cirrhosis, and liver damage caused by alcohol or drugs such as acetaminophen.
- Markers of liver failure:

✓ hypoalbuminemia and (less often) hypoproteinemia, increase

✓ the percentage of the alkaline fraction of albumin;

✓ decrease in the activity of cholinesterase in the blood plasma;

✓ reducing the concentration of cholesterol;

✓ decrease in the content of prothrombin in blood serum, fibrinogen;

✓ hyperbilirubinemia (mainly due to an increase in free bilirubin).

✓ decrease in the content of V and VII blood coagulation factors

Cirrhosis

- Cirrhosis (liver cirrhosis or hepatic cirrhosis) is the impaired liver function caused by the formation of scar tissue known as fibrosis, due to damage caused by liver diseaseThe disease typically develops slowly over months or years. Early symptoms may include tiredness, weakness, loss of appetite, unexplained weight loss, nausea and vomiting, and discomfort in the right upper quadrant of the abdomen. As the disease worsens, symptoms may include itchiness, swelling in the lower legs, fluid build-up in the abdomen, jaundice, bruising easily, and the development of spider-like blood vessels in the skin. The fluid build-up in the abdomen may become spontaneously infected. More serious complications include hepatic encephalopathy, bleeding from dilated veins in the esophagus, stomach or intestines, and liver cancer

✓ aminotransferases – AST and ALT are moderately elevated, with AST > ALT. However, normal aminotransferase levels do not preclude cirrhosis.

✓ alkaline phosphatase– slightly elevated but less than 2–3 times the upper limit of normal.

✓ gamma-glutamyl transferase – correlates with AP levels. Typically much higher in chronic liver disease from alcohol.[45]

✓ bilirubin – levels normal when compensated but may elevate as cirrhosis progresses.

✓ albumin – levels fall as the synthetic function of the liver declines with worsening cirrhosis, since albumin is exclusively synthesized in the liver

✓ prothrombin time – increases, since the liver synthesizes clotting factors.

✓ globulins – increased due to shunting of bacterial antigens away from the liver to lymphoid tissue.

✓ coagulation defects – the liver produces most of the coagulation factors and thus coagulopathy correlates with worsening liver disease.

✓ ferritin and transferrin saturation: markers of iron overload as in hemochromatosis, copper and ceruloplasmin: markers of copper overload as in Wilson's disease

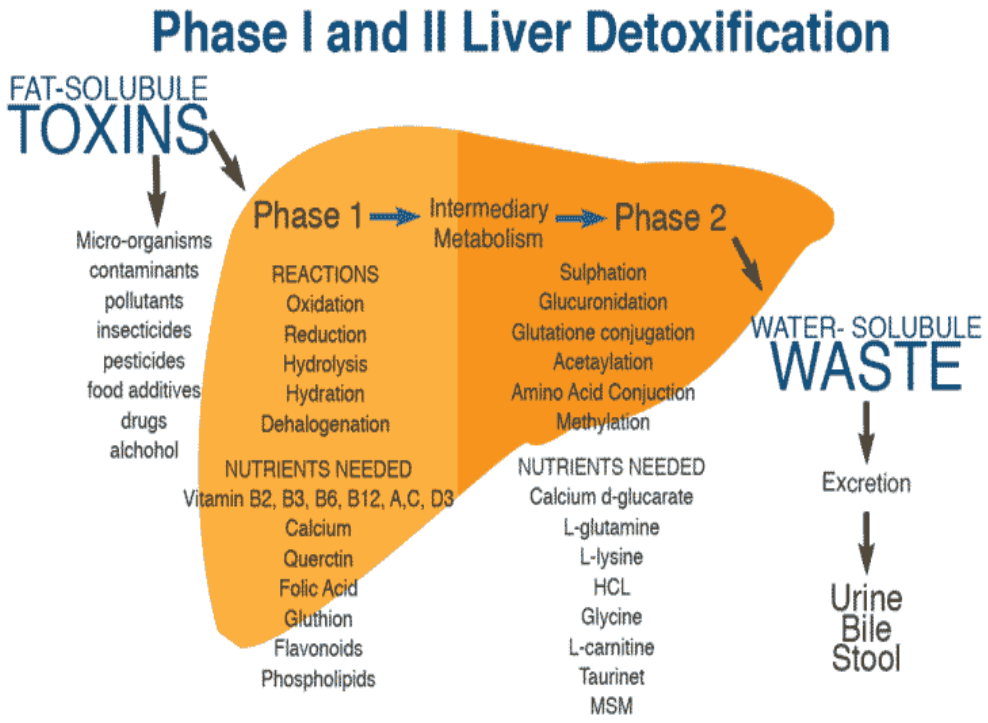
✓ immunoglobulin levels (IgG, IgM, IgA) – these immunoglobins are non-specific, but may help in distinguishing various causes

