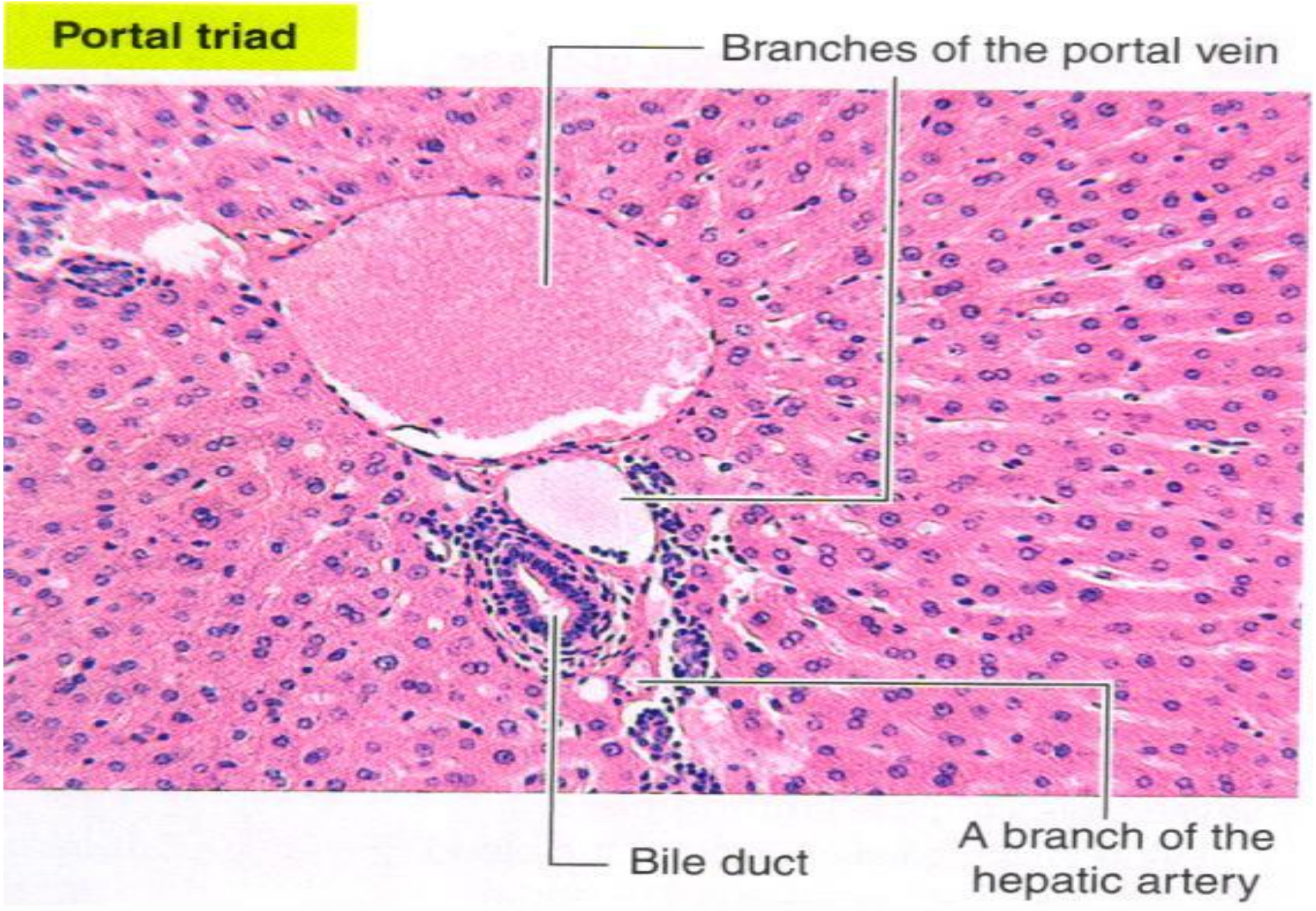
