**PATHOPHYSIOLOGY OF THE LIVER**

 The liver is the largest visceral organ in the body, weighing approximately 1.3 kg in the adult. It is located below the diaphragm and occupies much of the right hypochondrium. The liver is surrounded by a tough fibroelastic capsule called *Glisson’s capsule.* The falciform ligament, which extends from the peritoneal surface of the anterior abdominal wall between the umbilicus and diaphragm, divides the liver into two lobes, a large right lobe and a small left lobe. There are two additional lobes on the visceral surface of the liver: the caudate and quadrate lobes. Except for the portion that is in the epigastric area, the liver is contained within the rib cage and in healthy persons cannot normally be palpated.

The liver is unique among the abdominal organs in having a dual blood supply - the hepatic artery and the portal vein. Approximately 300 mL of blood per minute enters the liver through the hepatic artery; another 1050 mL/minute enters by way of the valveless portal vein, which carries blood from the stomach, the small and the large intestines, the pancreas, and the spleen. Although the blood from the portal vein is incompletely saturated with oxygen, it supplies approximately 60% to 70% of the oxygen needs of the liver. The venous outflow from the liver is carried by the valveless hepatic veins, which empty into the inferior vena cava just below the level of the diaphragm. The pressure difference between the hepatic vein and the portal vein normally is such that the liver stores approximately 450 mL of blood. This blood can be shifted back into the general circulation during periods of hypovolemia and shock. In congestive heart failure, in which the pressure in the vena cava increases, blood backs up and accumulates in the liver.

Terminology of the hepatic microarchitecture is based on two different concepts: *the hepatic lobule* and the *hepatic acinus*. According to the lobular model, the liver is divided into 1- to 2-mm diameter hexagonal *lobules* oriented around the terminal tributaries of the hepatic vein *(terminal hepatic veins)*, with portal tracts at the periphery of the lobule. The hepatocytes in the vicinity of the terminal hepatic vein are called *centrilobula*r; those near the portal tract are *periportal*. In the acinar model the hepatocytes near the terminal hepatic veins are the distal apices of roughly triangular *acini*, whose bases are formed by the penetrating septal venules from the portal vein extending out from the portal tracts. In the acinus the parenchyma is divided into three zones, *zone 1* being closest to the vascular supply, *zone 3* abutting the terminal hepatic venule and most remote from the afferent blood supply, and *zone 2* being intermediate. Regardless of the model used, zonation of the parenchyma is an important concept because of the gradient of activity displayed by many hepatic enzymes, and the zonal distribution of certain types of hepatic injury. While the acinar model best describes the physiologic relationships between hepatocytes and their vascular supply, the histopathology of the liver is usually discussed on the basis of a lobular architecture.



**Microscopic anatomy of the liver; the two models, hepatic lobular model and acinar model, are illustrated.**

**In the lobular model the terminal hepatic vein (CV) is at the center of a lobule, while the portal tracts (PV) are at the periphery. Pathologists refer to the regions of the parenchyma as periportal and centrilobular. In the acinar model, on the basis of blood flow, three zones can be defined, zone 1 being the closest to the blood supply and zone 3 being the farthest. BD, bile duct; HA, hepatic artery.** (From Robbins-Cotran; Pathological basis of disease)

The *lobules* are the functional units of the liver. Each lobule is a cylindrical structure that measures approximately 0.8 to 2 mm in diameter and several millimeters long. There are approximately 50,000 to 100,000 lobules in the liver. Each lobule is organized around a *central vein* that empties into the hepatic veins and from there into the vena cava. The terminal bile ducts and small branches of the portal vein and hepatic artery are located at the periphery of the lobule. Plates of hepatic cells radiate centrifugally from the central vein like spokes on a wheel. These hepatic plates are separated by wide, thin-walled channels, called *sinusoids,* that extend from the periphery of the lobule to its central vein. The sinusoids are supplied by blood from the portal vein and hepatic artery. Because the plates of hepatic cells are no more than two layers thick, every cell is exposed to the blood that travels through the sinusoids. Thus, the hepatic cells can remove substances from the blood or can release substances into the blood as it moves through the sinusoids.

Hepatocytes are organized into cribriform, anastomosing sheets or plates extending from portal tracts to the terminal hepatic veins. Between the plates of hepatocytes are vascular sinusoids. Blood traverses the sinusoids and exits into the terminal hepatic veins through numerous orifices in the vein wall. Hepatocytes are thus bathed on two sides by well-mixed portal venous and hepatic arterial blood, making hepatocytes among the most richly perfused cells in the body. The sinusoids are lined by fenestrated and discontinuous endothelial cells. Deep to the endothelial cells lies the *space of Disse*, into which protrude abundant microvilli of hepatocytes. Scattered *Kupffer cells* of the mononuclear phagocyte system are attached to the luminal face of endothelial cells, and fat-containing *hepatic stellate cells (HSCs)* are found in the space of Disse. Between abutting hepatocytes are *bile canaliculi*, which are channels 1 to 2 μm in diameter, formed by grooves in the plasma membranes of facing hepatocytes and separated from the vascular space by tight junctions. These channels drain into the *canals of Hering*, ductular structures that connect the bile canaliculi to *bile ductules* in the periportal region. The ductules empty into the *terminal bile ducts* within the portal tracts. The liver also contains lymphocytes, including relatively large numbers of natural killer cells, and NK-T cells.

The venous sinusoids are lined with two types of cells: the typical endothelial cells and Kupffer’s cells. *Kupffer’s cells* are reticuloendothelial cells that are capable of removing and phagocytizing old and defective blood cells, bacteria, and other foreign material from the portal blood as it flows through the sinusoid. This phagocytic action removes the enteric bacilli and other harmful substances that filter into the blood from the intestine. The lobules also are supplied by small tubular channels, called *bile canaliculi,* that lie between the cell membranes of adjacent hepatocytes. The bile produced by the hepatocytes flows into the canaliculi and then to the periphery of the lobules, which drain into progressively larger ducts, until it reaches the right and left hepatic ducts. The intrahepatic and extrahepatic bile ducts often are collectively referred to as the *hepatobiliary tree.* The hepatic and cystic ducts unite to form the common bile duct. The common bile duct, which is approximately 10 to 15 cm long, descends and passes behind the pancreas and enters the descending duodenum. The pancreatic duct joins the common duct at a short dilated tube called the *hepatopancreatic ampulla* (ampulla of Vater), which empties into the duodenum through the duodenal papilla. Muscle tissue at the junction of the papilla, sometimes called the *sphincter of Oddi,* regulates the flow of bile into the duodenum. When this sphincter is closed, bile moves back into the common duct and gallbladder.

**Metabolic functions of the liver**

The liver is one of the most versatile and active organs in the body. It produces bile; metabolizes hormones and drugs; synthesizes proteins, glucose, and clotting factors; stores vitamins and minerals; changes ammonia produced by deamination of amino acids to urea; and converts fatty acids to ketones. The liver degrades excess nutrients and converts them into substances essential to the body. It builds carbohydrates from proteins, converts sugars to fats that can be stored, and interchanges chemical groups on amino acids so that they can be used for a number of purposes. In its capacity for metabolizing drugs and hormones, the liver serves as an excretory organ. In this respect, the bile, which carries the end products of substances metabolized by the liver, is much like the urine, which carries the body wastes filtered by the kidneys.

*Carbohydrate metabolism***.** The liver plays an essential role in carbohydrate metabolism and glucose homeostasis. The liver stores excess glucose as glycogen (glycogenogenesis) and releases it into the circulation when blood glucose levels fall (glycogenolysis). The liver also synthesizes glucose from amino acids, glycerol, and lactic acid (gluconeogenesis) as a means of maintaining blood glucose during periods of fasting or increased need. The liver also converts excess carbohydrates to triglycerides for storage in adipose tissue.

*Protein synthesis and conversion of ammonia to urea***.** The liver is an important site for protein synthesis and degradation. It produces the proteins for its own cellular needs and secretory proteins that are released into the circulation. The most important of these secretory proteins is albumin. Albumin contributes significantly to the plasma colloidal osmotic pressure and to the binding and transport of numerous substances, including some hormones and drugs, fatty acids, bilirubin, and other anions. The liver also produces other important proteins, such as fibrinogen and the blood clotting factors. Through a variety of anabolic and catabolic processes, the liver is the major site of amino acid interconversion. These processes involve two major reactions: transamination and deamination. In *transamination,* anamino group (NH2) is transferred to an acceptor substance. As a result of transamination, amino acids can participate in the intermediary metabolism of carbohydrates and lipids. During periods of fasting or starvation, amino acids are used for producing glucose (gluconeogenesis). Most of the nonessential amino acids are synthesized in the liver by transamination. The process of transamination is catalyzed by *aminotransferases,* enzymes that are found in high amounts in the liver. Oxidative *deamination* involves the removal of the amino groups from the amino acids and conversion of amino acids to ketoacids and ammonia. This occurs mainly by transamination, in which the amino groups are removed and then transferred to another acceptor substance. The acceptor substance can then transfer the amino group to still another substance or release it as ammonia. Ammonia is very toxic to body tissues, particularly neurons. The ammonia that is released during deamination is removed from the blood almost immediately and converted to urea. Essentially all urea formed in the body is synthesized by the urea cycle in the liver and is then excreted by the kidneys. Although urea is mostly excreted by the kidneys, some diffuses into the intestine, where it is converted to ammonia by enteric bacteria. The intestinal production of ammonia also results from bacterial deamination of unabsorbed aminoacids and protein derived from the diet, exfoliated cells, or blood in the gastrointestinal tract. Ammonia produced in the intestine is absorbed into the portal circulation and transported to the liver, where it is converted to urea before being released into the systemic circulation. Intestinal production of ammonia is increased after ingestion of high protein foods and gastrointestinal bleeding. In advanced liver disease, urea synthesis often is impaired, leading to an accumulation of blood ammonia.

*Pathways of lipid metabolism***.** Although most cells of the body metabolize fat, certain aspects of lipid metabolism occur mainly in the liver, including oxidation of fatty acids to supply energy for other body functions; the synthesis of large quantities of cholesterol, phospholipids, and most lipoproteins; and the formation of triglycerides from carbohydrates and proteins. To derive energy from neutral fats, the fat must first be split into glycerol and fatty acids, and then the fatty acids split by *beta oxidation* into two-carbon acetyl-coenzyme A (acetyl-CoA) units. Acetyl-CoA is readily channeled into the citric acid cycle to produce adenosine triphosphate (ATP). Because the liver cannot use all the acetyl-CoA that is formed, it converts the excess into acetoacetic acid, a highly soluble ketoacid that is released into the bloodstream and transported to other tissues, where it is used for energy. During periods of starvation, ketones become a major source of energy as fatty acids released from adipose tissue are converted to ketones by the liver. Acetyl-CoA units from fat metabolism also are used to synthesize cholesterol and bile acids in the liver. Cholesterol has several fates in the liver. It can be esterified and stored; it can be exported bound to lipoproteins; or it can be converted to bile acids. The rate-limiting step in cholesterol synthesis is that which is catalyzed by *3-hydroxy-3-methylglutaryl-coenzyme A reductase* (HMG-CoA reductase).The HMG-CoA reductase inhibitors, or statins (*e.g.*, fluvastatin, lovastatin, pravastatin, atorvastatin), that are used to treat high cholesterol levels act by inhibiting this step in cholesterol synthesis. Almost all the fat synthesis in the body from carbohydrates and proteins occurs in the liver. As fat is synthesized in the liver, it is transported as triglycerides in the lipoproteins to adipose tissue to be stored.

**Bile production*.*** The secretion of bile is essential for digestion of dietary fats and absorption of fats and fat-soluble vitamins from the intestine. The liver produces approximately 600 to 1200 mL of yellow-green bile daily. Bile contains water, bile salts, bilirubin, cholesterol, and certain products of organic metabolism. Of these, only bile salts, which are formed from cholesterol, are important in digestion. The other components of bile depend on the secretion of sodium, chloride, bicarbonate, and potassium by the bile ducts. The liver forms approximately 0.6 g of bile salts daily. Bile salts serve an important function in digestion; they aid in emulsifying dietary fats, and they are necessary for the formation of the micelles that transport fatty acids and fat soluble vitamins to the surface of the intestinal mucosa for absorption. Approximately 94% of bile salts that enter the intestine are reabsorbed into the portal circulation by anactive transport process that takes place in the distal ileum. From the portal circulation, the bile salts pass into the liver, where they are recycled. Normally, bile salts travel this entire circuit approximately 18 times before being expelled in the feces. This system for recirculation of bile salts and other substances is called the *enterohepatic circulation.*

**Tests of hepatobiliary function.** The history and physical examination, in most instances, provide clues about liver function. Diagnostic tests help to evaluate liver function and the extent of liver damage. Laboratory tests commonly are used to assess liver function and confirm the diagnosis of liver disease.

Liver function tests, including serum levels of liver enzymes, are used to assess injury to liver cells, the liver’s ability to synthesize proteins, and the excretory functions of the liver. Elevated serum enzyme tests usually indicate liver injury earlier than other indicators of liver function. The key enzymes are *alanine aminotransferase* (ALT) and *aspartate aminotransferase* (AST), which are present in liver cells. ALT is liver specific, whereas AST is derived from organs other than the liver. In most cases of liver damage, there are parallel rises in ALT and AST. The most dramatic rise is seen in cases of acute hepatocellular injury, as occurs with viral hepatitis, hypoxic or ischemic injury, acute toxic injury, or Reye’s syndrome.

The liver’s synthetic capacity is reflected in measures of serum protein levels and prothrombin time (synthesis of coagulation factors). Hypoalbuminemia due to depressed synthesis may complicate severe liver disease. Deficiencies of coagulation factor V and vitamin K–dependent factors (II, VII, IX, and X) may occur.

Serum bilirubin, γ-glutamyltransferase (GGT), and alkaline phosphatase measure hepatic excretory function. Alkaline phosphatase is present in the membranes between liver cells and the bile duct and is released by disorders affecting the bile duct. GGT is thought to function in the transport of amino acids and peptides into liver cells; it is a sensitive indicator of hepatobiliary disease. Measurement of GGT may be helpful in diagnosing alcohol abuse.

Ultrasonography provides information about the size, composition, and blood flow of the liver. It has largely replaced cholangiography in detecting stones in the gallbladder or biliary tree. Computed tomography (CT) scanning provides information similar to that obtained by ultrasound.

Magnetic resonance imaging (MRI) has proved to be useful in some disorders. Selective angiography of the celiac, superior mesenteric, or hepatic artery may be used to visualize the hepatic or portal circulation. A liver biopsy affords a means of examining liver tissue without surgery.

There are several methods for obtaining liver tissue: percutaneous liver biopsy, which uses a suction, cutting, or spring-loaded cutting needle; laparoscopic liver biopsy; and fine-needle biopsy, which is performed under ultrasound or CT guidance. The type of method used is based on the number of specimens needed and the amount of tissue required for evaluation. Laparoscopic liver biopsy provides the means for examining abdominal masses, evaluating ascites of unknown cause, and staging liver cancers.

**General features of liver disease**

The liver is vulnerable to a wide variety of metabolic, toxic, microbial, circulatory, and neoplastic insults. The major primary diseases of the liver are viral hepatitis, nonalcoholic fatty liver disease, alcoholic liver disease, and hepatocellular carcinoma. Hepatic damage also occurs secondary to some of the most common diseases in humans, such as heart failure, disseminated cancer, and extrahepatic infections. The enormous functional reserve of the liver masks the clinical impact of mild liver damage, but with progression of diffuse disease or disruption of bile flow, the consequences of deranged liver function may become life-threatening.

With the exception of acute liver failure, liver disease is an insidious process in which clinical detection and symptoms of hepatic decompensation may occur weeks, months, or many years after the onset of injury. The ebb and flow of hepatic injury may be imperceptible to the patient and detectable only by abnormal laboratory tests; liver injury and healing may also occur without clinical detection. Hence, individuals with hepatic abnormalities who are referred to hepatologists most frequently have chronic liver disease.

The liver has a relatively limited repertoire of cellular and tissue responses to injury, regardless of cause. The most common are:

**•** Hepatocyte degeneration and intracellular accumulations;

**•** Hepatocyte necrosis and apoptosis;

**•** Inflammation;

**•** Regeneration;

**•** Fibrosis;

Hepatocytes can undergo a number of degenerative, but potentially reversible changes, such as accumulation of fat (*steatosis*) and bilirubin (*cholestasis*). When injury is not reversible, hepatocytes die principally by two mechanisms: necrosis or apoptosis.

**LIVER FAILURE, CIRRHOSIS and PORTAL HYPERTENSION**

The most serious consequences of many liver diseases reside in their ability to cause liver disease, cirrhosis and portal hypertension.

**Liver failure**

# The most severe clinical consequences of liver disease is hepatic failure. *Liver failure* represents disorder of one ore some functions of the liver as result of hepatocyte injury, a pathological state characterized by imbalance of functional capabilities of the liver and demands of the tissue and organs of the body.

# Etiologic factors of liver failure can be of different origin:

*Infectious*- bacteria (pneumococcus, streptococcus, spirochetes) and viruses (viral hepatitis A,B,C,D,E), and other forms of viruses like infectious mononucleosis produced by Epstein-Barr virus, cytomegalovirus, herpetic hepatitis.

*Toxic* – hepatotoxic action of different non-organic chemical substances (lead, benzole, phosphorus); chemical organic substances (alcohol, halogen derivates), acute intoxication with amanita phaloides. Alcohol abuse is one of the most common cause.