✓ cholesterol and glucose

✓ alpha 1-antitrypsin

Detoxification function of the liver

- **Xenobiotics** are foreign substances that enter the body from the environment and are not used for the plastic and energy purposes of the body.
- They enter the body through food, through the skin and lungs.
- Examples: petroleum products, plastics, detergents, perfumes, dyes, pesticides, etc.
- Hydrophilic xenobiotics are excreted from the body unchanged, mainly in the urine.
- Hydrophobic xenobiotics can accumulate and, interacting with proteins and lipids of cells, disrupt their structure and function.
- In addition to xenobiotics, exogenous toxins, for example, ammonia, indole, scadol, cadaverine, etc., can also be formed in the body. These compounds also require neutralization and elimination.
- Water-soluble substances are usually excreted unchanged in the urine or bile. Fat-soluble compounds must be converted into less active or water-soluble substances, otherwise they can accumulate in the body and affect its vital functions. The liver provides the elimination of many exo- and endogenous compounds. The intensity of the elimination of a particular compound depends on its binding to proteins, the activity of liver enzymes in relation to it, and hepatic blood flow. The elimination of a number of substances to a large extent occurs already during the first passage through the liver of blood flowing from the gastrointestinal tract through the portal vein.



https://www.thehealthproject.co.nz/blog/2019/9/3/the-anatomy-of-elimination-detox-pathways

Detoxification function of the liver

- The detoxification of substances in the liver can consist of one or two stages.
- Stages of neutralization of substances in the liver:
- increased hydrophilicity of foreign substances.
- Includes reactions of their hydrolysis, oxidation, hydroxylation, reduction, etc.
- The most common modification of a hydrophobic substance at **stage 1** is hydroxylation.
- conjugation of unchanged or chemically modified substances at the 1st stage with a number of metabolites.
- If the substance is hydrophobic, then its neutralization takes place in **2 stages**, if it is hydrophilic, then 1 stage may be absent.
- Some polar xenobiotics are excreted from the body without undergoing any transformations.
- Metabolism and excretion of xenobiotics from the body:

- Examples of xenobiotic modification in stage 1:

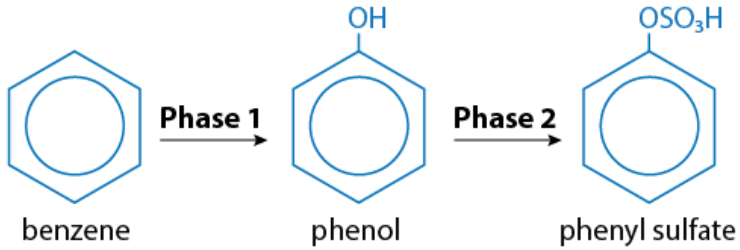
✓ hydroxylation

✓ oxidation at the S atom (sulfooxidation)

✓ oxidative deamination

✓ dealkylation for N, O, S.