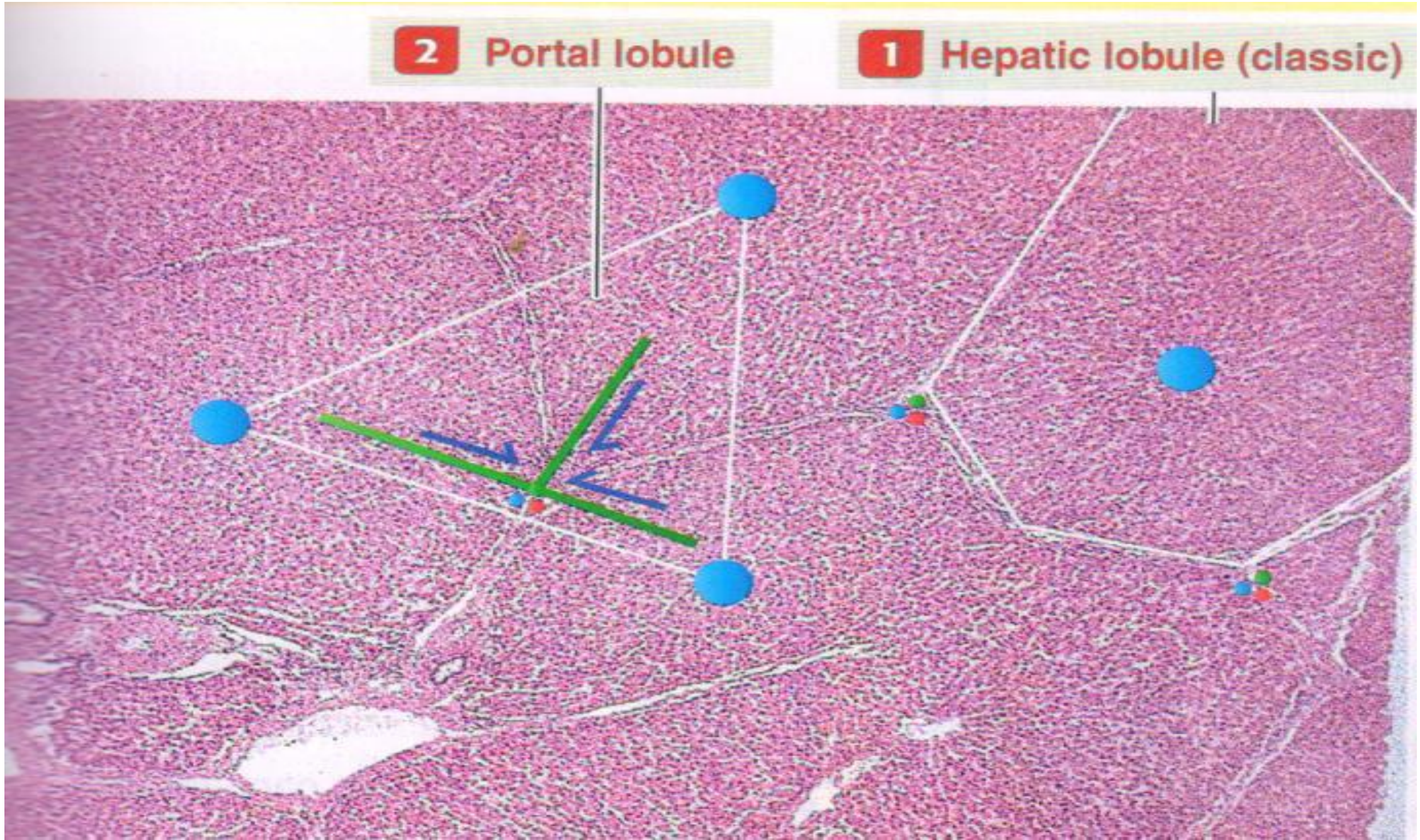
ПОРТАЛЬНАЯ ТРИАДА