*Toxico-allergic* – represents hepatotoxic action of different drugs. To be mention that a small number of drugs have direct hepatotoxic effect (tetracycline, griseofulvine). Tetracycline, when administered in IV doses >1.5 g daily, leads to microvesicular fat deposits in the liver. Other drugs have a toxico-allergic hepatotoxic effect: antibiotics (oxaciline, rifampicine, tetracycline), neuroleptics and anxyolitics (diazepam), diuretics (furosemid, spironolactone), anti-arrhythmic drugs (amiodarone), non-steroid anti-inflammatory drugs (indometacine, diclofenac, piroxicam),

# *Autoimmune*– autoimmune hepatitis as result of parenteral vaccines; sometimes sensitization to drugs or some foods, which create conditions for immune hepatocyte injury.

# *Physical and mechanical* – action of radiation or mechanical obstruction of the biliary ducts (intrahepatic or posthepatic cholestasis for long periods like in cystic fibrosis, stones in the common bile duct or tumors).

*Hemodynamic*– disorders of blood circulation, both local (ischemia or venous hyperemia at the level of the liver like in cardiovascular causes which impair venous return) or general (cardiovascular insufficiency) which can lead to hepatocyte hypoxia. These can happen also in diseases of subhepatic vena: Budd-Chiari syndrome (thrombosis of subhepatic vena), veno-occlusive disease (disease is associate to radiotherapy, administration of azathioprine and other cytotoxic agents used in renal and bone marrow transplantation – this agents can destroy endothelial cells at the level of the terminal hepatic venules and sinusoids);

A number of *inherited diseases*, for example, glycogen storage diseases, Wilson’s disease, galactosemia, hemochromatosis, α1-antitrypsin deficiency can led to liver failure;

# *Endocrine –* endocrine disorders in diabetes mellitus, hyperthyroidism, obesity which can affect hepatocyte functions.

*Hepatic cancer:* primary (hepatocellular carcinoma, hepatoblastoma, angiosarcoma etc…) and secondary (metastatic extension of primary cancer of large intestine, bronchial cancer, pancreas, stomach etc…)

# Hepatic failure developed as result of direct action of harmful agents is called *primary hepatic failure.* In case when hepatic failure develops as result of disorders located at distance from the liver (ex: blood stasis in cardiac failure, endocrine disorders), this form is named *secondary hepatic failure.*

Liver failure may result from sudden and massive liver destruction, as in fulminant hepatitis, or be the result of progressive damage to the liver, as occurs in alcoholic cirrhosis. Whatever the cause, 80% to 90% of hepatic functional capacity must be lost before liver failure occurs. In many cases, the progressive decompensating effects of the disease are hastened by intercurrent conditions such as gastrointestinal bleeding, systemic infection, electrolyte disturbances, or superimposed diseases such as heart failure. When the liver can no longer maintain homeostasis, transplantation offers the best hope for survival; the mortality rate in persons with hepatic failure without liver transplantation is about 80%.

*Pathogenesis.* Viral infection induces hepatic cell injury by inflammation and necrosis. Direct hepatotoxic effect caused by a physical or mechanical factor is due to direct injury which distort or destroy the main structures of hepatic cells and their organelles. Mechanisms of hepatocyte injury in case of hypoxia, liver congestion is because of ATP deficiency due to abnormal cellular energy metabolism as well as increased formation of highly reactive oxygen metabolites (O2–, OH-, H2O2) with concomitant deficiency of antioxidants (glutathione) and/or damage of protective enzymes (glutathione peroxidase, superoxide dismutase). The O2 metabolites react with unsaturated fatty acids in phospholipids (lipid peroxidation). This contributes to damage of plasma membranes and cell organelles (lysosomes, endoplasmic reticulum). As a result, cytosolic Ca2+ concentration rises, activating proteases and other enzymes so that the cells are ultimately irreversibly damaged (see cell injuries). In *hepatocyte necrosis*, the cell swells due to defective osmotic regulation at the cell membrane (intracellular hyperosmolarity due to accumulation of sodium ions), fluid flows into the cell, which swells and ruptures. Even before rupture, membrane blebs form, carrying off cytoplasmic contents (without organelles) into the extracellular compartment. Macrophages cluster at such sites of injury and mark the sites of hepatocyte necrosis since the dying cells essentially burst and disappear. This form of injury is the predominant mode of death in ischemic/hypoxic injury and a significant part of the response to oxidative stress. When there is widespread parenchymal loss there is often evidence of *confluent necrosis*, a severe, zonal loss of hepatocytes. This may be seen in acute toxic or ischemic injuries or in severe viral or autoimmune hepatitis. Confluent necrosis may begin as a zone of hepatocyte dropout around the central vein. The resulting space is filled by cellular debris, macrophages, and remnants of the reticulin meshwork. In *bridging necrosis* this zone may link central veins to portal tracts or bridge adjacent portal tracts (often with an in apparent central vein within the zone of injury). Even in diseases such as viral hepatitis in which hepatocytes are the principal targets of attack, vascular insults - via inflammation or thrombosis - lead to parenchymal extinction due to large areas of contiguous hepatocyte death. *Hepatocyte apoptosis* is an active form of “programmed” cell death resulting in hepatocyte shrinkage, nuclear chromatin condensation (*pyknosis*), fragmentation (*karyorrhexis*), and cellular fragmentation into acidophilic *apoptotic bodies*. Apoptotic hepatocytes were first clearly described in yellow fever by William Thomas Councilman and therefore have often been referred to as *Councilman bodies*; while apoptosis occurs in many forms of liver disease, by convention this eponym is restricted to that disease.

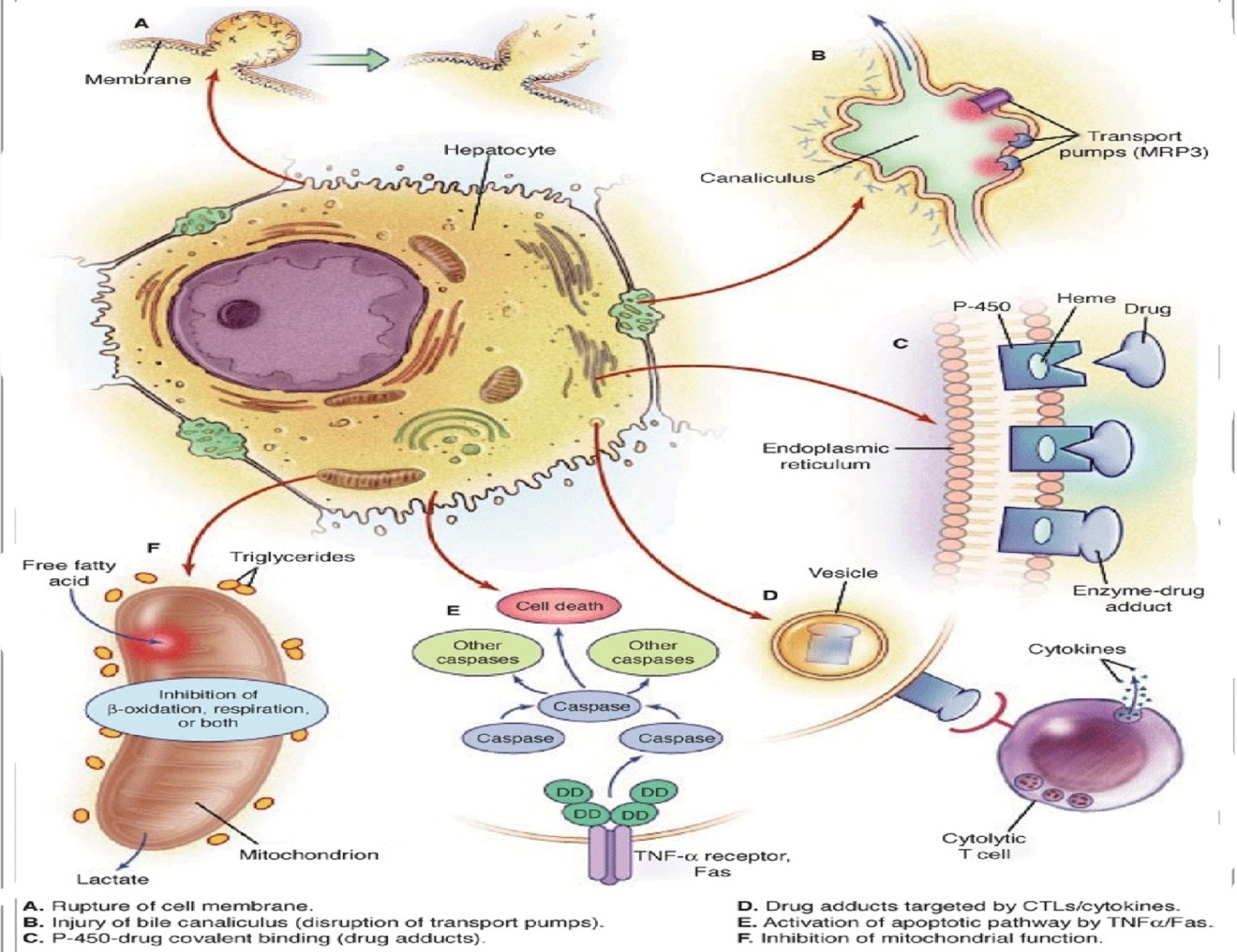
Innate and adaptive immune systems are, not surprisingly, involved in all manner of liver injury and repair. Antigens in the liver are taken up by antigen presenting cells, including, Kupffer cells and blood-derived dendritic cells, and presented to lymphocytes. Toll-like receptors detect host molecules, and also those derived from foreign invaders such as bacteria and viruses. These processes lead to elaboration of proinflammatory cytokines (IL, TNF, TGF), which have diverse effects on the liver, including recruitment of inflammatory cells, hepatocyte injury, vascular disturbances, promotion of scarring, and perhaps even malignant transformation. Adaptive immunity plays an even more critical role in viral hepatitis. Antigen-specific and CD8+T cells are involved in eradication of hepatitis B and C, the primary causes of chronic viral hepatitis, largely through elimination of infected hepatocytes. Lymphocytes, however, not only play a destructive role, but also help induce local hepatocyte replication through secretion of cytokines.

*Mechanisms of toxic hepatocyte injury.* Liver injury may follow the inhalation, ingestion, or parenteral administration of a number of pharmacologic and chemical agents. These include industrial toxins (carbon tetrachloride, trichloroethylene, and yellow phosphorus); the heat-stable toxic bicyclic octapeptides of certain species of Amanita and Galerina (hepatotoxic mushroom poisoning); The hepatotoxic octapeptides of Amanita phalloides usually produce massive hepatic necrosis; the lethal dose of the toxin is 10 mg, the amount found in a single death cap mushroom; and, more commonly, pharmacologic agents used in medical therapy. Hepatotoxic drugs can injure the hepatocyte directly (via a free-radical or metabolic intermediate that causes peroxidation of membrane lipids and that results in liver cell injury). Alternatively, the drug or its metabolite can distort cell membranes or other cellular molecules, bind covalently to intracellular proteins, activate apoptotic pathways, interfere with bile salt export proteins, or block biochemical pathways or cellular integrity (Fig.1).

Disruption of intracellular calcium homeostasis leads to the disassembly of actin fibrils at the surface of the hepatocyte, resulting in blebbing of the cell membrane, rupture, and cell lysis (Fig. 1, A). Disruption of actin filaments next to the canaliculus (the specialized portion of the cell responsible for bile excretion), leading to loss of villous processes and interruption of transport pumps such as multidrug resistance–associated protein 3 (MRP3), which, in turn, prevents the excretion of bilirubin and other organic compounds. Interference with bile canalicular pumps can allow endogenous bile acids, which can injure the liver, to accumulate (Fig.1 B). Such injuries, in turn, may lead to necrosis of hepatocytes; injure bile ducts, producing cholestasis; or block pathways of lipid movement, inhibit protein synthesis, or impair mitochondrial oxidation of fatty acids, resulting in lactic acidosis and intracellular triglyceride accumulation (expressed histologically as microvesicular steatosis).

In some cases, drug metabolites sensitize hepatocytes to toxic cytokines, and differences between susceptible and non-susceptible drug recipients may be attributable to polymorphisms in elaboration of competing, protective cytokines, as has been suggested for acetaminophen hepatotoxicity. Covalent binding of the heme-containing cytochrome P-450 enzyme to the drug, thus creating nonfunctioning adducts. Migration of these enzyme-drug adducts to the cell surface in vesicles to serve as target immunogens for cytolytic attack by T cells, stimulating an immune response involving cytolytic T cells and cytokines (Fig.1, C and D).

Other mechanisms of injury are activation of apoptotic pathways by tumor necrosis factor (TNF-α) receptor or Fas (DD denotes death domain), triggering the cascade of intercellular caspases, resulting in programmed cell death (Fig.1 E); or inhibition of mitochondrial function by a dual effect on both - oxidation and the respiratory-chain enzymes, leading to failure of free fatty acid metabolism, a lack of aerobic respiration, and accumulation of lactate and reactive oxygen species (which may disrupt mitochondrial DNA) (Fig.1 F). Additionally, toxic metabolites excreted in bile may damage bile-duct epithelium.

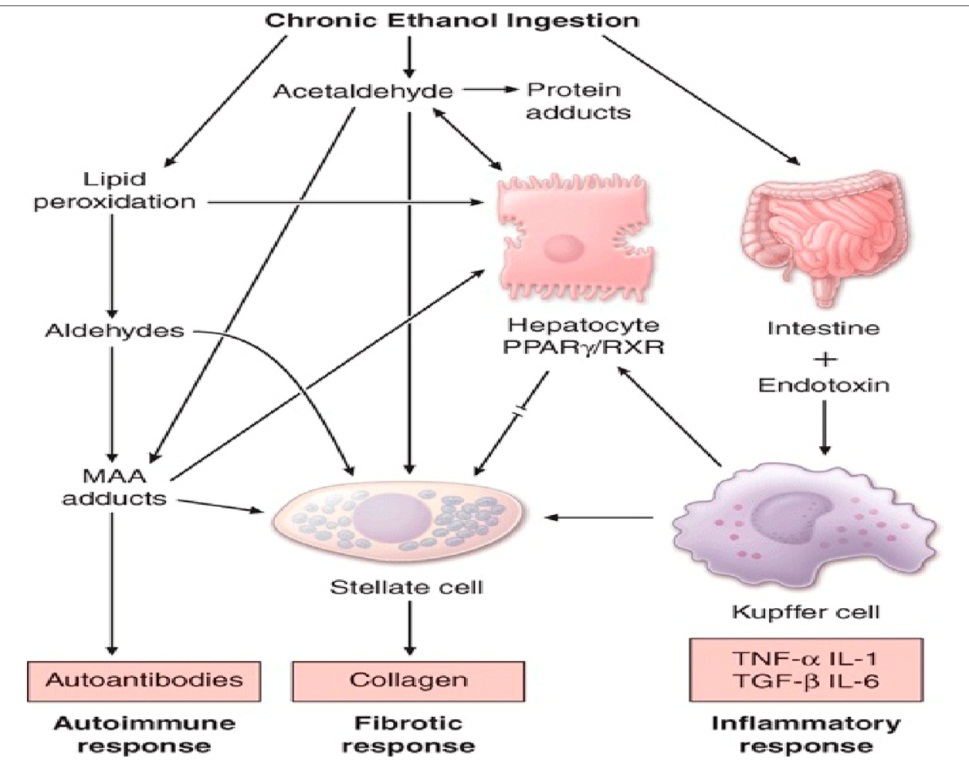
**

**Fig.1 Potential mechanisms of drug-induced liver injury**

(From Harrison's Principles of Internal Medicine, 18th Edition)

*Mechanisms of hepatocyte injury induced by alcohol.* The threshold for developing alcoholic liver disease in men is an intake of >60–80 g/d of alcohol for 10 years, while women are at increased risk for developing similar degrees of liver injury by consuming 20–40 g/d. Ingestion of 160 g/d is associated with a 25-fold increased risk of developing alcoholic cirrhosis. Ethanol is mainly absorbed by the small intestine and, to a lesser degree, through the stomach. Gastric *alcohol dehydrogenase (ADH)* initiates alcohol metabolism. Three enzyme systems account for metabolism of alcohol in the liver. These include cytosolic ADH, the microsomal ethanol oxidizing system (MEOS), and peroxisomal catalase. The majority of ethanol oxidation occurs via ADH to form *acetaldehyde*, which is a highly reactive molecule that may have multiple effects. Ultimately, acetaldehyde is metabolized to acetate by aldehyde dehydrogenase (ALDH).

Our understanding of the pathogenesis of alcoholic liver injury is incomplete. Alcohol is a direct hepatotoxin, but ingestion of alcohol initiates a variety of metabolic responses that influence the final hepatotoxic response. Intake of ethanol increases intracellular accumulation of triglycerides by increasing fatty acid uptake and by reducing fatty acid oxidation and lipoprotein secretion. Protein synthesis, glycosylation, and secretion are impaired. Oxidative damage to hepatocyte membranes occurs due to the formation of reactive oxygen species; acetaldehyde is a highly reactive molecule that combines with proteins to form *protein-acetaldehyde adducts*. These adducts may interfere with specific enzyme activities, including microtubular formation and hepatic protein trafficking. With acetaldehyde-mediated hepatocyte damage, certain reactive oxygen species can result in Kupffer cell activation. As a result, profibrogenic cytokines are produced that initiate and perpetuate stellate cell activation, with the resultant production of excess collagen and extracellular matrix. Endotoxins, oxidative stress, immunologic activity, and pro-inflammatory cytokine release contribute to the resulting liver injury. The complex interaction of intestinal and hepatic cells is crucial to alcohol-mediated liver injury. Tumor necrosis factor α (TNF-α) and intestine-derived endotoxemia facilitate hepatocyte apoptosis and necrosis. Stellate cell activation and collagen production are key events in hepatic fibrogenesis. The resulting fibrosis determines the architectural derangement of the liver following chronic alcohol ingestion (Fig.2 ).