✓ epoxidation



https://toxtutor.nlm.nih.gov/12-002.html

Microsomal oxidation system

- **Microsomal oxidation system**
- The microsomal oxidation system (MOS), localized in the membranes of the endoplasmic reticulum, is responsible for stage 1 of neutralization.
- MOS works in almost all body tissues, but most actively in the liver.
- In the liver, there are 2 electron transport chains of MOS, which catalyze the hydroxylation of substrates and are monooxygenases:
- ***1. The chain includes:***

✓ cytochrome P450 (hemoprotein), which has binding sites for O2 and a hydrophobic substrate and has a broad substrate specificity; enzyme NADPH-cytochrome P450 reductase containing coenzymes FAD and FMN; NADPH + H + is a donor of ē and H + in this electron transport chain; O2.

- ***2 The chain includes:*** cytochrome P450; the enzyme NADH-cytochrome b5-reductase, the coenzyme of which is FAD; cytochrome b5 - hemoprotein transferring ē from NADH-cytochrome b5-reductase to cytochrome P450; NADH + H + - donor ē and H +; O2.
- Cytochrome P450 includes one O2 atom in the substrate molecule, and the second one reduces with the formation of H2O due to the transfer of ē and H + from NADPH + H + with the participation of cytochrome P450 reductase
- (or from NADH + H + using cytochrome b5 reductase and cytochrome b5).
- Through their unique oxidative chemistry, cytochrome P450 monooxygenases (CYPs) catalyze the elimination of most drugs and toxins from the human body.
- CYPs metabolize polycyclic aromatic hydrocarbons, aromatic amines, heterocyclic amines, pesticides, and herbicides, and the vast majority of other drugs.
- However, CYPs also metabolize endogenous biochemicals (for example, CYP19A1, also called aromatase, transforms testosterone to estradiol).
- 57 human CYPs were identified. However, about 12 hepatic CYPs are responsible for the metabolism of the majority of drugs and other xenobiotics (approximately 93% of the drug metabolism).
- Among them, CYP3A4, CYP1A2, CYP2D6, CYP2C9, and CYP2C19 are responsible for nearly 60% of the drug metabolism.
- Although CYPs are detoxification enzymes, these reactions often convert less toxic molecules into more toxic active products. That is where the phase II detoxification steps in.
- For example, CYP1A1 can activate some carcinogens while CYP2E1 can activate several liver toxins and contribute to alcoholic liver damage.