ПЕЧЕНОЧНЫЕ ДОЛЬКИ

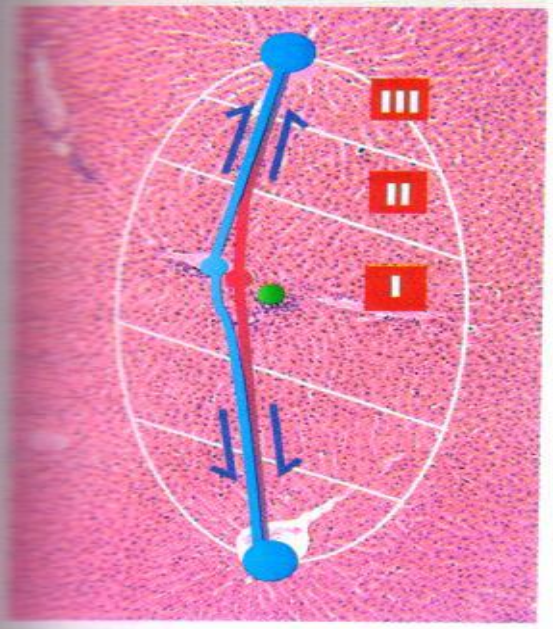


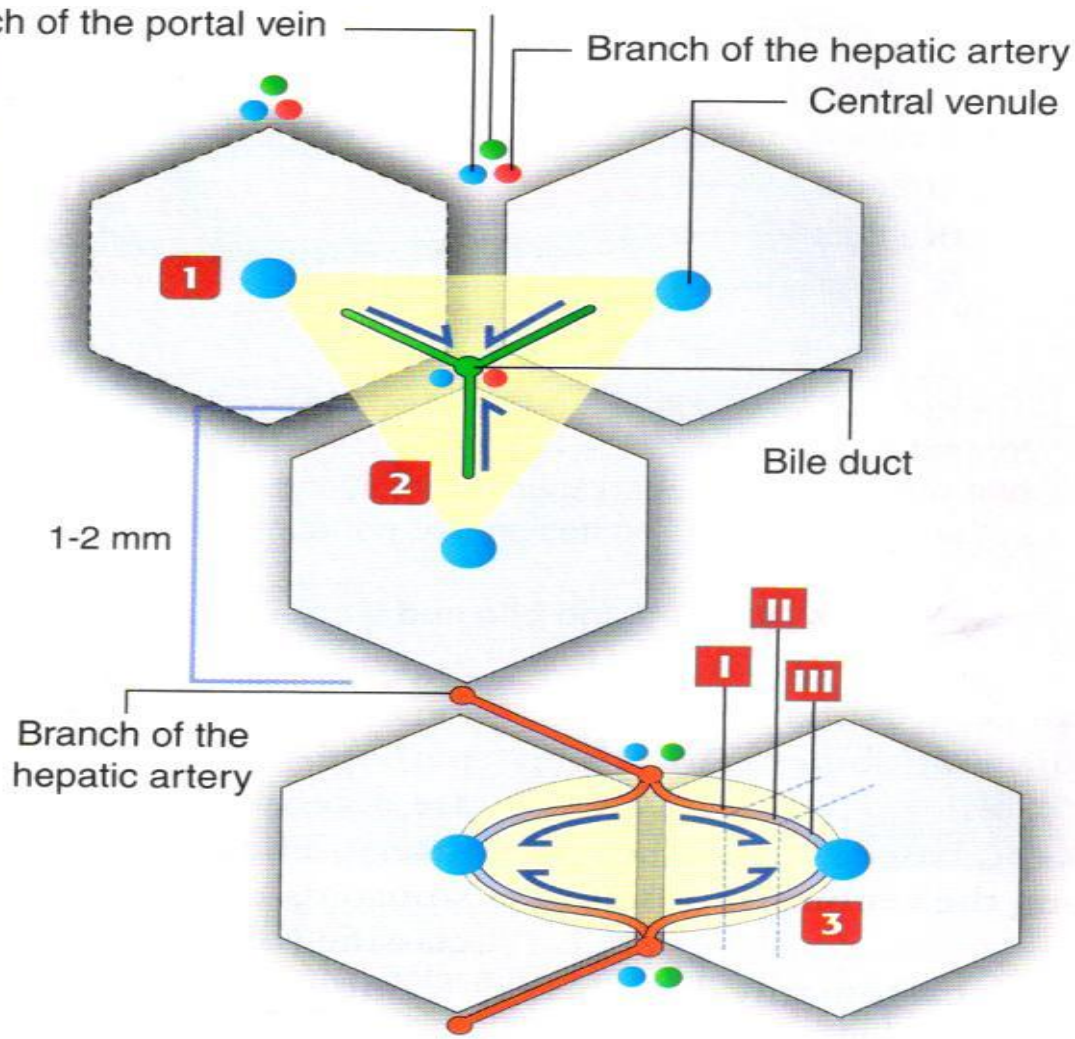
ПЕЧЕНОЧНЫЕ ДОЛЬКИ

1 Hepatic lobule (classic)

The classic hexagonal lobule contains a central venule and components of the portal triad at the angles.

3 Liver acinus





2 Portal lobule

A portal lobule includes portions of those lobules whose bile canaliculi drain into the same bile duct.

The boundaries of a portal lobule are the central veins of three classic lobules. The center of the portal lobule is the bile duct collecting the bile from all canaliculi.

3 Liver acinus

The three zones of a liver acinus are defined by hepatic tissue receiving blood from a branch of the hepatic artery conducting blood to opposite central veins. **The direction of arterial flow determines a metabolic gradient from the periportal space near the portal triad (zone I) to the zone of drainage (zone III).**

I In **zone I (periportal)**, hepatocytes actively synthesize glycogen and plasma proteins. Oxygen concentration in sinusoidal blood is high.

II **Zone II** is an intermediate region.