**Fig.2 Biomedical and cellular pathogenesis of liver injury**

**secondary to chronic ethanol ingestion**

MAA, malondialdehyde-acetaldehyde; TNF, tumor necrosis factor; TGF, transforming growth factor; IL, interleukin; PPAR, peroxisome proliferator-activated receptor; RXR, retinoid X receptor. (From Harrison's Principles Of Internal Medicine, 18th Edition)

**Manifestations in liver failure**

The manifestations of liver failure reflect the various changes in synthesis, storage, metabolic, and elimination functions of the liver.

*Acute liver failure* is defined as an acute liver illness associated with encephalopathy and coagulopathy that occurs within 26 weeks of the initial liver injury in the absence of pre-existing liver disease. Acute liver failure has been referred to as “*fulminant liver failure*” until recently. The term “acute liver failure” is preferred but since the older term remains entrenched in the literature, these terms are often used interchangeably. Acute liver failure is caused by massive hepatic necrosis, most often induced by drugs or toxins. Accidental or deliberate ingestion of acetaminophen accounts for almost 50% of cases in the United States, while autoimmune hepatitis, other drugs/toxins, and acute hepatitis A and B infections account for rest of cases. In Asia, acute hepatitis B and E predominate. With acetoaminophen toxicity, the liver failure occurs within a week of the onset of symptoms, whereas failure due to hepatitis viruses takes longer to develop. The mechanism of hepatocellular necrosis may be direct toxic damage (as with acetaminophen), but more often is a variable combination of toxicity and immune mediated hepatocyte destruction (e.g., hepatitis virus infection).

Acute liver failure manifests first with nausea, vomiting, and jaundice, followed by life-threatening encephalopathy, and coagulation defects. Typically, serum liver transaminases are markedly elevated. The liver is initially enlarged due to hepatocyte swelling, inflammatory infiltrates, and edema; as parenchyma is destroyed, however, the liver shrinks dramatically. Decline of serum transaminases as the liver shrinks is often not, therefore, a sign of improvement, but is rather an indication that there are few viable hepatocytes left; this suspicion is confirmed if there is worsening jaundice, coagulopathy, and encephalopathy. With unabated progression, multi-organ system failure occurs and, if transplantation is not possible, death ensues.

**Chronic liver failure**

The leading causes of chronic liver failure worldwide include chronic hepatitis B, chronic hepatitis C, nonalcoholic fatty liver disease, and alcoholic liver disease. Liver failure in chronic liver disease is most often associated with cirrhosis, a condition marked by the diffuse transformation of the entire liver into regenerative parenchymal nodules surrounded by fibrous bands and variable degrees of vascular (often portosystemic) shunting.

*Metabolic disorders in liver failure*

*Changes in protein metabolism.* In hepatic failure protein metabolism suffer multiple changes. Protein synthesis in the liver is reduced. Disorders in albumin synthesis are the first characteristic disorders in hepatic failure, characterized by diminished albumin concentration in the blood (*hypoalbuminemia*). Because half-life of albumins is high, signs of hypoalbuminemia will be manifested after several weeks of disease. In an early stage of hepatic failure the total amount of proteins is unchanged due to the fact that the liver, as a compensatory reaction, synthesizes globulins. This ultimately leads to changes of the albumin/globulin ratio. Decreased synthesis of protein can be also explained by hepatic ATP shortage and ribosome malfunction. Moreover, in the blood of patients with hepatic failure can be identified globulins with altered physic-chemical properties, the phenomenon known as *paraproteinemia*. Decreased level of plasmatic proteins leads to reduced oncotic pressure of the blood (*hypoonchia*) process which leads to extravasation of the intravascular fluid and development of interstitial edemas and ascites. In hepatic failure there can be diminished synthesis of specific proteins (prothrombin, proconvertin and fibrinogen). To be mentioned that in synthesis of clotting factors II, V, VII, X a big role has vitamin K, vitamin which in hepatic failure can be reduced as result of malabsorbtion. All these explain development of hemorrhagic syndrome.

Metabolic disorders of aminated aminoacids are characterized by altered transamination in the affected hepatocytes, these leading to accumulation of unused aminoacids in the blood with hyperaminoacidemia and aminoaciduria. To be mentioned that in hepatic failure there is a characteristic change of blood ratio of branched and aromatic aminoacids. In healthy conditions, branched aminoacids which are absorbed from the gastrointestinal tract enter the portal circulation and pass through the liver without being metabolized. These are metabolized only at the level of peripheral tissues. Aromatic aminoacids which are carried by portal blood, are metabolized in the liver. So, in healthy individuals blood ratio of branched aminoacids to aromatic aminoacids is 3:1. In liver failure there is a characteristic decreased plasmatic level of branched aminoacids (leucine, isoleucine, valine) as result of their increased peripheral breakdown in the muscular and adipose tissue (effect of excessive insulin, which is not inactivated in the liver) and increased level of aromatic aminoacids (tyrosine, phenylalanine, methionine) due to lack of their breakdown in the liver, so that blood ratio branched to aromatic aminoacids will be 1:2.

In hepatic failure there can be changes in the process of creatinine synthesis from creatine, which explain the increased level of creatine in the blood (hypercreatinemia) and in the urine (creaturia), meantime the creatinine excreted with urine is reduced. At the level of the liver, urea in synthetized from four aminoacids (ornithine, citrulline, arginine and aspartate). Because the enzymes involve in the urea cycle are of hepatic origin, in liver failure there is reduced synthesis of urea from aminoacids with decreased blood urea nitrogen (BUN) level. In the blood there can be attested increased level of ammonia (*hyperammoniemia*) with metabolic alcalosis and in a later stage with ammoniacal encephalopathy. It was demonstrated that in hepatic failure the process of urea synthesis is affected in case when the hepatic injury affect about 80-85% of total parenchymatous tissue. So, the final conclusion is that diminished urea synthesis is characteristic for late stage of hepatic failure.

*Carbohydrate metabolic changes* in hepatic failure refer to changes in glycogenogenesis, glycogenolysis, glycolysis and gluconeogenesis in the liver.

Glycogenogenesis is the first affected energetic process in hepatic failure. It was established that every hepatocyte injury is associated with cell membrane destabilization and this injury leads to increased permeability of mitochondrial membrane. The last will contribute to influx of Ca2+ ions in the mitochondria with inhibition of oxidative phosphorylation that ultimately will contribute to reduced ATP production and diminished glycogen synthesis in the liver. Glycogenolysis in hepatic failure is increased because of hypoxia and acidosis. Intensified glycogenolysis leads to depletion of glycogen storages in the liver. Gluconeogenesis in hepatic failure is reduced because of hypoxia.

In liver failure, after glucose intake there develop exaggerated hyperglycemia with late return to normal value of glycemia. Alimentary hyperglycemia stimulates insulin secretion, which in condition of hepatocytes incompetence, doesn’t assure synthesis and storage of glycogen in the liver and doesn’t reduce hyperglycemia. Exaggerated hyperglycemia can induce glucosuria. By the contrary, in intervals between food ingestion, lack of glycogen in the liver and inability of this to perform gluconeogenesis, make this hypoglycemia to persist, with characteristic clinical symptoms – nervous and muscular asthenia, weakness, tremor. Severe hypoglycemia induces reaction from the nervous system and endocrine system: excitation of the sympathetic nervous system, increased catecholamine secretion from medulla of adrenal glands, increased secretion of glucocorticoids and glucagon from endocrine pancreas. These reactions in association with glycogen exhaustion in the liver stimulate lipolysis in adipose tissue, release of free fatty acids in the blood and development of transport hyperlipidemia with high density lipoproteins. Due to inability of the liver to synthesize proteins which transport lipids (apoproteins), transport hyperlipidemia is associated with retention hyperlipidemia. Hyperlipidemia leads to fat infiltration and dystrophy of the liver, which finally affects more the hepatocytes – at this moment pathogenic chain closed – primary liver disorders - glycogen depletion in the liver – hyperlipidemia – fat dystrophy of the liver - disorders of metabolism in the liver.

Hypoglycemia in the patient with hepatic failure as well is due to increased level of insulin in the blood (hyperinsulinism). Increased insulin level in the blood can be explained by less inactivation of insulin on the first passage through the liver (in healthy condition 40% of insulin which is released from beta pancreatic cells at the first passage through the liver is inactivated) and increased release of insulin from the pancreas in response to hyperaminoacidemia.

It was established that hypoxia deviates the utilization of pyruvic acid in Krebs cycle towards overproduction of lactic acid. Injured hepatocyte is not able to transform the lactic acid in glycogen, such the concentration of lactic acid in the blood is increased (*lactacidemia*). In hepatic failure, glycolysis, because of hypoxia, stops at the stage of pyruvic acid. Pyruvate accumulates in the blood (*pyruvicemia*). The liver is not able to utilize the pyruvic acid in Krebs cycle. So, increased concentration of lactic and pyruvic acid explains the metabolic acidosis which develop in late stage (terminal stage) of hepatic failure.

In liver failure conversion of galactose to glucose in the liver is impaired, leading to galactosemia and galactozuria

*Disorders of lipid metabolism*

Lipids represent 5% from the liver weight. In hepatic failure there is characteristic fatty charge of the liver (steatosis) by accumulation into hepatocytes of triglycerides. This is because release of triglycerides from the liver is performed in form of lipoproteins. In liver failure there is decreased synthesis of apoproteins in the liver, as well as disturbances in coupling of lipid with apoproteins in the hepatocytes, all these leading to inability of lipids to exit from the liver. Another mechanism of fatty infiltration of the liver is because of diminished phospholipids synthesis with reduced production of lipotropic substances and reduced synthesis of lipoproteins in the liver.

# Due to inability of the liver to perform normal production of bile, in patient with liver failure there will develop malabsorbtion and maldigestion syndrome which will disturb mainly the fat absorbtion into gastrointestinal tube. There is characteristic development of avitaminosis as result of malabsorbtion of liposoluble vitamins (A,D,E,K) from food.

*Vitamin A* is a fat-soluble vitamin, and its absorption requires bile. Retinol (generally ingested as retinol ester) and β-carotene are absorbed in the intestine, where β-carotene is converted to retinol. Retinol is then transported in chylomicrons to the liver for esterification and storage. Uptake in liver cells takes place through the apolipoprotein E receptor. More than 90% of the body's vitamin A reserves are stored in the liver, predominantly in the perisinusoidal stellate (Ito) cells. In healthy persons who consume an adequate diet, these reserves are sufficient to meet the body's demands for at least 6 months. Retinol esters stored in the liver can be mobilized; before release, retinol binds to a specific retinol-binding protein (RBP), synthesized in the liver. In liver failure metabolism of vitamin A is impaired. Vitamin A is a component of *rhodopsin* and other visual pigments. Not surprisingly, one of the earliest manifestations of vitamin A deficiency is impaired vision, particularly in reduced light *(night blindness)*. Other effects of deficiency are related to the role of vitamin A in maintaining the differentiation of epithelial cells. Persistent deficiency gives rise to a series of changes involving epithelial metaplasia and keratinization. The most devastating changes occur in the eyes and are referred to as *xerophthalmia* (dry eye). First, there is dryness of the conjunctiva (xerosis conjunctivae) as the normal lacrimal and mucus-secreting epithelium is replaced by keratinized epithelium. This is followed by erosion of the roughened corneal surface with softening and destruction of the cornea *(keratomalacia)* and total blindness. In addition to the ocular epithelium, the epithelium lining the upper respiratory passage and urinary tract is replaced by keratinizing squamous cells *(squamous metaplasia)*. Loss of the mucociliary epithelium of the airways predisposes to secondary pulmonary infections, and desquamation of keratin debris in the urinary tract predisposes to renal and urinary bladder stones. Hyperplasia and *hyperkeratinization of the* *epidermis* with plugging of the ducts of the adnexal glands may produce follicular or papular dermatosis. Another very serious consequence is immune deficiency, which is responsible for higher mortality rates from common infections such as measles, pneumonia, and infectious diarrhea. *Vitamin D* is another fat-soluble vitamin which metabolism is disturbed in liver failure due to malabsorbtion related to bile deficiency. The liver also is involved in the process of conversion of vitamin D into *25-hydroxycholecalciferol* (25-OH-D), through the effect of 25- OHases (25-hydroxylases). The major function of the fat-soluble vitamin D is the maintenance of adequate plasma levels of calcium and phosphorus to support metabolic functions, bone mineralization, and neuromuscular transmission. Vitamin D is required for the prevention of bone diseases known as *rickets* (in children whose epiphyses have not already closed), *osteomalacia* (in adults), and hypocalcemic tetany. This latter condition is a convulsive state caused by an insufficient extracellular concentration of ionized calcium, which is required for normal neural excitation and the relaxation of muscles. Other effects of vitamin D in the innate and adaptive immune system have been reported, but the data are often contradictory. Vitamin D regulates the expression of more than 200 genes, including genes that participate in cell proliferation, differentiation, apoptosis, and angiogenesis. It has been reported that levels of vitamin D below 20 ng/mL are associated with a 30% to 50% increase in the incidence of colon, prostate, and breast cancers.

*Vitamin K* is required for the posttranslational carboxylation of glutamic acid, which is necessary for calcium binding to γ-carboxylated proteins such as prothrombin (factor II); factors VII, IX, and X; protein C; protein S; and proteins found in bone (osteocalcin) and vascular smooth muscle (matrix Gla protein). However, the importance of vitamin K for bone mineralization and prevention of vascular calcification is not known. In hepatic failure, deficit of vitamin K, as result of intestinal malabsorbtion, will lead to decreased synthesis of coagulation factors II,VII, IX, X, phenomenon that can explain hypocoagulation of blood and development of hemorrhagic syndrome.

*Vitamin E* is a collective name for all stereoisomers of tocopherols and tocotrienols, although only the RR tocopherols meet human requirements. Vitamin E acts as a chain-breaking antioxidant and is an efficient pyroxyl radical scavenger that protects low-density lipoproteins (LDLs) and polyunsaturated fats in membranes from oxidation. A network of other antioxidants (vitamin C, glutathione) and enzymes maintains vitamin E in a reduced state. Vitamin E also inhibits prostaglandin synthesis and the activities of protein kinase C and phospholipase A2. After absorption, vitamin E is taken up from chylomicrons by the liver, and a hepatic tocopherol transport protein mediates intracellular vitamin E transport and incorporation into very low density lipoprotein (VLDL). Vitamin E deficiency causes axonal degeneration of the large myelinated axons and results in posterior column and spinocerebellar symptoms. Peripheral neuropathy is initially characterized by areflexia, with progression to an ataxic gait, and by decreased vibration and position sensations. Ophthalmoplegia, skeletal myopathy, and pigmented retinopathy may also be features of vitamin E deficiency.

In liver failure there are present disturbances in cholesterol metabolism. In liver failure both, synthesis as well as esterification of cholesterol is disturbed. Esterified fraction of cholesterol is reduced (up to 10%, from normal values of 60-70%) or can be completely absent; meantime the free cholesterol in the bloodstream is increased*.* In advanced hepatic failure, total cholesterol in the blood is reduced as result of diminished ability of hepatocytes to synthesize it. Anyway, there should be mentioned that in hepatic failure which develop in the result of biliary obstruction, total blood cholesterol can be increased as result of cholestasis and cholemia (presence of bile in the blood) and reduced activity of lecithin-cholesterol-acetyltranferase – enzyme which transforms free cholesterol in esterified cholesterol.

Disorders of lipid metabolism in liver failure are in close relation with carbohydrate metabolic disorders. In liver failure there is glycogen depletion in the liver and a tendency toward hypoglycemia. These will stimulate lipolysis in the adipose tissue and increased release of fatty acids. Their oxidation increases the levels of acetyl-KoA (acetate).Surplus of acetyl-KoA is transformed in ketones bodies – *β oxibutyric acid, acetone* and *acetylacetate.* Surplus of acetyl-KoA is due to it underutilization in another metabolic pathways. Acetyl-KoA represents the final product of protein, lipid and carbohydrate metabolism. Such, is evident that fatty acids can be synthesized from protein and carbohydrates passing though a stage of acetyl-KoA*.* One of the blocked pathways which uses the acetyl-KoA is resynthesis of free fatty acids. Biosynthesis of saturated fatty acids is performed from malonyl-KoA with participation of cytoplasmatic enzymes, and malonyl-KoA is formed from plasmatic acetyl-KoA and carbon oxide with participation of the enzyme acetyl-KoA-cocarboxilase.Removal of the chain from the fatty acid needs ions of hydrogen. In this physiological condition the ion H+ are supplied by the enzyme – NADPH, formed in the pentosephosphate cycle. So, intensiveness of fatty acid synthesis is directly proportional with intensity of this cycle which generates NADPH. At the level of adipose tissue the ratio between pentosephosphate cycle and glycolytic cycle is 1:1; in the liver the ratio is 1:12, but in the muscular tissue the pentosephosphate cycle is almost lacking. So, this metabolic pathway is almost completely happening at the level of the liver. In liver failure this metabolic process is disturbed and there is a deficiency of NADPH. Another blockage is at the level of involvement of Acetyl-KoA in Krebs cycle due to deficiency of oxalacetate (first reaction in Krebs cycle) due to decreased glycolysis in the liver. Finally there is accumulation of Acetyl-CoA. Initially, from 2 molecules of acetyl-KoA, acetoacetyl KoA is synthesized. The last, adding one more molecule of acetyl-KoA is transformed in β-oxi-β-metilglutaril-KoA, which is broken down in acetyl-KoA and acetylacetic acid. Acetylacetic acid by reduction forms β-oxibutiric acid, and by decarboxilation – acetone**.**  Accumulation of ketones bodies deviates the blood pH to acidosis with development of ketoacidosis. Ketones bodies, affect the cerebral cells, blocking the enzymes (hexokynases) that will further block the utilization of glucose in the neurons. As result, there will develop a large nervous symptomatology.