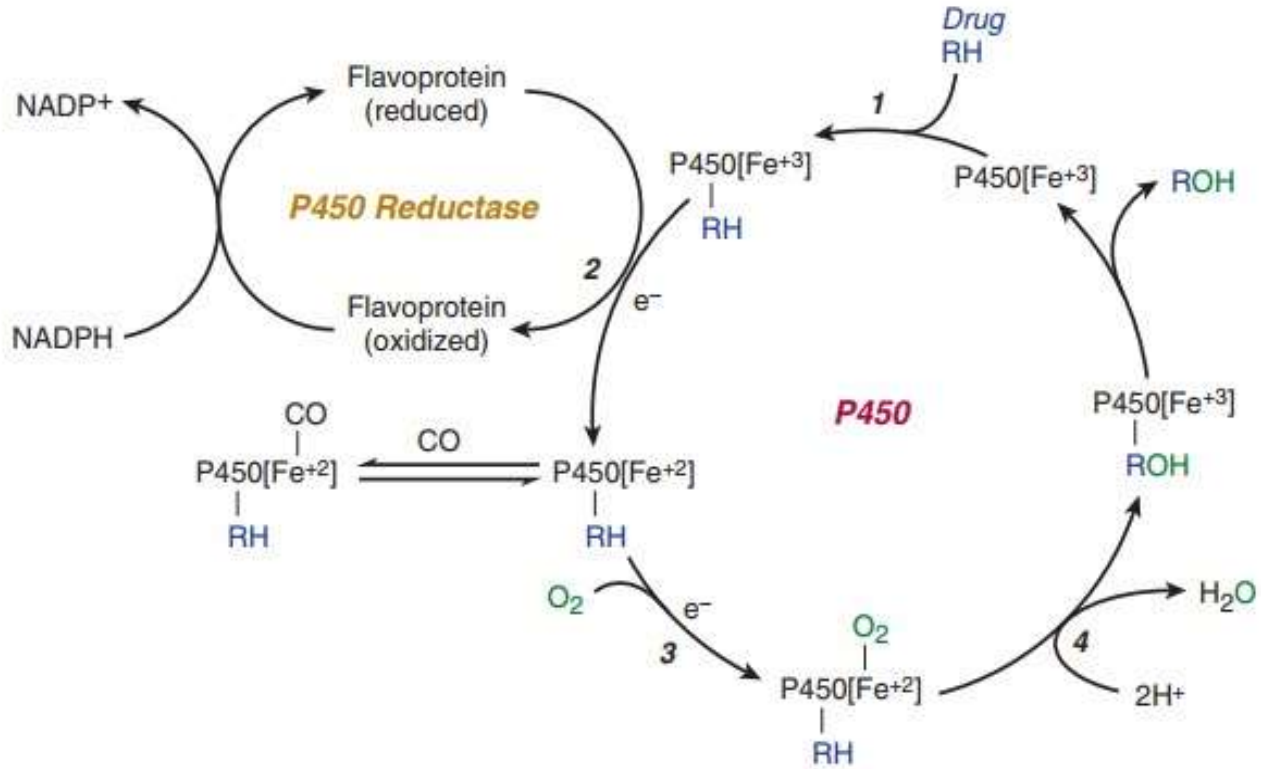
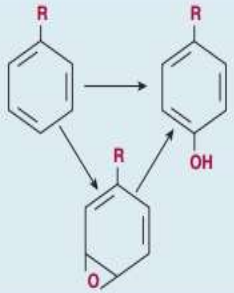
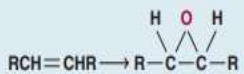
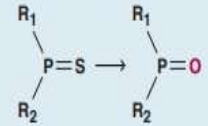
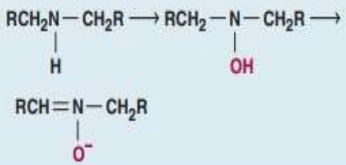
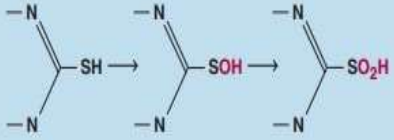


FIGURE 4–3 Cytochrome P450 cycle in drug oxidations. RH, parent drug; ROH, oxidized metabolite; e^-, electron.

https://www.brainkart.com/article/Microsomal-Mixed-Function-Oxidase-System---Phase-I-Reactions_24435/

TABLE 4–1 Phase I reactions.

Reaction Class	Structural Change	Drug Substrates
Oxidations		
Cytochrome P450-dependent oxidations:		
Aromatic hydroxylations		Acetanilide, propranolol, phenobarbital, phenytoin, phenylbutazone, amphetamine, warfarin, 17α-ethinyl estradiol, naphthalene, benzpyrene
Aliphatic hydroxylations	$RCH_2CH_3 \longrightarrow RCH_2CH_2OH$ $RCH_2CH_3 \longrightarrow RCHCH_3$ (OH)	Amobarbital, pentobarbital, secobarbital, chlorpropamide, ibuprofen, meprobamate, glutethimide, phenylbutazone, digitoxin
Epoxidation		Aldrin
Oxidative dealkylation		
N-Dealkylation	$RNHCH_3 \longrightarrow RNH_2 + CH_2O$	Morphine, ethylmorphine, benzphetamine, aminopyrine, caffeine, theophylline
O-Dealkylation	$ROCH_3 \longrightarrow ROH + CH_2O$	Codeine, *p*-nitroanisole
S-Dealkylation	$RSCH_3 \longrightarrow RSH + CH_2O$	6-Methylthiopurine, methitural
Cytochrome P450- dependent oxidations: (continued)		
		Parathion
Dechlorination	$CCl_4 \longrightarrow [CCl_3^{\bullet}] \longrightarrow CHCl_3$	Carbon tetrachloride
Cytochrome P450-independent oxidations:		
Flavin monooxygenase (Ziegler's enzyme)	$R_3N \longrightarrow R_3N^+ \rightarrow O^- \xrightarrow{H^+} R_3N^+OH$	Chlorpromazine, amitriptyline, benzphetamine
		Desipramine, nortriptyline
		Methimazole, propylthiouracil
Amine oxidases	$RCH_2NH_2 \longrightarrow RCHO + NH_3$	Phenylethylamine, epinephrine
Dehydrogenations	$RCH_2OH \longrightarrow RCHO$	Ethanol