III **Zone III (central venous drainage)** is the region where oxygen concentration is the poorest. Zone III has a role in detoxification. Hepatocytes are susceptible to damage caused by hypoxia.

ОРГАНИЗАЦИЯ ПЕЧЕНОЧНОЙ ДОЛЬКИ

Figure 17-13. Organization of the hepatic lobule

1 The perisinusoidal **space of Disse** separates the basolateral domain of the hepatocyte from blood circulating in the hepatic sinusoid.

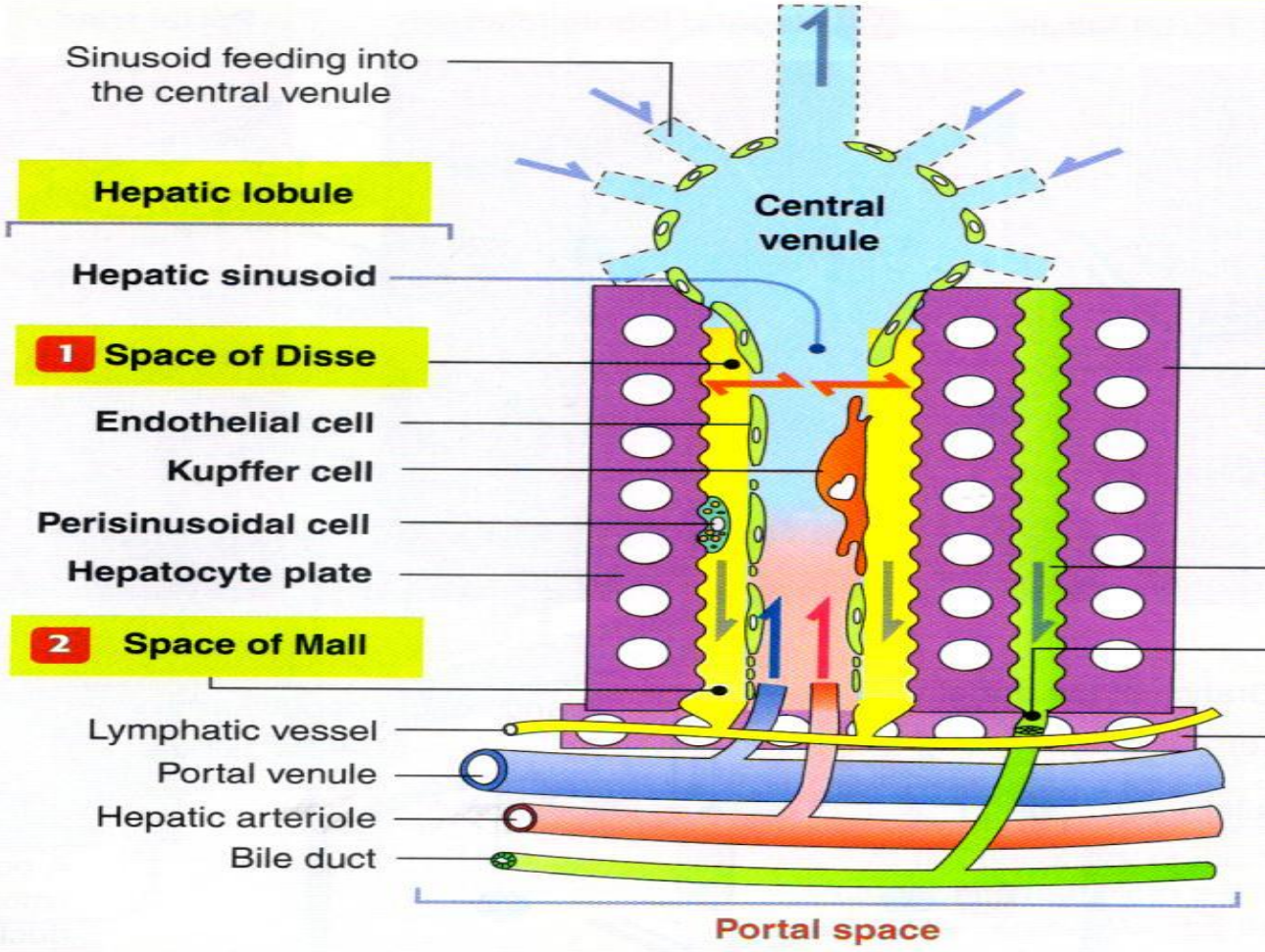
The space of Disse contains types I, III, and IV collagen fibers. Protein absorption and secretion take place across the narrow space of Disse (0.2 to 0.5 μm wide).