*Disturbances of hydro-electrolytic and pH balance.* Injuries at the level of hepatocyte membrane lead to outflow of K+ ions with hyperkalemia. Into hepatic cells enter Na+ and H+ ions , and the K+ ions are lost with urine. Finally there will develop hypokalemia with alkalosis. The phenomenon is worsen by hypovolemia (edema, ascites), which activates the renin- angiotensin-aldosterone system that will additionally lead to retention of sodium ions with hypernatremia and loss of potassium and hydrogen ions. To these will be added the effects of secondary hyperaldosteronism (due to deficiency in aldosterone breakdown in the liver). Should be mentioned that level of natremia will not reflect truly the level of sodium retention as the sodium ions enter into the cells.

Phospho-calcic balance is affected as well. There is characteristic hypocalcemia due to deficiency in serine, which fix and carry up to 40% of blood calcium; alimentary deficiency due to anorexia characteristic for liver failure; defect in calcium absorbtion because of diminished secretion of HCl in the stomach, pancreatic insufficiency; inability of the liver to convert calcipherol in colecalcipherol.

In patients with liver failure volume of total water in the body is increased, especially at the level of venous circulation, due to hyperaldosteronism (absolute and relative) as well as increased level of ADH.

In an early stage of hepatic failure metabolic alcalosis can develop, explained by ionic disturbances: H+ and Na+ ions influx in the cells associated with increased excretion of K+, H+, Cl+ at the level of renal glomeruli. Also, alkalosis can be due to inability of the liver to eliminate the alkaline valences with bile. Usually, increased level of ammonia in the blood the same is associated with alkalosis. In a late stage metabolic acidosis is characteristic, and is explained by metabolic disturbances with accumulation of lactic acid, pyruvic acid, ketones bodies in the blood.

*Hematologic disorders*. Liver failure can cause anemia, thrombocytopenia, coagulation defects, and leukopenia. Anemia may be caused by blood loss, excessive red blood cell destruction, and impaired formation of red blood cells. A folic acid deficiency may lead to severe megaloblastic anemia. Changes in the lipid composition of the red cell membrane increase hemolysis. Because factors V, VII, IX, X, prothrombin, and fibrinogen are synthesized by the liver, their decline in liver disease contributes to bleeding disorders. Malabsorption of the fat-soluble vitamin K contributes further to the impaired synthesis of these clotting factors. Thrombocytopenia often occurs as the result of splenomegaly. The person with liver failure is subject to purpura, easy bruising, hematuria, and abnormal menstrual bleeding, and is vulnerable to bleeding from the esophagus and other segments of the gastrointestinal tract.

*Hormonal disturbances***.** In liver failure develop hormonal dyshomeostasis in the result of diminished ability of the liver to breakdown hormones. Hyperestrogenism leads to menstrual disorders, diminished libido, impotence, female type distribution of hair, testicular atrophy, gynecomastia, palmar erythema and vascular stars (by openings of peripheral shunts). Insufficiency of inactivation of adrenal hormones leads to hirsutism, acne, abdominal striae and “moon” face. Hyperaldosteronism leads to salt and water retention (hypernatremia) with hypokalemia and alkalosis. Retention of ADH leads to hypervolemia and contribute secondarily to edema and ascites.

*Skin disorders*. Liver failure brings on numerous skin disorders. These lesions, called variously vascular spiders, telangiectases, spider angiomas, and spider nevi, are seen most often in the upper half of the body. They consist of a central pulsating arteriole from which smaller vessels radiate. Palmar erythema is redness of the palms, probably caused by increased blood flow from higher cardiac output. Clubbing of the fingers may be seen in persons with cirrhosis.

Jaundice usually is a late manifestation of liver failure.

*Fetor hepaticus* refers to a characteristic musty, sweetish odor of the breath in the patient in advanced liver failure. Fetor hepaticus is due to exhalation of mercaptans produced in the large intestine under influence of microflora on aromatic aminoacids which have sulfur (methionine). Mercaptans, mainly *methylmercaptan* and *dimethyl sulfide*, pass in the systemic circulation through the porto-systemic shunts and are exhaled in the lungs.

*Cholestasis* occurs producing not only liver damage but also aggravating any bleeding tendency, because the lack of bile salts decreases micellar formation and with it the absorption of vitamin K from the intestine, so that carboxylation of the vitamin K-dependent clotting factors prothrombin (II), VII, IX, and X is reduced.

**Hepatic encephalopathy *(hepatic coma)***. Hepatic encephalopathy refers to the totality of central nervous system manifestations of liver failure. In acute liver failure there is characteristic a sudden change in consciousness with increased intracranial pressure and massive cerebral edema which can lead to cerebral herniation and death. In chronic hepatic failure it is characterized by neural disturbances ranging from a lack of mental alertness to confusion, coma, and convulsions. A very early sign of hepatic encephalopathy is a flapping tremor called *asterixis.* *Asterixis* is manifested as non-rhythmic, rapid extension-flexion movements of the head and extremities, best seen when the arms are held in extension with dorsiflexed wrists. Various degrees of memory loss may occur, coupled with personality changes such as euphoria, irritability, anxiety, and lack of concern about personal appearance and self. Speech may be impaired, and the patient may be unable to perform certain purposeful movements. The encephalopathy may progress to decerebrate rigidity and then to a terminal deep coma. Hepatic encephalopathy develops in approximately 10% of persons with portosystemic shunts.

Although molecular mechanisms of HE are not definitely known there is an attempt to explain them by several pathophysiological concepts.

- *Concept of porto-caval shunts*. Is the oldest theory and try to explain development of HE by several mechanisms: brain intoxication with portal blood which by-pass the liver and reach the brain non-detoxified; inability of the liver to detoxify all the toxic substances from the portal blood.

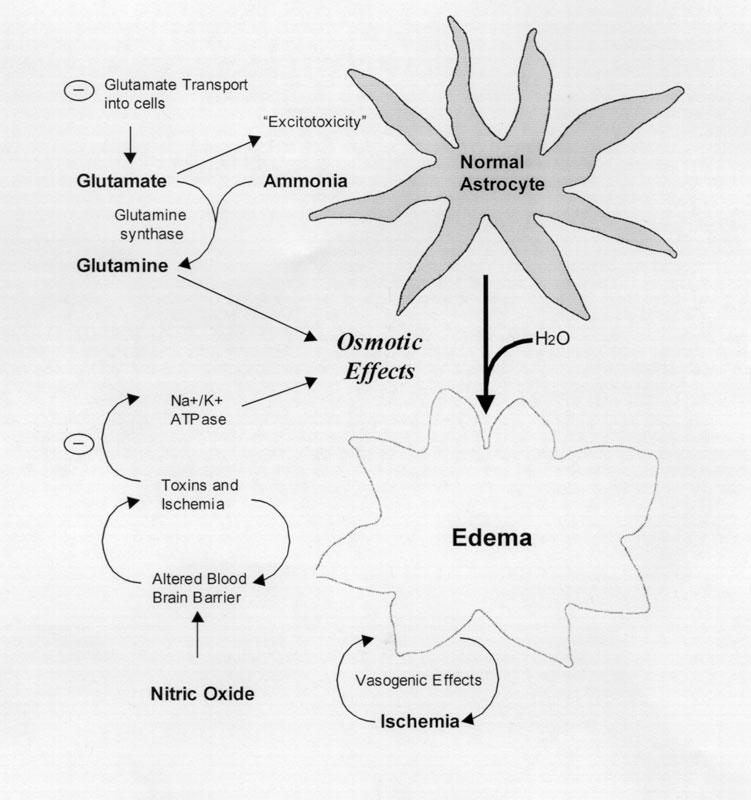
- *Concept of ammonia intoxication*.

Ammonia is considered a key pathogenic factor in development of HE. In 90% of patient with HE level of ammonia in the blood is elevated. A particularly important function of the liver is the conversion of ammonia, a byproduct of protein and amino acid metabolism, to urea. The ammonium ion is produced in abundance in the intestinal tract, particularly in the colon, by the bacterial degradation of luminal proteins and amino acids. Normally, these ammonium ions diffuse into the portal blood and are transported to the liver, where they are converted to urea before entering the general circulation. When the blood from the intestine bypasses the liver or the liver is unable to convert ammonia to urea, ammonia moves directly into the general circulation and from there to the cerebral circulation. Hepatic encephalopathy may become worse after a large protein meal or gastrointestinal tract bleeding.

In the human body, ammonia clearance is performed, physiologically at the level of the liver by synthesis of urea (ureogenesis) and at the level of the muscle (by synthesis of glutamine). Healthy liver extracts from the blood at the first passage up to 80% of ammonia. In the liver reactions which lead to synthesis of urea from ammonia are known as *ureogenetic cycle Krebs-Henseleit* (ornithine + ammonia + CO2+ATP → Citrulline + ammonia → Arginine → Urea + ornithine). Transformation of ammonia into glutamine occurs at the level of the liver and the CNS. Glutamine represents an important transport and storage form of ammonia. In condition of excessive blood ammonia, ammonia can be detoxified at the level of astrocytes by conversion of glutamic acid into glutamine. So, astrocytes in the CNS are the key cells on which ammonia exert its neurotoxic effects:

* Glutamate is an amino acid that acts as an excitatory neurotransmitter and is present in presynaptic vesicles in more than 90% of the neurons. After its release and activation of different postsynaptic receptors, glutamate is removed from the synaptic cleft by transporters located at the astrocytes. In the astrocytes, glutamate is transformed into glutamine with the incorporation of one molecule of ammonia and transported into the presynaptic neuron, where glutamine will be transformed again into glutamate. This cycle is affected at several steps by ammonia. At physiological pH, blood ammonia is mostly ionized (NH4+). Small changes in pH have effects in the equilibrium and affect the amount of un-ionized ammonia (NH3), which is the form that passes the blood-brain barrier by diffusion. High concentration of ammonia which pass the hematoencephalic barrier enters into astrocytes where combine with glutamate and form glutamine. Increased demand for glutamate lead to enhanced consumption of alpha-ketoglutaric acid, which is withdrawn from the Krebs cycle. Finally, ammonia leads to decreased activity of Krebs cycle at the level of the CNS with energy deficiency in the neurons and astrocytes.
* Excessive ammonia reduces cerebral blood flow and cerebral glucose consumption in the Krebs cycle, these worsening the energy production in the Krebs cycle;
* Hyperammoniemia leads to changes in mitochondrial membrane permeability at the level of astrocytes. This process is dependent on Ca2+ ions and is represented by a pore opening at the level of internal mitochondrial membrane, leading to collapse of ionic gradient and final mitochondrial dysfunction. Other factors as well can be involved in development of mitochondrial dysfunction, from these the most important are: reactive oxygen species, nitric oxide, alkaline pH, glutamine. Thus, mitochondrial dysfunction represents an important pathogenic mechanism in HE.
* High level of ammonia in the brain lead to increased number of benzodiazepine receptors at the level of external mitochondrial membrane in the astrocytes. This leads to increased synthesis of *neurosteroids* (tetrahydroprogesteron and tetrahydrodeoxycorticosteron). Activation of neurosteroids, which are agonists of the γ-aminobutyric acid (GABA) receptors may be responsible for the inhibitory pattern of neuronal function that characterizes HE.
* Ammonia has been shown to evoke oxidative stress inducing the generation of free radicals and the nitro-tyrosination of proteins in the brain. This process is critical for mitochondrial function and secondarily may cause failure of normal neurotransmission.
* Ammonia enhances permeability of hematoencephalic barrier by this facilitating diffusion in the CNS of other toxic substances absorbed from large intestine (short chain fatty acids, phenols, mercaptanes, etc ..) and aromatic aminoacids.

So, increased level of ammonia in the brain has main neurotoxic effects on astrocytes. There is known that astrocytes are supporting cells in the CNS with have a high role in control of electrolyte, water and nutritive substances flow between neurons and microcirculation (buffer cells). By inactivating ammonia, astrocytes fill with glutamine, which is an active osmotic substance, leading to shift of water inside the cell with development of astrocyte edema. The same effect has also inhibition of Na+/K+ ATPase by other toxic substances which are no detoxified in the liver.



**Fig. 3. Effects of ammonia in the astrocytes**

*Synergic concept*

There is considered that to toxic effects of ammonia in development of HE should be added as well toxic effects of other substances, mainly: short chain fatty acids, mercaptanes, amines and phenols.

- *Short chain fatty* *acids* are synthetized in the large intestine from polysaccharides by intestinal microflora, are absorbed in the portal blood and ultimately are inactivated in the liver. In patient with liver failure systemic concentration of short chain fatty acids (the best known are acetic acid, propionic acid, butyric acid) is high and have a neurotoxic effect mainly by reducing energetic metabolism at the level of CNS by inhibiting Na+/K+ATPase and increasing level of intracellular sodium.

- *Mercaptanes* are thiol-alcohols, produced by bacterial catabolism of sulphuric aminoacids (mainly methionine) in the large intestine and have synergic effects with NH3. From mercaptanes, metylsulphid and metanetiol enhance the neurotoxic effects of ammonia, by this worsening the energy deficiency at the level of the neurons and astrocytes. Additionally, mercaptans inhibit the enzymes of the urea cycle in the liver, enhancing production of ammonia, as well as diminish the activity of Na+/K+ATPase

- *Phenols* results from catabolism of phenylalanine and tyrosine, and together with neurotoxic amines (octopamine, tiramine, phenyletanolamine) act as false neurotransmitters.

*Concept of intracerebral neurotransmission disorders*

In HE there can be attested a disbalance between excitatory and inhibitory neurotransmitters. There is characteristic an increase of inhibitory neurotransmitters: real (GABA, serotonin) and false (octopamine and phenyletanolamine). Concentration of excitatory neurotransmitters (dopamine, glutamate, norepinephrine) is dramatically reduced or even totally absent.

Glutamic acid is one of the most important excitatory neurotransmitters in the brain, which metabolism is performed in two compartments: astrocytes and neurons. This neurotransmitter is very important for removal of ammonia which passes the hematoencephalic barrier, as in the CNS there are no enzymes of urea cycle. This leads to depletion of glutamate in the CNS. Other two important excitatory mediators are dopamine and noradrenaline, which synthesis is dramatically diminished in HE. This is due to increased blood concentration of aromatic aminoacids and decreased concentration of branched aminoacids in hepatic failure. In this condition, hematoencephalic barrier becomes more permeable for aromatic aminoacids. High level of phenylalanine in the excitatory neurons inhibits thyrosin-3-hydrohylase by this reducing synthesis of DOPA, which is the precursor of norepinephrine. Dopamine depletion explain some neuropshycic manifestations in HE: reduced motor activity, hypokinesia, tremor, cognitive disturbances, memory disturbances. Depletion of noradrenaline in HE is responsible for depression, diminished selective attention, apathy, nonchalance.

Inhibitory neurotransmitters, mainly *GABA* and *serotonin* are synthetized excessively. GABA in HE has two sources, one endogenous by decarboxylation of glutamic acid in the inhibitory neurons, and another is the colonic source (synthesis of GABA from glutamic acid in the large intestine under the effect of bacterial decarboxylases) which by-pass the liver by porto-systemic shunts. GABA which passes the hematoencephalic barrier as well as GABA synthetized in the neurons is stored in the presynaptic vesicles. After release in synaptic cleft, GABA act on postsynaptic receptors and open the Cl- channels leading to hyperpolarization of postsynaptic membrane, by this leading to inhibition. The same effect will have endogenous benzodiazepines, which are synthetized in the large intestine under influence of microflora. Level of benzodiazepines in the blood, cerebrospinal fluid and urine is increase in patients with HE. High level of GABA and endogenous benzodiazepines are responsible for drowsiness, reduced muscle tonus, memory disturbances (anterograde amnesia). Increased level of serotonin in the CNS is due to high level of tryptophan in the blood, which passes the hematoencephalic barrier. At the level of the neuron tryptophan in the presence of enzyme *tryptophan-hydrolase* is converted to 5-hydrotriptamin (serotonin). High serotonin is responsible for depression, drowsiness, inversion of day-night rhythm characteristic for patients wit HE.

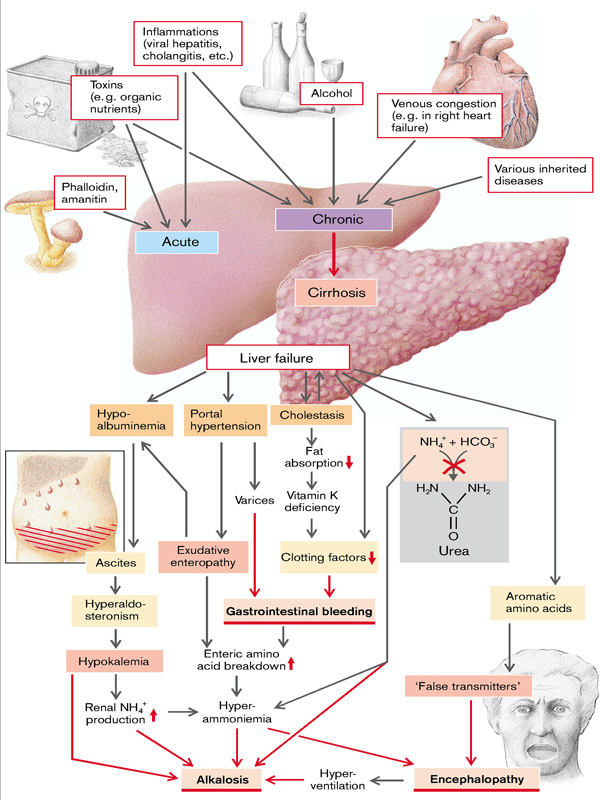
False neurotransmitters (pseudoneurotransmitters) have origin from two sources. One source is the result of bacterial decarboxylation of phenylalanine and tyrosine in the colon, with formation of phenyletanolamine and octopamine respectively. These pseudoneurotransmitters pass the hematoencephalic barrier and reach the neurons. The second source of false neurotransmitters is directly at the level of the neurons in the result of intracerebral metabolism of phenylalanine and tyrosine. In the specialized neurons, phenylalanine and tyrosine are catabolized by other metabolic pathway with formation of pseudoneurotransmitters. These two false neurotransmitters (octopamine and phenyletanolamine) together with serotonin and GABA are responsible for predominance of inhibitory effect on excitatory ones in patients with HE.