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Conjugation reactions

- Parent drugs or their phase I metabolites that contain suitable chemical groups often undergo coupling or conjugation reactions with an endogenous substance to yield drug conjugates.
- In general, conjugates are polar molecules that are readily excreted and often inactive.
- Conjugate formation involves high-energy intermediates and specific transfer enzymes.
- Such enzyme es (**transferases**) may be located in microsomes or in the cytosol. Of these, uridine 5′-diphosphate (UDP)-glucuronosyl transferases (UGTs) are the most dominant enzymes.
- These microsomal enzymes catalyze the coupling of an activated endogenous substance (such as the UDP derivative of glucuronic acid) with a drug (or endogenous compound such as bilirubin, the end product of heme metabolism). Nineteen UGT genes (UGTA1and UGT2) encode UGT proteins involved in the metabolism of drugs and xenobiotics.
- Similarly, 11 human sulfotransferases (SULTs) catalyze the sulfation of substrates using 3′-phosphoadenosine 5′-phosphosulfate (PAPS) as the endogenous sulfate donor.
- Cytosolic and microsomal glutathione (GSH) transferases (GSTs) are also engaged in the metabolism of drugs and xenobiotics, and in that of leukotrienes and prostaglandins, respectively.
- Chemicals containing an aromatic amine or a hydrazine moiety (eg, isoniazid) are substrates of cytosolic N-acetyltransferases(NATs), encoded by NAT1 and NAT2 genes, which utilize acetyl-CoA as the endogenous cofactor.

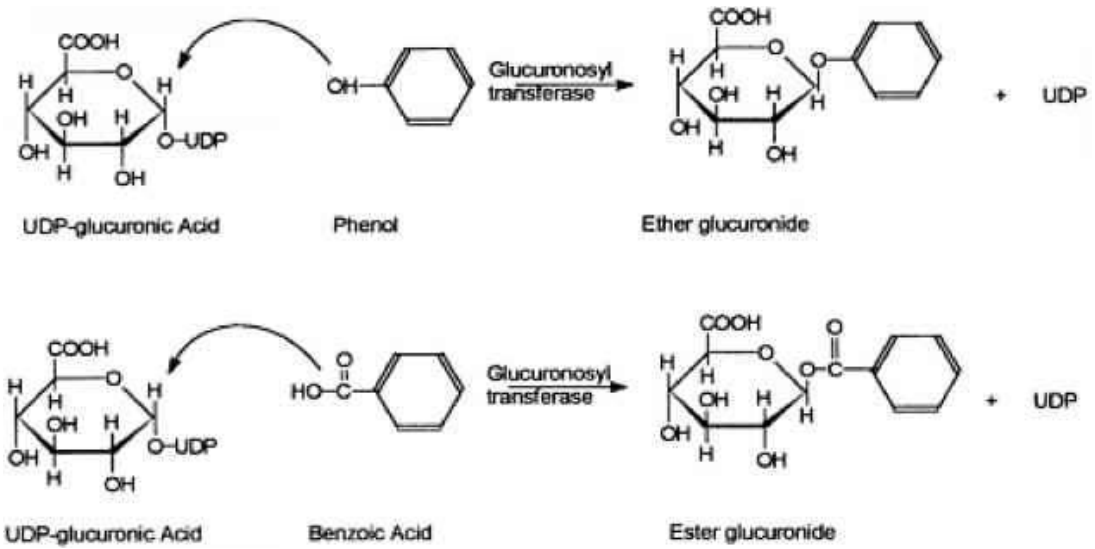
TABLE 4–3 Phase II reactions.