2 The **space of Mall**, found at the periphery of the hepatic lobule, is continuous with the space of Disse. The space of Mall is drained by lymphatic vessels piercing the **limiting plate**.

Lymphatic vessels surround the blood vessels and bile ductules in the portal space.

3 The **canal of Hering** (or cholangiole) is the terminal point of the network of bile canalicular trenches found on the hepatocyte surfaces.

The canal of Hering is located at the periphery of the hepatic lobule (periportal site), is lined by a squamous-to-cuboidal simple epithelium, and connects with the bile ductules in the portal space after perforating the limiting plate.

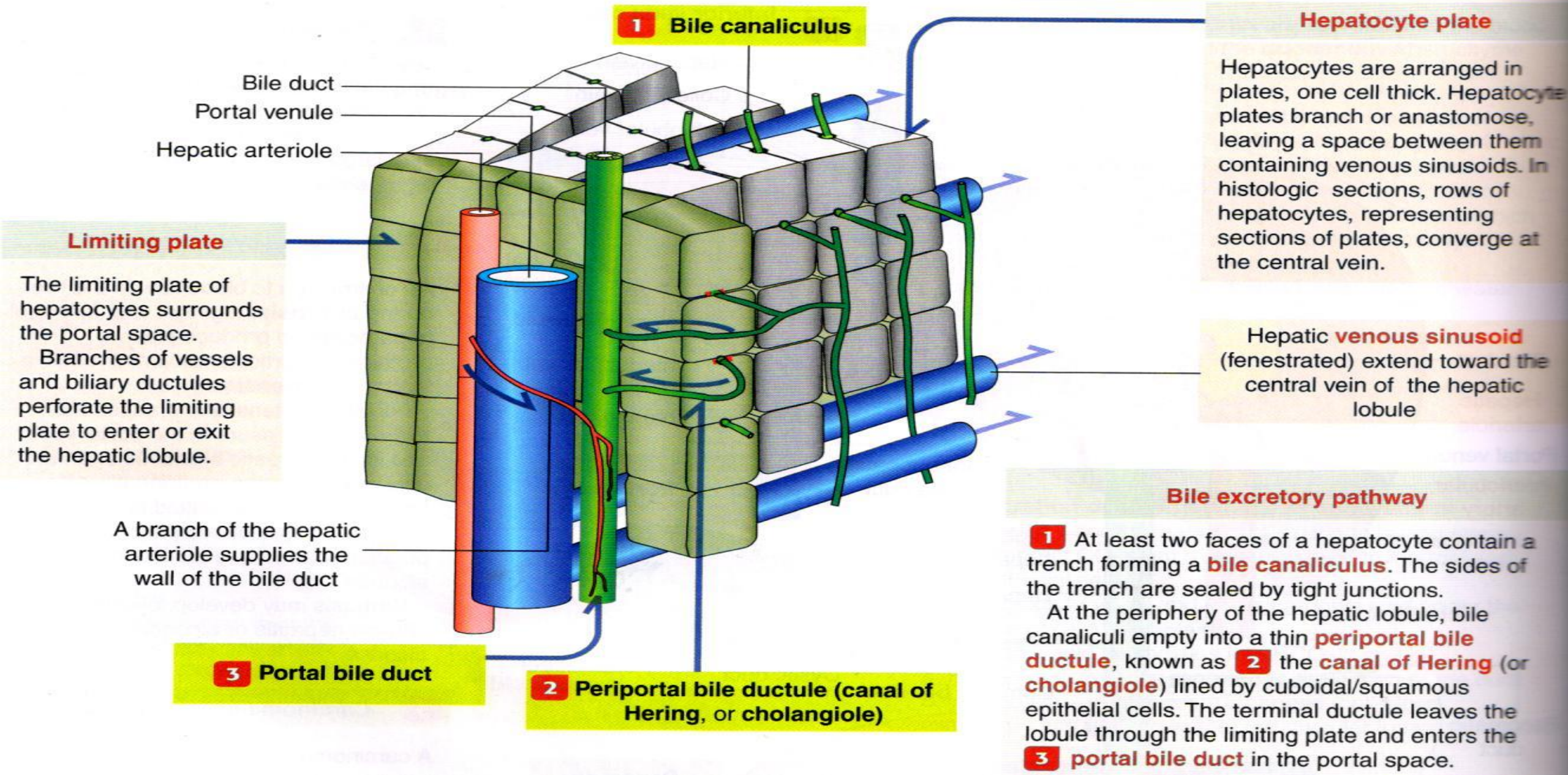


The connective tissue of the **portal space** provides support to the **portal triad** formed by branches of the **hepatic artery** (arteriole), **portal vein** (venule), and **bile duct** (ductule). In addition, lymphatic vessels and nerve fibers are present in the portal space (also designated portal canal, portal area, or portal tract).