*Concept of reduced energogenesis*

This concept can be explained by many pathogenic factor. Hypoglycemia due to reduced gluconeogenesis and increased level of insulin, effects of ammonia (see above), effects of mercaptanes.

*Concept of oxidative and nitrosative stress*

Reactive oxygen species act like modulators at the level of synapses*.* When these accumulate in high amount (chronic alcohol use, hepatotoxins) free radicals trigger the oxidative stress which interferes with synaptic transmission. Long term exposure of neurons to high concentration of H2O2 leads to activation of NMDA receptors. Activation of NMDA receptors lead to accumulation of Ca2+ ions inside the neurons, which trigger a series of pathological event as well as release of nitric oxide (NO). Both in acute HE as well as in chronic HE there is increase expression of nitric oxide synthase (NOS) associated with increased uptake of L-arginine by neurons (arginine is the precursor for NO). Hyperammoniemia in liver failure is responsible also for increased production of NO, leading subsequently to memory disturbances, acute cerebral edema.



**Fig. 4. Causes and consequences of liver failure**

(From S. Silbernagl and F. Lang; Color Atlas of Pathophysiology)

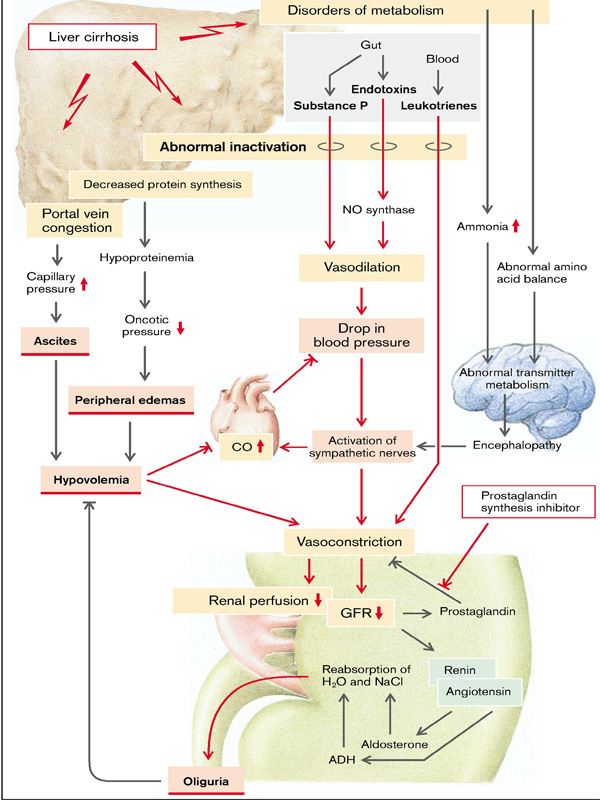
*Hepatorenal syndrome*. The hepatorenal syndrome refers to a functional renal failure sometimes seen during the terminal stages of liver failure with ascites. It is characterized by progressive azotemia, increased serum creatinine levels, and oliguria. Although the basic cause is unknown, a decrease in renal blood flow is believed to play a part. Ultimately, when renal failure is superimposed on liver failure, azotemia and elevated levels of blood ammonia occur; this condition is thought to contribute to hepatic encephalopathy and coma. Several factors contribute to the development of this syndrome.

In liver cirrhosis, congestion in the portal venous system due to narrowing of the vascular

bed within the liver occurs initially. The hydrostatic pressure in the capillaries rises and excessive amounts of fluid are filtered into the abdominal cavity (ascites). Because of the high protein permeability of the liver sinusoid, plasma proteins are also lost into the extracellular space. In addition, fewer plasma proteins are produced in the liver parenchyma. The resulting hypoproteinemia leads to increased filtration of plasma water and thus in the development of peripheral edemas. The formation of ascites and peripheral edemas occurs at the expense of the circulating plasma volume. The result is hypovolemia. In the further course of the disease peripheral vasodilation occurs. Vasodilating mediators (substance P) produced in the gut and endotoxins released by bacteria are normally detoxified in the liver. In liver cirrhosis the loss of liver parenchyma and the increased amount of blood passing from the portal circulation directly into the systemic circulation, short-circuiting the liver, brings those substances into the systemic circulation unhindered. The mediators have a direct vasodilator effect, while the endotoxins exert a vasodilator effect by stimulating the expression of nitric oxide synthase (iNOS). This may lead to a fall in blood pressure, causing massive sympathetic stimulation. This, together with the hypovolemia, results in diminished renal perfusion and thus a fall in GFR. The reduced renal blood flow promotes the release of renin and thus the formation of angiotensin II, aldosterone and ADH. ADH and aldosterone increase the tubular reabsorption of water and sodium chloride (loss of potassium), and the kidney excretes small volumes of highly concentrated urine (oliguria).

Incomplete hepatic inactivation of mediators that have a direct vasoconstrictor effect on the kidney (leukotrienes) also contributes to renal vasoconstriction. Renal ischemia normally stimulates the release of vasodilating prostaglandins that prevent further reduction in renal perfusion. If there is insufficient formation of prostaglandins (due to administration of prostaglandin synthesis inhibitors), this protective mechanism is abolished and the development of renal failure accelerated. A decreased ability to synthesize prostaglandins (lack of precursors?) has in fact been found in patients with the hepatorenal syndrome. Renal vasoconstriction can possibly also be elicited by hepatic encephalopathy. The reduced metabolic activity of the liver leads to a change in aminoacid concentration and a rise in NH4+ concentration in blood and brain. This causes swelling of the glial cells (astrocytes) and a profound disturbance of transmitter metabolism in the brain that, via activation of the sympathetic nervous system, causes renal vascular constriction. Due to the impaired synthesizing activity of the liver, less kininogen is formed, and therefore too few vasodilating kinins (bradykinin), facilitating renal vasoconstriction.

Lastly, an abnormal fat metabolism may contribute to kidney damage in liver failure. Among other consequences, the liver forms less lecithin-cholesterol acyltransferase (LCAT), an enzyme that esterifies cholesterol with fatty acids and plays an important part in breaking down or transforming lipoproteins. In familial LCAT deficiency (due to an enzyme defect) renal failure regularly occurs, probably through lipid deposition in the kidney (Fig.5).



**Fig. 5 Hepatorenal syndrome**

(From S. Silbernagl and F. Lang; Color Atlas of Pathophysiology)

*Hepatopulmonary syndrome* is seen in up to 30% patients with cirrhosis of the liver and portal hypertension. These patients develop intrapulmonary vascular dilations involving capillary and pre-capillary vessels up to100 μM in size. The blood flows rapidly through such dilated vessels, giving inadequate time for oxygen diffusion and leading to ventilation-perfusion mismatch and right-to-left shunting, manifesting as hypoxia. Hypoxia and resultant dyspnea occur preferentially in an upright position rather than in the recumbent position, as gravity exacerbates the ventilation-perfusion mismatch. Patients with this syndrome have a poorer prognosis than patients without hepatopulmonary syndrome. The pathogenesis of hepatopulmonary syndrome is unclear, although it has been postulated that the diseased liver may not clear vasoconstrictors such as endothelin-1 or may produce some vasodilators such as NO.

**Liver cirrhosis**

*Cirrhosis* represents the end stage of chronic liver disease in which much of the functional liver tissue has been replaced by fibrous tissue. It is characterized by diffuse fibrosis and conversion of normal liver architecture into structurally abnormal nodules. It is a disease in which necrosis, inflammation, fibrosis, nodular regeneration, and formation of vascular anastomoses develop more or less simultaneously. The fibrous tissue replaces normally functioning liver tissue and forms constrictive bands that disrupt flow in the vascular channels and biliary duct systems of the liver. The disruption of vascular channels predisposes to portal hypertension and its complications; obstruction of biliary channels and exposure to the destructive effects of bile stasis; and loss of liver cells, leading to liver failure.

It is usually caused by the long-term action of noxious factors, especially alcohol abuse, which is the cause in 50% of cases worldwide. While the probability of cirrhosis developing after a cumulative uptake of 13 kg ethanol/kg body weight is only about 20%, it rises to over 90% after 40 kg. The substance that is most responsible for the development of fibrosis, and thus cirrhosis, is the ethanol metabolite acetaldehyde. Cirrhosis can also be the final stage of viral hepatitis (20–40% of cirrhosis cases in Europe). In acute fulminant disease it may develop in a matter of weeks; in chronic recurrent disease after months or years. It can also occur after an obstruction to blood outflow (congestive liver) or after other liver damage, for example, as final stage of a storage disease (hemochromatosis, Wilson’s disease) or genetically determined enzyme deficiency.

*Pathogenesis*

Fibrosis of the liver develops in several steps. When damaged hepatocytes die, lysosomal enzymes, among others, leak out and release cytokines from the extracellular matrix. These cytokines and the debris of the dead cells activate the Kupffer cells in the liver sinusoids and attract inflammatory cells (granulocytes, lymphocytes, and monocytes) (Fig.6). Diverse growth factors and cytokines are then liberated from the Kupffer cells and the recruited inflammatory cells. These growth factors and cytokines now:

– transform the fat-storing Ito cells of the liver into myofibroblasts;

– transform the immigrated monocytes into active macrophages;

* trigger the proliferation of fibroblasts;

The principal cell type involved in scar deposition is the hepatic stellate cell (Ito cell). Although normally functioning as vitamin A fat-storing cells, during the development of cirrhosis they become activated, a process that includes (1) robust mitotic activity in areas developing new parenchymal fibrosis, (2) a shift from the resting-state lipocyte phenotype to a transitional myofibroblast phenotype, and (3) increased capacity for synthesis and secretion of extracellular matrix. The greatest activation of stellate cells is in areas of severe hepatocellular necrosis and inflammation. The stimuli for stellate cell activation may originate from several sources:

(1) chronic inflammation, with production of inflammatory cytokines such as tumor necrosis factor (TNF), lymphotoxin, and interleukin-1β (IL- 1β), and lipid peroxidation products;

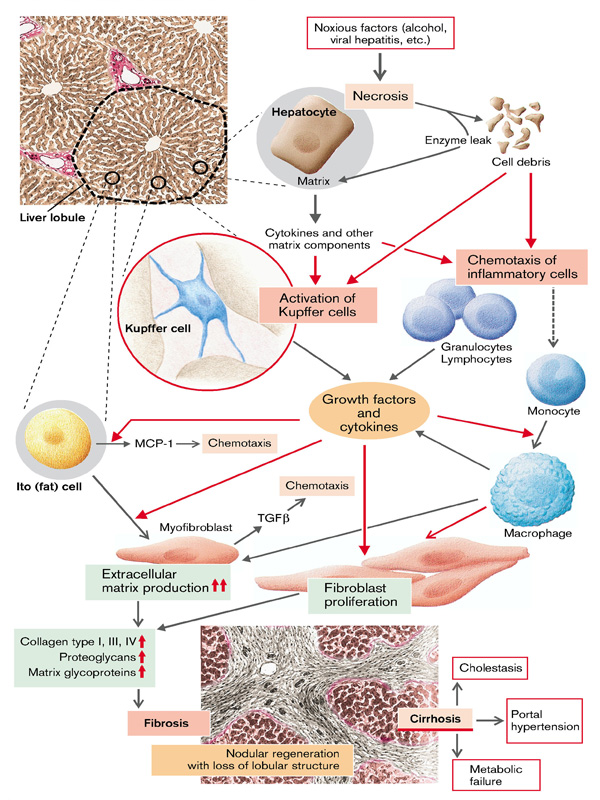
(2) cytokine and chemokine production by Kupffer cells, endothelial cells, hepatocytes, and bile duct epithelial cells;

(3) in response to disruption of the extracellular matrix (ECM);

(4) direct stimulation of stellate cells by toxins.

These cytokines "activate" stellate cells, whereby they loose their lipid droplets (which are present in the quiescent state) and acquire a myofibroblastic state. Stellate cell proliferation is stimulated in particular by platelet-derived growth factor (PDGF); tumor necrosis factor (TNF) is a potent stimulant of the change to a myofibroblastic phenotype. Contraction of the activated stellate cells is stimulated by endothelin-1 (ET-1). Deposition of extracellular matrix (*fibrogenesis)* is stimulated especially by transforming growth factor b (TGF-b). Chemotaxis of activated stellate cells to areas of injury, such as where hepatocytes have undergone apoptosis, is promoted by PDGF and monocyte chemotactic protein-1 (MCP-1). Kupffer cells also are a major source of TNF released into the system circulation. Other cells probably contribute significantly to scar deposition in different settings, including portal fibroblasts. Ductular reactions also play a role, both through activation and recruitment of all these fibrogenic cells, but also, perhaps, through epithelial-mesenchymal transition. The relative roles played by these other cells and processes are less well understood.

As a result of these numerous interactions, the production of the extracellular matrix is increased by myofibroblasts and fibroblasts, leading to an increased deposition of collagens (types I, III, and IV), proteoglycans (decorin, biglycan, lumican, aggrecan), and glycoproteins (fibronectin, laminin, tenascin, undulin) in the Dissé space. In the normal liver, interstitial collagens (types I and III) are concentrated in portal tracts and around central veins, with occasional bundles in the space of Disse. The collagen (reticulin) coursing alongside hepatocytes is composed of delicate strands of type IV collagen in the space of Disse. In cirrhosis, types I and III collagen are deposited in the lobule, creating delicate or broad septal tracts. New vascular channels in the septae connect the vascular structures in the portal region (hepatic arteries and portal veins) and terminal hepatic veins, shunting blood around the parenchyma. Continued deposition of collagen in the space of Disse within preserved parenchyma is accompanied by the loss of fenestrations in the sinusoidal endothelial cells. In the process, the sinusoidal space comes to resemble a capillary rather than a channel for exchange of solutes between hepatocytes and plasma. In particular, hepatocellular secretion of proteins (e.g., albumin, clotting factors, lipoproteins) is greatly impaired. The net outcome is a fibrotic, nodular liver in which delivery of blood to hepatocytes is severely compromised, as is the ability of hepatocytes to secrete substances into plasma. Disruption of the interface between the parenchyma and portal tracts obliterates biliary channels as well. Acquisition of myofibers by perisinusoidal stellate cells also increases vascular resistance within the liver parenchyma, since tonic contraction of these "myofibroblasts" constricts the sinusoidal vascular channels. Throughout the process of liver damage and fibrosis, remaining hepatocytes are stimulated to regenerate and proliferate as spherical nodules within the confines of the fibrous septae.



**Fig. 6. Pathogenesis of liver cirrhosis**

(From S. Silbernagl and F. Lang; Color Atlas of Pathophysiology)



**Fig.7 Role of stellate cell activation and liver fibrosis**

Kupffer cell activation leads to secretion of multiple cytokines. Platelet-derived growth factor (PDGF) and tumor necrosis factor (TNF) activate stellate cells, and contraction of the activated stellate cells is stimulated by endothelin-1 (ET-1). Fibrosis is stimulated by transforming growth factor β (TGF-β). Chemotaxis of activated stellate cells to areas of injury is promoted by PDGF and monocyte chemotactic protein-1 (MCP-1). (From Robbins-Cotran; Pathological basis of disease).

If the chronic injury leading to scar formation is interrupted (clearance of hepatitis virus infection, cessation of alcohol use), then stellate cell activation ceases, scars condense, becoming more dense and thin, and then, due to metalloproteinases produced by hepatocytes, begin to break apart. In this way, scar formation can be reversed. If the necroses are limited to the centers of the liver lobules, full restitution of the liver’s structure is possible. However, if the necroses have broken through the peripheral parenchyma of the liver lobules, connective tissue septa are formed. As a result, full functional regeneration is no longer possible and nodules are formed.

The manifestations of cirrhosis are variable, ranging from asymptomatic hepatomegaly to hepatic failure. Often there are no symptoms until the disease is far advanced. The late manifestations of cirrhosis are related to portal hypertension and liver cell failure. Splenomegaly, ascites, and porto-systemic shunts (i.e., esophageal varices, anorectal varices, and caput medusae) result from portal hypertension.

**Portal hypertension**

Venous blood from stomach, intestines, spleen, pancreas, and gallbladder passes via the portal vein to the liver where, in the sinusoids after mixture with oxygen-rich blood of the hepatic artery, it comes into close contact with the hepatocytes. About 15% of cardiac output flows through the liver, yet its resistance to flow is so low that the normal portal vein pressure is only 4 - 8 mmHg. If the cross-sectional area of the liver’s vascular bed is restricted, portal vein pressure rises and portal hypertension develops.

*Portal hypertension* is characterized by increased resistance to flow in the portal venous system and sustained portal vein pressure above 12 mm Hg.

Portal hypertension can be caused by a variety of conditions that increase resistance to hepatic blood flow, including prehepatic, posthepatic, and intrahepatic obstructions (with hepatic referring to the liver lobules rather than the entire liver) (Fig.8).

*Prehepatic causes* of portal hypertension include portal vein thrombosis and external compression due to cancer or enlarged lymph nodes that produce obstruction of the portal vein before it enters the liver.