Type of Conjugation	Endogenous Reactant	Transferase (Location)	Types of Substrates	Examples
Glucuronidation	UDP glucuronic acid	UDP glucuronosyltransferase (microsomes)	Phenols, alcohols, carboxylic acids, hydroxylamines, sulfonamides	Nitrophenol, morphine, acetaminophen, diazepam, *N*-hydroxydapsone, sulfathiazole, meprobamate, digitoxin, digoxin
Acetylation	Acetyl-CoA	*N*–Acetyltransferase (cytosol)	Amines	Sulfonamides, isoniazid, clonazepam, dapsone, mescaline
Glutathione conjugation	Glutathione (GSH)	GSH-*S*-transferase (cytosol, microsomes)	Epoxides, arene oxides, nitro groups, hydroxylamines	Acetaminophen, ethacrynic acid, bromobenzene
Glycine conjugation	Glycine	Acyl-CoA glycinetransferase (mitochondria)	Acyl-CoA derivatives of carboxylic acids	Salicylic acid, benzoic acid, nicotinic acid, cinnamic acid, cholic acid, deoxycholic acid
Sulfation	Phosphoadenosyl phosphosulfate	Sulfotransferase (cytosol)	Phenols, alcohols, aromatic amines	Estrone, aniline, phenol, 3-hydroxycoumarin, acetaminophen, methyldopa
Methylation	*S*-Adenosylmethionine	Transmethylases (cytosol)	Catecholamines, phenols, amines	Dopamine, epinephrine, pyridine, histamine, thiouracil
Water conjugation	Water	Epoxide hydrolase (microsomes)	Arene oxides, *cis*-disubstituted and monosubstituted oxiranes	Benzopyrene 7,8-epoxide, styrene 1,2-oxide, carbamazepine epoxide
		(cytosol)	Alkene oxides, fatty acid epoxides	Leukotriene A_4

https://www.brainkart.com/article/Phase-II-Reactions_24437/

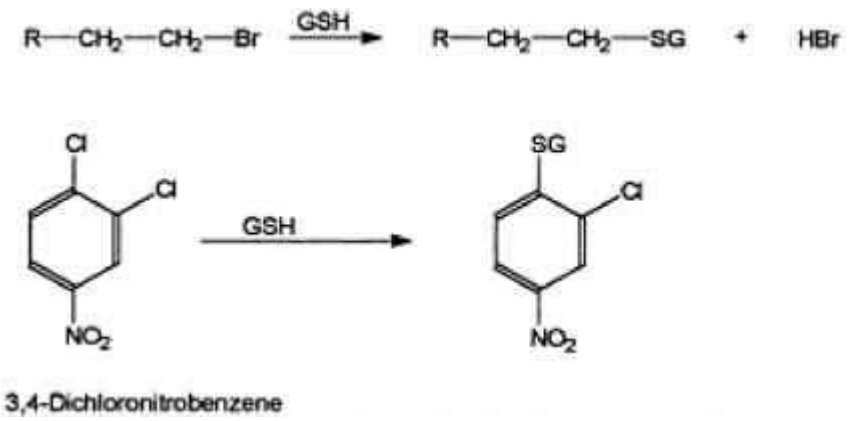
Examples of conjugation reactions

Formation of ether and ester glucuronides of phenol and benzoic acid respectively.



https://www.europeanmedical.info/metabolic-activation/glucuronide-formation.html

Displacement of aliphatic and aromatic halogens by glutathione.