Note that blood and bile and lymph flow in opposite directions

ПОРТАЛЬНОЕ ПРОСТРАНСТВО И ЖЕЛЧНЫЕ ПРОТОКИ

Figure 17-11. Portal space and the bile ducts



Limiting plate

The limiting plate of hepatocytes surrounds the portal space.

Branches of vessels and biliary ductules perforate the limiting plate to enter or exit the hepatic lobule.

Hepatocyte plate

Hepatocytes are arranged in plates, one cell thick. Hepatocyte plates branch or anastomose, leaving a space between them containing venous sinusoids. In histologic sections, rows of hepatocytes, representing sections of plates, converge at the central vein.

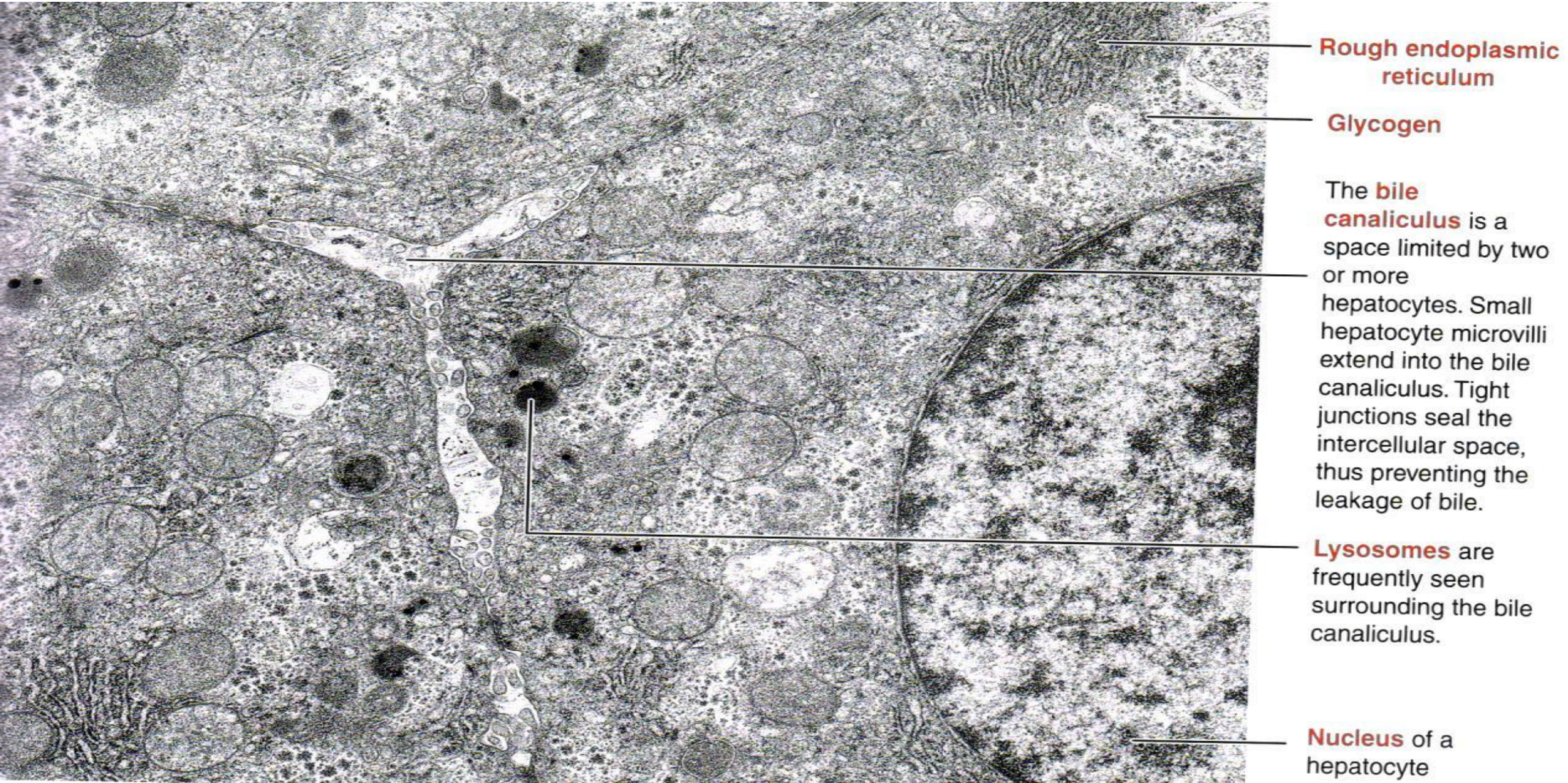
Hepatic **venous sinusoid** (fenestrated) extend toward the central vein of the hepatic lobule