*Intrahepatic causes of portal hypertension* include conditions that cause obstruction of blood flow within the liver. In alcoholic cirrhosis, which is the major cause of portal hypertension, bands of fibrous tissue and fibrous nodules distort the architecture of the liver and increase the resistance to portal blood flow, which leads to portal hypertension. Far less frequent intrahepatic causes are schistosomiasis, massive fatty change, diffuse fibrosing granulomatous disease such as sarcoidosis, and diseases affecting the portal microcirculation such as nodular regenerative hyperplasia.

*Posthepatic obstruction* refers to any obstruction to blood flow through the hepatic veins beyond the liver lobules, either within or distal to the liver. It is caused by conditions such as thrombosis of the hepatic veins, veno-occlusive disease, and severe right-sided heart failure that impede the outflow of venous blood from the liver. *Budd-Chiari syndrome* refers to congestive disease of the liver caused by occlusion of the portal veins and their tributaries. The principal cause of the Budd-Chiari syndrome is thrombosis of the hepatic veins, in association with diverse conditions such as polycythemia vera, hypercoagulability states associated with malignant tumors, pregnancy, bacterial infection, metastatic disease of the liver, and trauma.

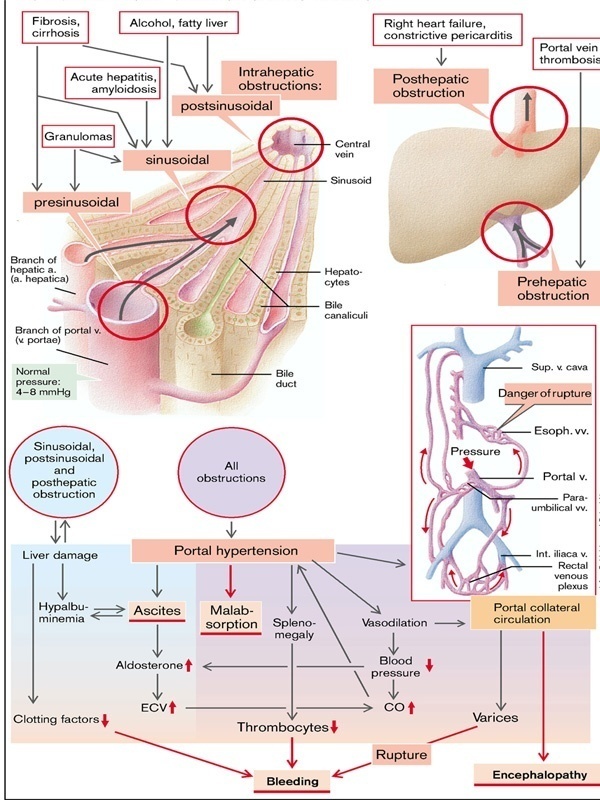
Pathophysiology of portal hypertension is complex and involves resistance to portal flow at the level of sinusoids and an increase in portal flow caused by hyperdynamic circulation. The increased resistance to portal flow at the level of the sinusoids is caused by contraction of vascular smooth muscle cells and myofibroblasts, and disruption of blood flow by scarring and the formation of parenchymal nodules. Alterations in sinusoidal endothelial cells that contribute to the intrahepatic vasoconstriction associated with portal hypertension include a decrease in nitric oxide production, and increased release of endothelin-1 (ET-1), angiotensinogen, and eicosanoids. Sinusoidal remodeling and anastomosis between the arterial and portal system in the fibrous septa contribute to portal hypertension by imposing arterial pressures on the low pressure portal venous system. Sinusoidal remodeling and intrahepatic shunts also interfere with the metabolic exchange between sinusoidal blood and hepatocytes.

Another major factor in the development of portal hypertension is an increase in portal venous blood flow resulting from a hyperdynamic circulation. This is caused by arterial vasodilation, primarily in the splanchnic circulation. The increased splanchnic arterial blood flow in turn leads to increased venous efflux into the portal venous system. While various mediators such as prostacyclin and TNF have been implicated in the causation of the splanchnic arterial vasodilation, NO has emerged as the most significant one.

Wherever the site of obstruction, an increased portal vein pressure will lead to disorders in the preceding organs (malabsorption, splenomegaly with anemia and thrombocytopenia) as well as to blood flowing from abdominal organs via vascular channels that bypass the liver. These portal bypass circuits use collateral vessels that are normally thin-walled but are now greatly dilated (formation of varices; “haemorrhoids” of the rectal venous plexus; caput medusae at the paraumbilical veins). The enlarged esophageal veins are particularly in danger of rupturing. This fact, especially together with thrombocytopenia and a deficiency in clotting factors (reduced synthesis in a damaged liver), can lead to massive bleeding that can be acutely life-threatening. The vasodilators liberated in portal hypertension (glucagon, VIP, substance P, prostacyclins, NO, etc.) also lead to a fall in systemic blood pressure. This will cause a compensatory rise in cardiac output, resulting in hyperperfusion of the abdominal organs and the collateral (bypass) circuits.

Liver function is usually unimpaired in prehepatic and presinusoidal obstruction, because blood supply is assured through a compensatory increase in flow from the hepatic artery. Still, in sinusoidal, postsinusoidal, and posthepatic obstruction liver damage is usually the cause and then in part also the result of the obstruction. As a consequence, drainage of protein-rich hepatic lymph is impaired and the increased portal pressure, sometimes in synergy with a reduction in the plasma’s osmotic pressure due to liver damage (hypoalbuminemia), pushes a protein-rich fluid into the abdominal cavity, i.e., ascites develops. This causes secondary hyperaldosteronism that results in an increase in extracellular volume.

As blood from the intestine bypasses the liver, toxic substances (NH3, biogenic amines, short-chain fatty acids, etc.) that are normally extracted from portal blood by the liver cells reach the central nervous system, among other organs, so that portal-systemic (“hepatic”) encephalopathy develops. Finally, portal hypertension can cause an exudative enteropathy. This will increase the ascites due to loss of albumin from the plasma, while at the same time favoring bacteria in the large intestine being “fed” with proteins that have passed into the intestinal lumen, and thus increasing the liberation of ammonium, which is toxic to the brain.



**Fig. 8 Causes and consequences in portal hypertension**

(From S. Silbernagl and F. Lang; Color Atlas of Pathophysiology)

**Portopulmonary hypertension**refers to pulmonary arterial hypertension arising in liver disease and portal hypertension. Poorly understood, it seems to depend on concomitant portal hypertension and excessive pulmonary vasoconstriction and vascular remodeling. The most common clinical manifestations are dyspnea on exertion and clubbing of the fingers.

**Ascites.** Ascites occurs when the amount of fluid in the peritoneal cavity is increased, and is a late-stage manifestation of cirrhosis and portal hypertension. It is not uncommon for persons with advanced cirrhosis to present with an accumulation of 15 L or more of ascitic fluid. In 85% of cases, ascites is caused by cirrhosis. Ascites usually becomes clinically detectable when at least 500 mL have accumulated. The fluid is generally serous, having less than 3 gm/dL of protein (largely albumin), and a serum to ascites albumin gradient of ≥1.1 gm/dL. The fluid may contain a scant number of mesothelial cells and mononuclear leukocytes. Influx of neutrophilssuggests infection, whereas the presence of blood cells points to possible disseminated intra-abdominal cancer. With long-standing ascites, seepage of peritoneal fluid through trans-diaphragmatic lymphatics may produce hydrothorax, more often on the right side.Those who gain this much fluid often experience abdominal discomfort, dyspnea, and insomnia. Some persons may have difficulty walking or living independently.

Although the mechanisms responsible for the development of ascites are not completely understood, several factors seem to contribute to fluid accumulation, including an increase in hydrostatic capillary pressure due to portal hypertension and obstruction of venous flow through the liver (hydrostatic mechanism), salt and water retention by the kidney (osmotic mechanism), decreased oncotic pressure due to impaired synthesis of albumin by the liver (hypooncotic mechanisms), impairment of lymphatic drainage (lymphostatic mechanism) and direct increased permeability of vessel walls (membranogenous mechanism) .

Diminished blood volume (*underfill theory*) and excessive blood volume *(overfill theory*) have been used to explain the increased salt and water retention by the kidney. According to the *underfill theory*, a contraction in the effective blood volume constitutes an afferent signal that causes the kidney to retain salt and water. The effective blood volume may be reduced because of loss of fluid into the peritoneal cavity as well as edema or because of vasodilatation caused by the presence of circulating vasodilating substances. Arterial vasodilation in the splanchnic circulation tends to reduce arterial blood pressure. With worsening of the vasodilation, the heart rate and cardiac output are unable to maintain the blood pressure. This triggers the activation of vasoconstrictors, including the renin-angiotensin system, and also increases the secretion of antidiuretic hormone. The combination of portal hypertension, vasodilation, and sodium and water retention increases the perfusion pressure of interstitial capillaries, causing extravasation of fluid into the abdominal cavity. The *overfill theory* proposes that the initial event in the development of ascites is renal retention of salt and water caused by disturbances in the liver itself. These disturbances include failure of the liver to metabolize aldosterone, causing an increase in salt and water retention by the kidney (secondary hyperaldosteronism).

Another mechanism in ascites development is the lymphatic one due to percolation of hepatic lymph into the peritoneal cavity. Normal thoracic duct lymph flow approximates 800 to 1000mL/day. With cirrhosis, hepatic lymphatic flow may approach 20 L/day, exceeding thoracic duct capacity. Hepatic lymph is rich in proteins and low in triglycerides, which explains the presence of protein in the ascitic fluid.

*Spontaneous bacterial peritonitis* is a complication in persons with both cirrhosis and ascites. The infection is serious and carries a high mortality rate even when treated with antibiotics. Presumably, the peritoneal fluid is seeded with bacteria from the blood or lymph or from passage of bacteria through the bowel wall. Symptoms include fever and abdominal pain. Other symptoms include worsening of hepatic encephalopathy, diarrhea, hypothermia, and shock. It is diagnosed by a neutrophil count of 250 cells/ mm3 or higher and a protein concentration of 1 g/dL or less in the ascitic fluid.

*Splenomegaly*. The spleen enlarges progressively in portal hypertension because of shunting of blood into the splenic vein. The degree of splenic enlargement varies widely and may reach as much as 1000 gm, but it is not necessarily correlated with other features of portal hypertension. The enlarged spleen often gives rise to sequestering of significant numbers of blood elements and development of a syndrome known as *hypersplenism*. Hypersplenism is characterized by a decrease in the life span and a subsequent decrease in all the formed elements of the blood, leading to anemia, thrombocytopenia, and leukopenia. The decreased life span of the blood elements is thought to result from an increased rate of removal because of the prolonged transit time through the enlarged spleen.

*Portosystemic shunts*. With the gradual obstruction of venous blood flow in the liver, the pressure in the portal vein increases, and large collateral channels develop between the portal and systemic veins that supply the lower rectum and esophagus and the umbilical veins of the falciform ligament that attaches to the anterior wall of the abdomen. The collaterals between the inferior and internal iliac veins may give rise to hemorrhoids. In some persons, the fetal umbilical vein is not totally obliterated; it forms a channel on the anterior abdominal wall. Dilated veins around the umbilicus are called *caput medusae*. Portopulmonary shunts also may develop and cause blood to bypass the pulmonary capillaries, interfering with blood oxygenation and producing cyanosis. Clinically, the most important collateral channels are those connecting the portal and coronary veins that lead to reversal of flow and formation of thin-walled varicosities in the submucosa of the esophagus. These thin walled esophageal varices are subject to rupture, producing massive and sometimes fatal hemorrhage. Impaired hepatic synthesis of coagulation factors and decreased platelet levels (thrombocytopenia) due to splenomegaly may further complicate the control of esophageal bleeding. Esophageal varices develop in approximately 65% of persons with advanced cirrhosis and cause massive hemorrhage and death in approximately half of them. Each episode of bleeding is associated with a 30% mortality.

**Disorders of bilirubin elimination**

**Jaundice and cholestasis**

** **Bile secretion and composition.** Bile formed in the hepatic lobules is secreted into a complex network of canaliculi, small bile ductules, and larger bile ducts that run with lymphatics and branches of the portal vein and hepatic artery in portal tracts situated between hepatic lobules. These interlobular bile ducts coalesce to form larger septal bile ducts that join to form the right and left hepatic ducts, which in turn, unite to form the common hepatic duct. The common hepatic duct is joined by the cystic duct of the gallbladder to form the common bile duct (CBD), which enters the duodenum (often after joining the main pancreatic duct) through the ampulla of Vater.Hepatic bile is an isotonic fluid with an electrolyte composition resembling blood plasma. The electrolyte composition of gallbladder bile differs from that of hepatic bile because most of the inorganic anions, chloride and bicarbonate, have been removed by reabsorption across the gallbladder epithelium. As a result of water reabsorption, total solute concentration of bile increases from 3–4 g/dL in hepatic bile to 10–15 g/dL in gallbladder bile.Major solute components of bile by moles percent include *bile acids* (80%), *lecithin* and traces of other phospholipids (16%), and *unesterified cholesterol* (4.0%). In the lithogenic state, the cholesterol value can be as high as 8–10%. Other constituents include *conjugated bilirubin*; proteins (all immunoglobulins, albumin, metabolites of hormones, and other proteins metabolized in the liver); electrolytes; mucus; and, often, drugs and their metabolites.

The total daily basal secretion of hepatic bile is 500–600 mL. Many substances taken up or synthesized by the hepatocyte are secreted into the bile canaliculi. The canalicular membrane forms microvilli and is associated with microfilaments of actin, microtubules, and other contractile elements. Prior to their secretion into the bile, many substances are taken up into the hepatocyte, while others, such as phospholipids, a portion of primary bile acids, and some cholesterol are synthesized de novo in the hepatocyte. Three mechanisms are important in regulating bile flow: (1) active transport of bile acids from hepatocytes into the bile canaliculi, (2) active transport of other organic anions, and (3) cholangiocellular secretion. The last is a secretin-mediated and cyclic AMP–dependent mechanism that results in the secretion of a sodium- and bicarbonate-rich fluid into the bile ducts.

*The bile acids.*The primary bile acids, *cholic* *acid* and *chenodeoxycholic acid* (CDCA), are synthesized from cholesterol in the liver, conjugated with glycine or taurine, and secreted into the bile. Secondary bile acids, including *deoxycholate* and *lithocholate,* are formed in the colon as bacterial metabolites of the primary bile acids. However, lithocholic acid is much less efficiently absorbed from the colon than deoxycholic acid. Another secondary bile acid, found in low concentration, is *ursodeoxycholic acid* (UDCA), a stereoisomer of CDCA. In healthy subjects, the ratio of glycine to taurine conjugates in bile is 3:1. Bile acids are detergent-like molecules that in aqueous solutions and above a critical concentration of about 2 mM form molecular aggregates called *micelles*. Cholesterol alone is sparingly soluble in aqueous environments, and its solubility in bile depends on both the total lipid concentration and the relative molar percentages of bile acids and lecithin. Normal ratios of these constituents favor the formation of solubilizing mixed micelles, while abnormal ratios promote the precipitation of cholesterol crystals in bile via an intermediate liquid crystal phase. In addition to facilitating the biliary excretion of cholesterol, bile acids facilitate the normal intestinal absorption of dietary fats, mainly cholesterol and fat-soluble vitamins, via a micellar transport mechanism. Bile acids also serve as a major physiologic driving force for hepatic bile flow and aid in water and electrolyte transport in the small bowel and colon.

*Enterohepatic circulation*.Bile acids are efficiently conserved under normal conditions. Unconjugated, and to a lesser degree also conjugated, bile acids are absorbed by passive diffusion along the entire gut. Quantitatively much more important for bile salt recirculation, however, is the active transport mechanism for conjugated bile acids in the distal ileum. Conjugated bile salts are reabsorbed from the terminal ileum by the Na+ symport carrier *ISBT* (= ***i****leal* ***s****odium* ***b****ile acid co****t****ransporter*). The reabsorbed bile acids enter the portal bloodstream and are taken up rapidly by hepatocytes, reconjugated, and resecreted into bile (enterohepatic circulation). The normal bile acid pool size is approximately 2–4 g. During digestion of a meal, the bile acid pool undergoes at least one or more enterohepatic cycles, depending on the size and composition of the meal. Normally, the bile acid pool circulates 5–10 times daily. Intestinal absorption of the pool is about 95% efficient; therefore, fecal loss of bile acids is in the range of 0.2–0.4 g/d. In the steady state, this fecal loss is compensated by an equal daily synthesis of bile acids by the liver, and, thus, the size of the bile acid pool is maintained. Bile acids returning to the liver suppress de novo hepatic synthesis of primary bile acids from cholesterol by inhibiting the rate-limiting enzyme cholesterol 7-hydroxylase. While the loss of bile salts in stool is usually matched by increased hepatic synthesis, the maximum rate of synthesis is 5 g/d, which may be insufficient to replete the bile acid pool size when there is pronounced impairment of intestinal bile salt reabsorption.

*Gallbladder.* When the sphincter of Oddi between the common bile duct and duodenum is closed, *hepatic bile* (*C bile*) is diverted to the gallbladder, where it is concentrated (1:10) and stored. The gallbladder epithelium reabsorbs Na+, Cl– and water from the stored bile, thereby greatly raising the concentration of specific bile components (bile salts, bilirubin-diglucuronide, cholesterol, phosphatidylcholine, etc.). If bile is used for fat digestion (or if a peristaltic wave occurs in the interdigestive phase), the gallbladder contracts and its contents are mixed in portions with the duodenal chyme. Cholesterol in the bile is transported inside micelles formed by aggregation of cholesterol with lecithin and bile salts. A change in the ratio of these threesubstances in favor of cholesterol leads to theprecipitation of cholesterol crystals responsible forgallstone development in the highly concentratedgallbladder bile (B bile). Gallbladder contraction is triggered by CCK, which binds to CCKA receptors, and the neuronal plexus of the gallbladder wall, which is innervated by preganglionic parasympathetic fibers of the vagus nerve. CGRP and substance P released by sensory fibers appear to stimulate the gallbladder musculature indirectly by increasing acetylcholine release. The sympathetic nervous system inhibits gallbladder contractions via α2 adrenoreceptors located on cholinergic fiber terminals. As *cholagogues*, fatty acids and products of protein digestion as well as egg yolk and MgSO4 effectively stimulate CCK secretion.