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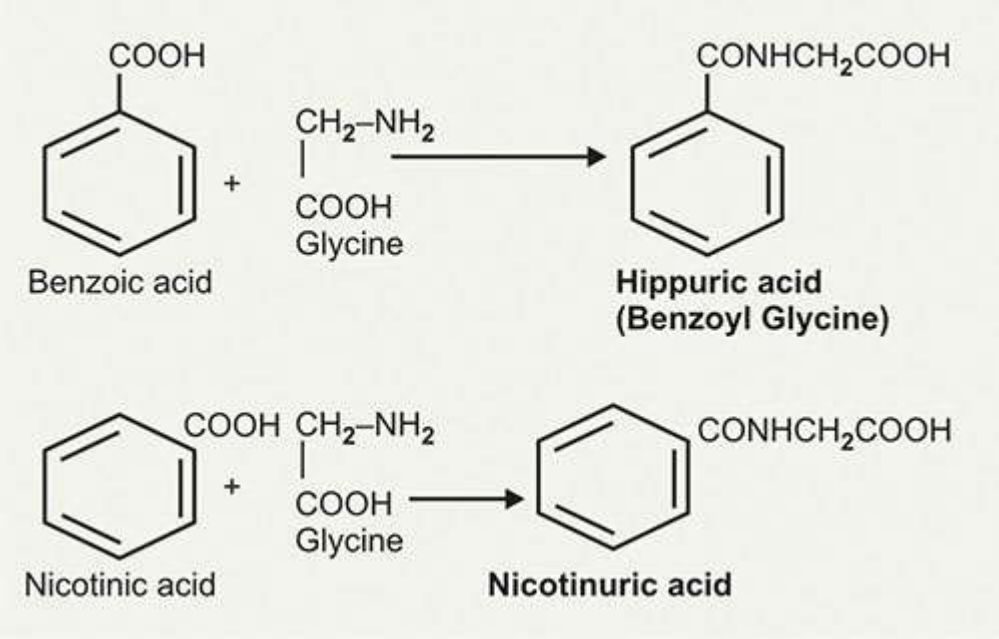
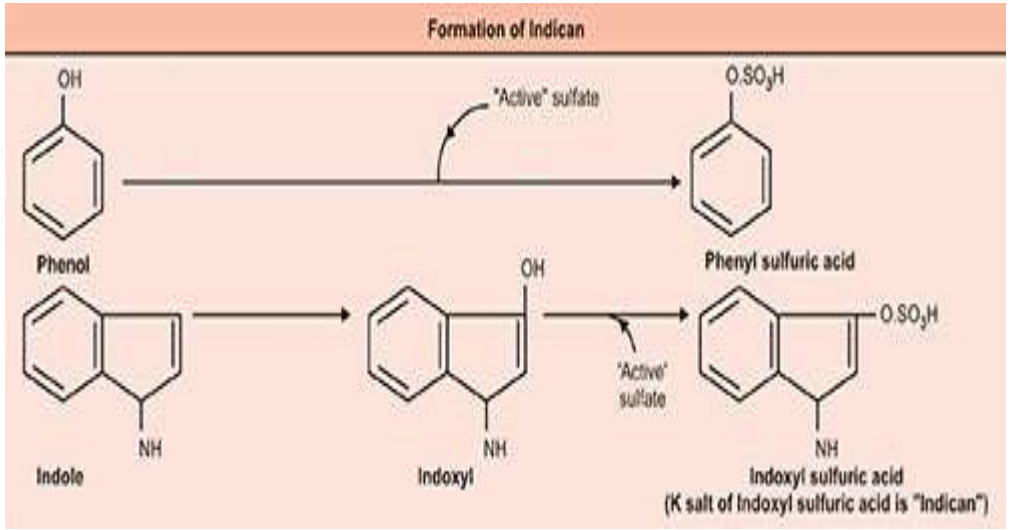
Examples of conjugation reactions





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