Bile excretory pathway

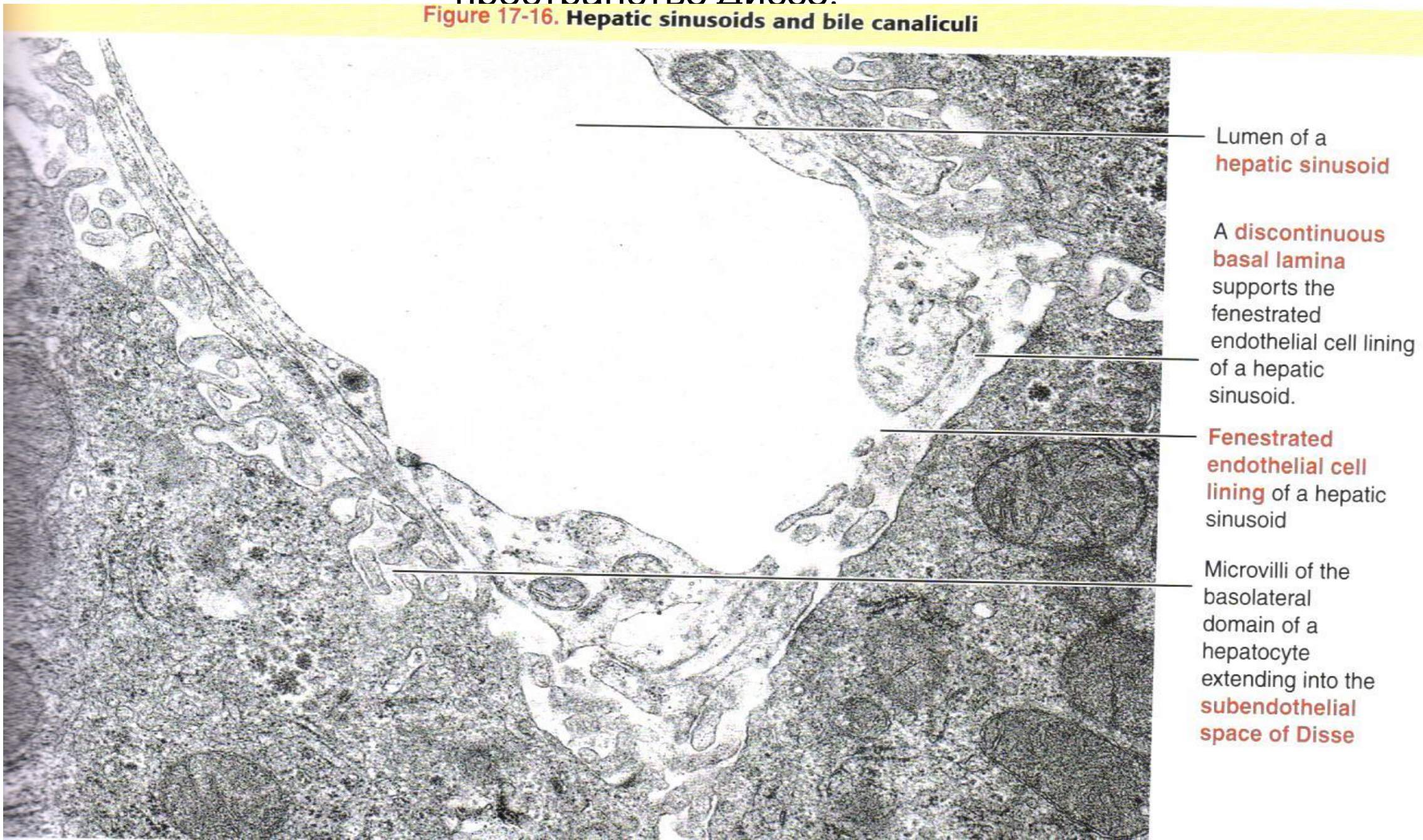
1 At least two faces of a hepatocyte contain a trench forming a **bile canaliculus**. The sides of the trench are sealed by tight junctions.

At the periphery of the hepatic lobule, bile canaliculi empty into a thin **periportal bile ductule**, known as 2 the **canal of Hering** (or **cholangiole**) lined by cuboidal/squamous epithelial cells. The terminal ductule leaves the lobule through the limiting plate and enters the 3 **portal bile duct** in the portal space.