*Excretory liver function of the liver.*The liver detoxifies and excretes many mostly lipophilic substances, which are either generated during metabolism (bilirubin or steroid hormones) or come from the intestinaltract (the antibiotic chloramphenicol).However, this requires prior biotransformation of the substances. In the first step of the process, reactive OH, NH2 or COOH groups are enzymatically added (by monooxygenases)to the hydrophobic substances. In the second step, the substances are conjugated with glucuronic acid, acetate, glutathione, glycine, sulfates, etc. The conjugates are now water-soluble and can be either further processed in the kidneys and excreted in the urine, or secreted into bile by liver cells and excreted in the feces. Glutathione conjugates, for example, are further processed in the kidney excreted as mercapturic acids in the urine.

*Carriers.*The canalicular membrane of hepatocytes contains various carriers, most of which are direct fueled by ATP. The principal carriers are: *MDR1* (multidrug resistance protein 1) for relatively hydrophobic, mainly cationic metabolites, *MDR3* for phosphatidylcholine, and *cMOAT*(canalicular multispecific organic anion transporter = *multidrug resistance protein MRP2*) for conjugates (formed with glutathione, glucuronic acid or sulfate) and many other organic anions.

*Production and metabolism of bilirubin***.** Bilirubin, a tetrapyrrole pigment, is a breakdown product of heme (ferroprotoporphyrin IX). About 70–80% of the 250–300 mg of bilirubin produced each day is derived from the breakdown of hemoglobin in senescent red blood cells. The remainder comes from prematurely destroyed erythroid cells in bone marrow and from the turnover of hemoproteins such as myoglobin and cytochromes found in tissues throughout the body.

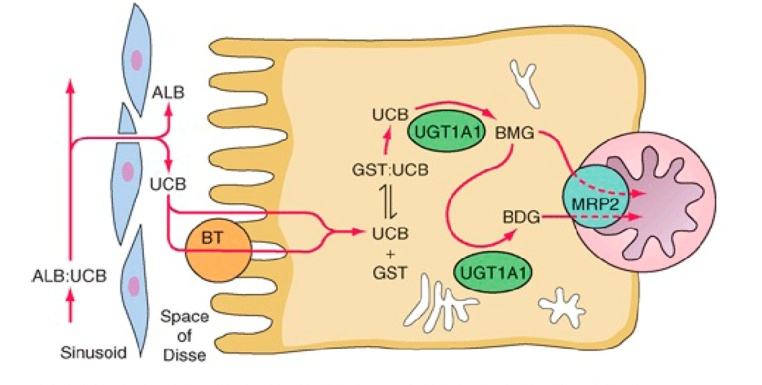
The formation of bilirubin occurs in reticuloendothelial cells, primarily in the spleen and liver.Each gram of hemoglobin yields ca. 35 mg of bilirubin. The first reaction, catalyzed by the microsomal enzyme *heme oxygenase*, oxidatively cleaves the bridge of the porphyrin group and opens the heme ring. The end products of this reaction are *biliverdin,* carbon monoxide, and iron. The second reaction, catalyzed by the cytosolic enzyme *biliverdin reductase*, reduces the central methylene bridge of biliverdin and converts it to *bilirubin.* Bilirubin formed in the reticuloendothelial cells is virtually insoluble in water. This is due to tight internal hydrogen bonding between the water-soluble moieties of bilirubin, proprionic acid carboxyl groups of one dipyrrolic half of the molecule with the imino and lactam groups of the opposite half. This configuration blocks solvent access to the polar residues of bilirubin and places the hydrophobic residues on the outside. Free unconjugated bilirubin (*“indirect” bilirubin*) is poorly soluble in water, yet lipid-solubleand toxic. To be transported in blood, bilirubin must be solubilized. This is accomplished by its reversible, non-covalent binding to albumin (2 molbilirubin : 1 mol albumin). Unconjugated bilirubin bound to albumin is transported to the liver, where it, but not the albumin, is taken up by hepatocytes via a process that at least partly involves carrier-mediated membrane transport. Transfer of bilirubin from blood to bile involves four distinct but interrelated steps:

*Hepatocellular uptake*: Uptake of bilirubin by the hepatocyte has carrier-mediated kinetics. Although a number of candidate bilirubin transporters have been proposed, the actual transporter remains elusive.

*Intracellular binding*: After entering the hepatocyte, unconjugated bilirubin is bound in the cytosol to a number of proteins including proteins in the glutathione-S-transferase superfamily formerly called *ligandins*. These proteins serve both to reduce efflux of bilirubin back into the serum and to present the bilirubin for conjugation.

*Conjugation*: In the endoplasmic reticulum, bilirubin is conjugated with one or two glucuronic acid moieties by a specific *UDP-glucuronosyltransferase* to form bilirubin mono- and diglucuronide, respectively. Conjugation disrupts the internal hydrogen bonding that limits aqueous solubility of bilirubin, and the resulting glucuronide conjugates are highly soluble in water. Conjugation is obligatory for excretion of bilirubin across the bile canalicular membrane into bile. The UDP-glucuronosyltransferases have been classified into gene families based on the degree of homology among the mRNAs for the various isoforms. Those that conjugate bilirubin and certain other substrates have been designated the UGT1 family.

*Biliary excretion*: Bilirubin mono- and diglucuronides are excreted across the canalicular plasma membrane into the bile canaliculus by an ATP-dependent transport process mediated by a canalicular membrane protein called *multidrug resistance–associated protein 2 (MRP2)*. Mutations of MRP2 result in the Dubin-Johnson syndrome (see below).



**Hepatocellular bilirubin transport**

Albumin-bound bilirubin in sinusoidal blood passes through endothelial cell fenestrae to reach the hepatocyte surface, entering the cell by both facilitated and simple diffusional processes. Within the cell it is bound to glutathione-S-transferases and conjugated by bilirubin-UDP-glucuronosyltransferase (*UGT1A1*) to mono - and diglucuronides, which are actively transported across the canalicular membrane into the bile. ALB, albumin; BDG, bilirubin diglucuronide; BMG, bilirubin monoglucuronide; BT, proposed bilirubin transporter; GST, glutathione-S-transferase; MRP2, multidrug resistance–associated protein 2; UCB, unconjugated bilirubin; UGT1A1, bilirubin-UDP-glucuronosyltransferase. (From Harrison's Principles of Internal Medicine, 18th Edition)

*Bilirubin in the gut.* The conjugated bilirubin excreted into bile drains into the duodenum and passes unchanged through the proximal small bowel. Conjugated bilirubin is not taken up by the intestinal mucosa. When the conjugated bilirubin reaches the distal ileum and colon, it is hydrolyzed to unconjugated bilirubin by bacterial glucuronidases. The unconjugated bilirubin is reduced by normal gut bacteria to form a group of colorless tetrapyrroles called *urobilinogens.* About 80–90% of these products in the gut, is converted by bacteria into the colorless compound*, stercobilinogen.* The remaining 10–20% of the urobilinogens are passively absorbed, enter the portal venous blood, and are reexcreted by the liver. A small fraction (usually <3 mg/dL; 5%) escapes hepatic uptake, filters across the renal glomerulus, and is excreted in urine as *urobilin*. Further, stercobilinogen at the level of large intestine is partly oxidized into *stercobilin*, the brown compound that colors the stools. A small portion (ca. 1%) reaches the systemic circulation via hemorrhoidal vena and is excreted by the kidneys as stercobilinogen and stercobilin. The renal excretion rate increases when the liver is damaged.

Unconjugated bilirubin ordinarily does not reach the gut except in neonates or, by ill-defined alternative pathways, in the presence of severe unconjugated hyperbilirubinemia [e.g., Crigler-Najjar syndrome, type I (CN-I)]. Unconjugated bilirubin that reaches the gut is partly reabsorbed, amplifying any underlying hyperbilirubinemia. Recent reports suggest that oral administration of calcium phosphate with or without the lipase inhibitor orlistat may be an efficient means to interrupt bilirubin enterohepatic cycling to reduce serum bilirubin levels in this situation. Although orlistat administration for 4–6 weeks to 16 patients with Crigler-Najjar syndrome was associated with a 10-20% decrease in serum bilirubin in 7 patients, the cost and side effects (diarrhea) may obviate the small benefit achievable with this treatment.

*Renal excretion of bilirubin conjugates.* Unconjugated bilirubin is not excreted in urine, as it is too tightly bound to albumin for effective glomerular filtration and there is no tubular mechanism for its renal secretion. In contrast, conjugated bilirubin is readily filtered at the glomerulus and can appear in urine in disorders characterized by increased bilirubin conjugates in the circulation. In healthy state, in the urine can be found the summary fraction of urobilin (derivate of urobilinogen) and stercobilin (derivate of stercobilinogen) known as *urobilinoid bodies.*

Only a small amount of bilirubin is found in the blood; the normal level of total serum bilirubin is 0.1 to1.2 mg/dL. Laboratory measurements of bilirubin usually measure the free (indirect or unconjugated bilirubin) and the conjugated bilirubin (direct) as well as the total bilirubin.

# **Cholestasis**

*Cholestasis* represents a decrease in bile flow through the intrahepatic canaliculi and a reduced secretion of water, bilirubin, and bile acids by the hepatocytes. As a result, the materials normally transferred to the bile, including bilirubin, cholesterol, and bile acids, accumulate in the blood a condition known as *cholemia*.

The condition may be caused by intrinsic liver disease, in which case it is referred to as *intrahepatic cholestasis,* or by obstruction of the large bile ducts, a condition known as *extrahepatic cholestasis.* A number of mechanisms are implicated in the pathogenesis of cholestasis. Primary biliary cirrhosis and primary sclerosing cholangitis are caused by disorders of the small intrahepatic canaliculi and bile ducts lead to intrahepatic cholestasis. Genetic disorders involving the transport of bile into the canaliculi also can result in intrahepatic cholestasis.

Common to all types of obstructive and hepatocellular cholestasis is the accumulation of bile pigment in the liver. Elongated green-brown plugs of bile are visible in the dilated bile canaliculi. Rupture of the canaliculi leads to extravasation of bile and subsequent degenerative changes in the surrounding hepatocytes. As result of intrahepatic cholestasis concentration of biliary acids in hepatic cell is increased, mainly chenodeoxycholic acid that will cause changes of hepatocyte membrane and its injury, as well as inhibition of cholesterol-hidroxilase – an enzyme responsible for synthesis of biliary acids. The final result is reduced synthesis of biliary acids with all characteristic consequences. In the case of extrahepatic obstruction, such as that caused by conditions such as cholelithiasis, common duct strictures, or obstructing neoplasms, the effects begin with increased pressure in the large bile ducts.

In cholestasis the bile canaliculi are enlarged, the *fluidity* of the canalicular cell membrane is decreased (cholesterol embedding, bile salt effect), their brush border is deformed (or totally absent) and the function of the cytoskeleton, including *canalicular motility*, is disrupted. Retained bile salts increase the permeability of the tight junctions and reduce mitochondrial ATP synthesis. Prolonged obstructive cholestasis leads not only to fatty changes in the hepatocytes but also to destruction of the supporting connective tissue, giving rise to bile lakes filled with cellular debris and pigment.

Most of the consequences of cholestasis are a result of retention of bile components: bilirubin leads to jaundice (in neonates there is a danger of kernicterus). Skin xanthomas (focal accumulations of cholesterol) may occur, the result of hyperlipidemia and impaired excretion of cholesterol. Pruritus is the most common presenting symptom in persons with cholestasis, probably related to an elevation in plasma bile acids, as well as can be the effects of retained endorphins. The absence of bile in the intestine results in fatty stools (steatorrhea) and malabsorption (also malabsorbtion of fat soluble vitamins). Finally, infection of accumulated bile leads to cholangitis, which has its own cholestatic effect. A characteristic laboratory finding is an elevated level of serum *alkaline phosphatase*. Alkaline phosphatase is produced by the bile duct epithelium and canalicular membranes of hepatocytes and is excreted with the bile; when bile flow is obstructed, the blood alkaline phosphatase level becomes elevated.

# *Cholemia*is a complex syndrome determined by presence of bile in the blood. Is characterized by increase concentration of all bile components in the blood: biliary acids, conjugated bilirubin, cholesterol, phospholipids etc…

# Biliary acids acting on the centre of vagal nerve as well as at the level of sinoatrial node, lead to reduction of impulses in sinoatrial node with bradycardia, reduction of cardiac output and collapse (reduced blood pressure). Biliary acids excite nervous ending of the skin with pruritus. Biliary acids can bind Ca+ ions and lead to coagulation disorders.

# *Acolia* represent a pathological state characterized by blockage of bile secretion in the duodenum. Usually is characteristic for obstruction or compression of biliary ducts. Is characterized by disorders of fat emulsification, break-down and absorbtion of lipids in the intestine and development of maldigestion, malabsorbtion syndrome accompanied by fatty stool (steatorrhea). In acholia there are disorders of liposoluble vitamins absorbtion, mainly vitamin K, consequently leading to decreased synthesis of clotting factors and hypocoagulation of the blood.

**Pathophysiology of jaundice**

# The normal plasma concentration of bilirubin is maximally 17 μmol/L (1 mg/dL). *Jaundice* (icterus) results from an abnormally high accumulation of bilirubin in the blood, as a result of which there is a yellowish discoloration to the skin and deep tissues. Jaundice becomes evident when the serum bilirubin levels rise above 2.0 to 2.5 mg/dL; levels as high as 30 to 40 mg/dL can occur with severe disease. If it rises to more than 30 μmol/L, the sclera become yellow; if the concentration rises further, the skin turns yellow as well. Because normal skin has a yellow cast, the early signs of jaundice often are difficult to detect, especially in persons with dark skin. Bilirubin has a special affinity for elastic tissue. The sclera of the eye, which contains considerable elastic fibers, usually is one of the first structures in which jaundice can be detected.

# Yellow discoloration of the skin can occur as well as result of overconsumption of some vegetables like carrots, pumpkin, and administration of some drugs. In these situations we speak about *false jaundice*.

Serum bilirubin levels in the normal adult vary between 0.3 and 1.2 mg/dL, and the rate of systemic bilirubin production is equal to the rates of hepatic uptake, conjugation, and biliary excretion. Both unconjugated bilirubin and conjugated bilirubin (bilirubin glucuronides) may accumulate systemically. There are two important pathophysiologic differences between the two forms of bilirubin. *Unconjugated bilirubin* (free bilirubin) is virtually insoluble in water at physiologic pH and exists in tight complexes with serum albumins, is very toxic and can cross the hematoencephalic barrier. This form cannot be excreted in the urine even when blood levels are high. Normally, a very small amount of unconjugated bilirubin is present as an albumin-free anion in plasma. This fraction of unbound bilirubin may diffuse into tissues, particularly the brain in infants, and produce toxic injury. The unbound plasma fraction may increase in severe hemolytic disease or when protein-binding drugs displace bilirubin from albumin. Hence, *hemolytic disease of the newborn (erythroblastosis fetalis)* may lead to accumulation of unconjugated bilirubin in the brain, which can cause severe neurologic damage, referred to as *kernicterus.* In contrast, *conjugated bilirubin* (direct bilirubin) is water-soluble, nontoxic, can’t cross the hematoencephalic barrier and only loosely bound to albumin. Because of its solubility and weak association with albumin*,* excess conjugated bilirubin in plasma can be excreted in urine. With prolonged conjugated hyperbilirubinemia, a portion of circulating pigment may become covalently bound to albumin; this is termed the *bilirubin delta* fraction.

Jaundice occurs when the equilibrium between bilirubin production and clearance is disturbed by one or more of the following mechanisms:

1. excessive extrahepatic production of bilirubin;
2. reduced hepatocyte uptake*;*
3. impaired conjugation;
4. decreased hepatocellular excretion;
5. impaired bile flow.

The first three mechanisms produce *unconjugated hyperbilirubinemia*, and the latter two produce predominantly *conjugated hyperbilirubinemia*. Although more than one mechanism may be operative, generally one mechanism predominates, so knowledge of the major form of plasma bilirubin is of value in evaluating possible mechanisms of development.

**Causes of jaundice**

(From Robbins-Cotran; Pathological basis of disease)

|  |  |
| --- | --- |
| **PREDOMINANTLY UNCONJUGATED HYPERBILIRUBINEMIA** | |
| **Excess production of bilirubin**   * Hemolytic anemias * Resorption of blood from internal hemorrhage (e.g., alimentary tract bleeding, hematomas) * Ineffective erythropoiesis (e.g., pernicious anemia, thalassemia) | |
| **Reduced hepatic uptake**   * Drug interference with membrane carrier systems * Some cases of Gilbert syndrome | |
| **Impaired bilirubin conjugation**  Physiologic jaundice of the newborn (decreased UGT1A1 activity, decreased excretion)  Breast milk jaundice (β-glucuronidases in milk)  Genetic deficiency of UGT1A1 activity (Crigler-Najjar syndrome types I and II)  Gilbert syndrome  Diffuse hepatocellular disease (e.g., viral or drug-induced hepatitis, cirrhosis**)** | |
|  |  |
| **PREDOMINANTLY CONJUGATED HYPERBILIRUBINEMIA** | |
| Deficiency of canalicular membrane transporters (Dubin-Johnson syndrome, Rotor syndrome)  Impaired bile flow | |

UGT, uridine diphosphate-glucuronyltransferase

**Neonatal jaundice**

Bilirubin produced by the fetus is cleared by the placenta and eliminated by the maternal liver. Immediately after birth, the neonatal liver must assume responsibility for bilirubin clearance and excretion. However, many hepatic physiologic processes are incompletely developed at birth. Levels of UGT1A1 are low, and alternative excretory pathways allow passage of unconjugated bilirubin into the gut. Since the intestinal flora that convert bilirubin to urobilinogen are also undeveloped, an enterohepatic circulation of unconjugated bilirubin ensues. As a consequence, most neonates develop mild unconjugated hyperbilirubinemia between days 2 and 5 after birth. Peak levels are typically <85–170 mol/L (5–10 mg/dL) and decline to normal adult concentrations within 2 weeks, as mechanisms required for bilirubin disposition mature. Prematurity, often associated with more profound immaturity of hepatic function and hemolysis, can result in higher levels of unconjugated hyperbilirubinemia. A rapidly rising unconjugated bilirubin concentration, or absolute levels >340 mol/L (20 mg/dL), puts the infant at risk for bilirubin encephalopathy, or *kernicterus*. Under these circumstances, bilirubin crosses an immature blood-brain barrier and precipitates in the basal ganglia and other areas of the brain. The consequences range from appreciable neurologic deficits to death. Treatment options include phototherapy, which converts bilirubin into water-soluble photoisomers that are excreted directly into bile, and exchange transfusion. The canalicular mechanisms responsible for bilirubin excretion are also immature at birth, and their maturation may lag behind that of UGT1A1; this can lead to transient conjugated neonatal hyperbilirubinemia, especially in infants with hemolysis.

**Hereditary hyperbilirubinemias**

Multiple genetic mutations can cause hereditary hyperbilirubinemia.

In *Crigler-Najjar syndrome type I* hepatic UGT1A1 is completely absent, and the colorless bile contains only trace amounts of unconjugated bilirubin. The liver is morphologically normal by light and electron microscopy. However, serum unconjugated bilirubin reaches very high levels, producing severe jaundice and icterus. Without liver transplantation, this condition is invariably fatal, causing death secondary to kernicterus within 18 months of birth. *Crigler-Najjar syndrome type II* is a less severe, nonfatal disorder in which UGT1A1 enzyme activity is greatly reduced, and the enzyme is capable of forming only monoglucuronidated bilirubin. Unlike Crigler-Najjar syndrome type I, the only major consequence is extraordinarily yellow skin. Phenobarbital treatment can improve bilirubin glucuronidation by inducing hypertrophy of the hepatocellular endoplasmic reticulum.

*Gilbert syndrome* is a relatively common, benign, inherited condition presenting with mild, fluctuating hyperbilirubinemia, in the absence of hemolysis or liver disease. In Gilbert syndrome, hepatic bilirubin-glucuronidating activity is about 30% of normal, a less severe reduction than in Crigler-Najjar syndromes. It is caused in most patients by the homozygous insertion of two extra bases in the 5′ promoter region of the *UGT1* gene, leading to reduced transcription. The mild hyperbilirubinemia may go undiscovered for years and is not associated with functional derangements. When detected in adolescence or adult life it is typically in association with stress, such as an intercurrent illness, strenuous exercise, or fasting. Gilbert syndrome itself has no clinical consequence except for the anxiety that a jaundiced sufferer might justifiably experience with this otherwise innocuous condition. However, individuals who have Gilbert syndrome may be more susceptible to adverse effects of drugs that are metabolized by UGT1A1.

*Dubin-Johnson syndrome* is an autosomal recessive disorder characterized by chronic conjugated hyperbilirubinemia. It is caused by a defect in hepatocellular excretion of bilirubin glucuronides across the canalicular membrane. The molecular basis for this syndrome is absence of the canalicular protein, *multidrug resistance protein 2*, which is responsible for transport of bilirubin glucuronides and related organic anions into bile. The liver is darkly pigmented because of coarse pigmented granules within the cytoplasm of hepatocytes. Electron microscopy reveals that the pigment is located in lysosomes: it appears to be composed of polymers of epinephrine metabolites. The liver is otherwise normal. Apart from chronic or recurrent jaundice of fluctuating intensity, most patients are asymptomatic and have a normal life expectancy.

*Rotor syndrome* is a rare form of asymptomatic conjugated hyperbilirubinemia associated with multiple defects in hepatocellular uptake and excretion of bilirubin pigments. The precise molecular basis for this syndrome is unknown. The liver is morphologically normal. As with Dubin-Johnson syndrome, patients with Rotor syndrome have jaundice but otherwise have normal lives.

**Hereditary hyperbilirubinemias**

(From Robbins-Cotran; Pathological basis of disease)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Disorder** | **Inheritance** | **Defects in Bilirubin Metabolism** | **Liver Pathology** | **Clinical Course** |
| **UNCONJUGATED HYPERBILIRUBINEMIA** | | | | |
| **Crigler-Najjar**  **syndrome**  **type I** | Autosomal  recessive | Absent UGT1A1 activity | None | Fatal in  neonatal period |
| **Crigler-Najjar**  **syndrome**  **type II** | Autosomal  dominant with  variable  penetrance | Decreased UGT1A1 activity | None | Generally mild,  occasional  kernicterus |
| **Gilbert**  **syndrome** | Autosomal  recessive | Decreased UGT1A1 activity | None | Innocuous |
| **CONJUGATED HYPERBILIRUBINEMIA** | | | | |
| **Dubin-**  **Johnson**  **syndrome** | Autosomal  recessive | Impaired biliary excretion of  bilirubin glucuronides due to  mutation in canalicular multidrug  resistance protein 2 (MRP2) | Pigmented cytopasmic  globules; ?epinephrine  metabolites | Innocuous |
| **Rotor**  **syndrome** | Autosomal  recessive | Decreased hepatic uptake  and storage?  Decreased biliary excretion? | None | Innocuous |

The four major causes of acquired jaundice are excessive destruction of red blood cells (*hemolytic jaundice*), impaired uptake of bilirubin by the liver cells and decreased conjugation of bilirubin (*hepatic jaundice*), and obstruction of bile flow in the canaliculi of the hepatic lobules or in the intrahepatic or extrahepatic bile ducts (*mechanic jaundice*). From an anatomic standpoint, jaundice can be categorized as prehepatic,intrahepatic, and posthepatic.

# **PREHEPATIC JAUNDICE** (*hemolytic jaundice*)

*Prehepatic jaundice*is the result of increased bilirubin production, for example, in hemolysis(hemolytic anemia, toxins), inadequate erythropoiesis (megaloblastic anemia), massive transfusion (transfused erythrocytes are short-lived), or absorption of large hematomas. In all these conditions *unconjugated* (*indirect* reacting) *bilirubin* in plasma is increased.

# *Etiology*: etiological factors are identical with factors that provoke intracellular or intravascular hemolysis (see hemolytic anemias).

# *Pathogeny.* Main pathogenetic loop in prehepatic jaundice (hemolytic) is hyperhemolysis with unconjugated hyperbilirubinemia (free fraction), although hyperbilirubinemia in hemolytic jaundice can be explained by some additional mechanisms. One of this mechanism is explained by the fact that overproduction of free bilirubin in hemolysis exceed functional capabilities of hepatocytes (can be interpreted like a functional or relative hepatic inability to take-up and conjugate free bilirubin from the blood). Other mechanism is explained by the fact that some hemolysing factors have as well hepatotoxic effects and can alter capability of the liver to conjugate free bilirubin.

# *Manifestations:* High amount of free bilirubin that is up-take by the liver will intensify conjugation of free bilirubin. The amount of conjugated bilirubin produced by the liver will be considerably increased. That conjugated bilirubin that is excreted in the intestine will be converted in high amounts of urobilinogen, stercobilinogen and stercobilin, leading to intense coloration of the feces. This jaundice is an acoluric one, so in the urine conjugated bilirubin will be absent. But, in urine there will be found high amounts of urobilinoid bodies (summary fraction of stercobilin+urobilin), stercobilin predominates.

## IN MACROPHAGAL SYSTEM

From hemoglobin there is produced high level of unconjugated bilirubin

## IN BLOODSTREAM

### there is high concentration of unconjugated bilirubin

# **IN SMALL INTESTINE**

### Conjugated bilirubin is transformed in high amounts of urobilinogen, higher amount as well will enter in the enterohepatic circulation.

## IN THE LIVER

## Free bilirubin is captured and converted to excessive amounts of conjugated bilirubin

#### **IN URINE**

Increased summary fraction of urobilinoid bodies (stercobilin and urobilin) confer to urine a dark appearance

# **IN LARGE INTESTINE**

# Urobilinogen is transformed in stercobilinogen and ultimately in stercobilin (feces are overcolorated)

**Metabolism of biliary pigments in hemolytic jaundice**

# Mechanism of urobilin presence in fraction of urobilinoids can be explained by the fact that altered hepatocytes, being overcharged with conjugation of free bilirubin are not able to transform the entire quantity of urobilinogen (hepatoenteral circuit) in diglucuronyl bilirubin, this explaining presence of urobilinogen in blood stream (crosses renal filter) and in the urine.

**HEPATIC JAUNDICE** (*hepatocellular or parenchymatous jaundice*)

Intrahepatic or hepatocellular jaundice is caused by disorders that directly affect the ability of the liver to remove bilirubin from the blood or to conjugate it, so that it can be eliminated in the bile. It is caused by complex alterations of hepatic parenchyma, manifested by disorders in biliary pigments uptake, transportation, metabolism and excretion. This occurs in liver diseases and disorders like in viral hepatitis, alcohol abuse, drug side effects (isoniazid, phenytoin, halothane), liver congestion (right heart failure), sepsis (endotoxins), or poisoning (the Amanita phalloides mushroom).

# *Pathogeny*: should be mentioned that character and clinical symptoms depends in function of place were etiological factors act, on degree of injuries and on mass of altered hepatocytes.

## IN MACROPHAGAL SYSTEM

## from hemoglobin is synthetised a normal amount of free bilirubin

## IN BLOODSTREAM

### there is an increased amount of free bilirubin and conjugated bilirubin

IN SMALL INTESTINE

Conjugated bilirubin moderately decreased

Urobilinogen production is decreased

**IN THE LIVER**

### Less unconjugated bilirubin is captured and is transformed in less conjugated bilirubin

# **IN LARGE INTESTINE**

# a small amount of stercobilinogen and stercobilin are produced.

# Feces are decolorated.

Intrahepatic cholestasis

Moderate cholemia

Moderate cholemia

**IN THE URINE**

Moderate bilirubinuria

Pronounced urobilinuria pronunţată

**Metabolism of biliary pigments in hepatic jaundice**

# 

# Usually, injuries can begin with changes in the structure of cellular membrane, changes in activity of microsomial enzymes and dystrophy of hepatocytes (cytolytic syndrome). In pathogeny of hepatic jaundice can be recognized 2 main mechanisms. *Hepatocellular mechanism* – determined by some structural changes accompanied by functional disorders of hepatocytes, which ultimately lead to cytolytic syndrome that finally will cause hepatic failure and *cholestatic mechanism* – developed as result of intrahepatic cholestasis at the level of hepatocytes associated with disorders of biliary pigments metabolism that can complicate cytolytic syndrome.

*Manifestations***.** Should be mentioned that in hepatic jaundice any hepatocyte injury will lead to regurgitation of bile from intrahepatic biliary ducts in the blood (cholemia) and increased concentration of conjugated bilirubin mostly that of monoglicuronid bilirubin in the bloodstream. So, cholemia and conjugated hyperbilirubinemia in hepatic jaundice primarily develops at the level of central vena of the hepatic lobule. Meantime can be found increased concentration of free bilirubin – unconjugated hyperbilirubinemia - due to reduced activity of glucuroniltransferase in the injured hepatocytes.Cholemia will determine evolution of cholemic syndrome, characterized by increased concentration in the blood of all bile components: hypercholesterolemia, cholalemia (presence of bile acids in the blood) (see above). To be mentioned that in hepatic jaundice, cholemic syndrome is moderate in comparison with mechanic jaundice when cholemic syndrome is very pronounced. Pruritus in hepatic jaundice is explained not only by action of biliary acids which regurgitated in the blood but also due to increased concentration of some biological substances (histamine, serotonin, bradykinin) which are insufficiently metabolized in the liver and are eliminated in the blood from injured hepatocytes. The hemorrhagic syndrome in hepatic jaundice is because of increased concentration of biliary acids in the blood (cholalemia) which bind Ca+ ions, as well as because of diminished synthesis of clotting factors in the liver. A specific sign in the early stage of hepatic jaundice, determined by hepatocytes injury, is increased levels of hepatic transaminase in the blood – alaninaminotransferase and aspartataminotransferase eliminated from injured hepatocytes (cytolytic syndrome) .

Dark color of urine in hepatic jaundice can be explained by bilirubinuria (conjugated bilirubin is permeable for renal filter) and increased concentration of urobilinoids (stercobilin+urobilin) in the urine. Exaggerated urobilinuria in hepatic jaundice develops as result of inability of the liver to metabolize urobilinogen which comes from the hepatoenteral circuit. This disorder can be found even in an early stage of acute viral hepatitis. Dark colored urine in first hours of disease is a specific syndrome which is essential in early diagnostic of acute hepatitis.

Should be mentioned that in hepatic jaundice quantity of bile excreted in duodenum is decreased; hypocholia develops (decreased amount of bile in duodenum), digestive disorders being much less expressed in comparison with acholia (lack of bile in duodenum). Feces are slightly decolorated because of reduced stercobilin concentration.

Inflammatory-degenerative changes at the level of the liver in this form of jaundice are the most expressed and lead to disturbances in all hepatic functions, mainly disorders of intermediary metabolism of protein, lipids and carbohydrates (see liver failure).

**POSTHEPATIC JAUNDICE (***mechanic or cholestatic jaundice*)

Posthepatic or obstructive jaundice, also called cholestatic jaundice*,* occurs when bile flow is obstructed between the liver and the intestine, with the obstruction located at any point between the junction of the right or left hepatic duct and the point where the bile duct opens into the intestine. In posthepatic jaundicethe extrahepatic bile ducts are blocked, in particular by gallstones, tumors (carcinoma of the head of the pancreas), or in cholangitis (inflammatory processes in biliary ducts) or pancreatitis. It is characterized by increased level of conjugated bilirubin in the blood as result of obstruction or compression of biliary ducts and development of severe cholestasis and cholemia. In these conditions passage of bile in the intestine is blocked, and lack of bile in the duodenum (acolia), mainly lack of biliary salts will disturb activity of pancreatic lipase, emulsification and absorbtion of lipids and development of maldigestion malabsorbtion syndrome with steatorrhea. Moreover, insufficient excretion of bile in mechanic jaundice leads to accumulation of bile in biliary ducts with cholestatic syndrome. In case of cholestasis there are dilation of biliary ducts and capillaries with regurgitation and return of bile from extrahepatic ducts in intrahepatic ducts, Disse space, lymphatic ducts and finally in blood vessels with development of *cholemia*. As result of cholemia in the blood will be present all components of bile. Can be found increased concentration of conjugated bilirubin, cholesterol, biliary acids, acid phosphatase. Biliary acids can lead to collapse and bradycardia, and by stimulation of skin nerve endings cause pruritus.

Biliary acids have a toxic effect on central nervous system, decreasing activity of inhibitory neurons of the brain leading to exaggerated excitation which alternates with depression, daily drowsiness and night insomnia. Because biliary acids easily bound ion of Ca+, they will be involved in blood coagulation disorders. To be remembered that due to malabsorbtion of vitamin K clotting disorders develops as result of decreased synthesis of clotting factors in the liver. Increased level of cholesterol in the blood (hypercholesterolemia) lead to its deposition in the skin with xantomatosis.

Because of acholia (lack of bile in the duodenum) there is reduced activity of lipase, tripsine, amylase associated with protein and carbohydrates maldigestion, decoloration of feces (lack of stercobilin). In absence of biliary acids, dysbacteriosis can develops which lead to increased intestinal fermentation with reduced intestinal peristalsis, meteorism and constipation. Sometimes constipation can alternates with diarrhea due to absence of bactericide effect of the bile. In the urine can be found conjugated bilirubin (bilirubinuria) and high amount of biliary acids (*cholaluria*).

When biliary stasis is prolonged it can lead to intrahepatic cholestasis and increased bile components in the hepatocyte hyaloplasm and some metabolic disorders (can be inhibited oxidative reaction and ATP synthesis). Biliary acids act directly on endoplasmic reticulum. Biliary pigments inhibit enzymatic synthesis by consuming energy. So, in these circumstances, mechanic jaundice can be accompanied by hepatic jaundice having a much more severe evolution, sometimes leading to hepatic failure.

## IN MACROPHAGALSYSTEM

from hemoglobin is synthetised a normal amount of free bilirubin

## IN BLOODSTREAM

### there is a normal concentration of free bilirubin and high concentration of conjugated bilirubin

# **IN SMALL INTESTINE**

### Acholia

### Bile is lacking, conjugated bilirubine is absent also, so urobilinogen can’t be formed.

## IN LIVER

## free bilirubin is captured and is transformed to conjugated bilirubin

# **IN LARGE INTESTINE**

# Strecobilinogen and stercobilin are absent.

# Feces are decolourised and fatty (steatorea)

Severe cholestasis

Pronounced cholemia

In the urine pronounced bilirubinuria, cholaluria (dark urine)

**Biliary pigments metabolism in mechanic jaundice**