ТРИ ГЕПАТОЦИТА ОКРУЖАЮТ ЖЕЛЧНЫЙ КАНАЛЕЦ



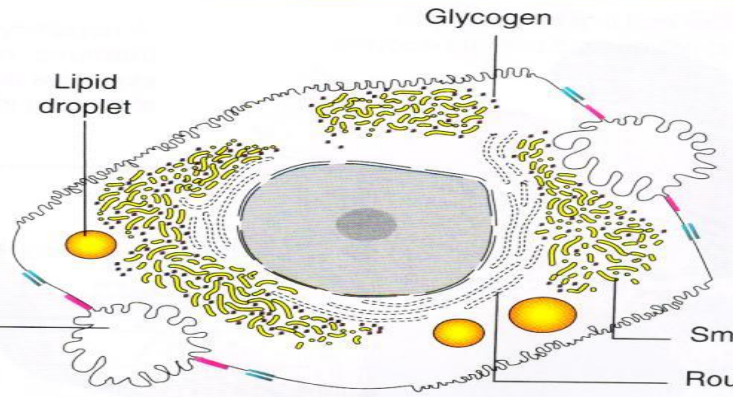
ПЕЧЕНОЧНЫЕ СИНУСОИДЫ И ЖЕЛЧНЫЕ КАНАЛЬЦЫ. Микроворсинки в пространстве Диссе.



ЭНДОПЛАЗМАТИЧЕСКИЙ РЕТИКУЛУМ В ГЕПАТОЦИТЕ

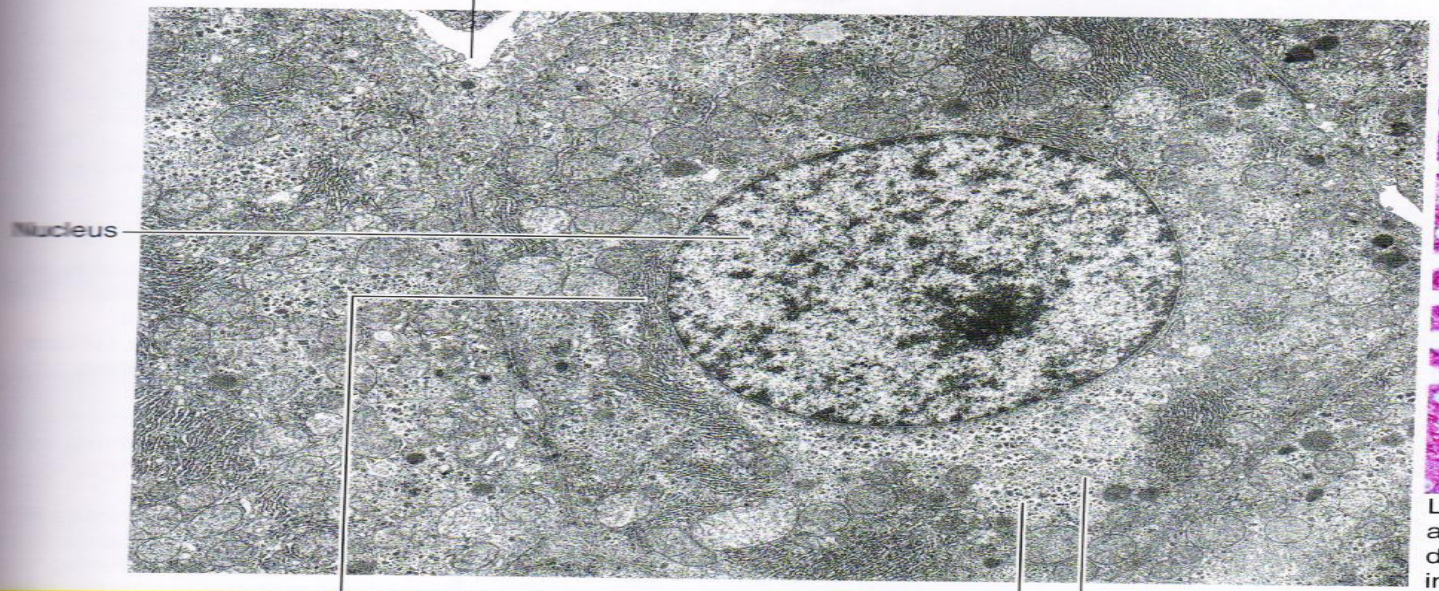
Figure 17-14. Endoplasmic reticulum in hepatocytes

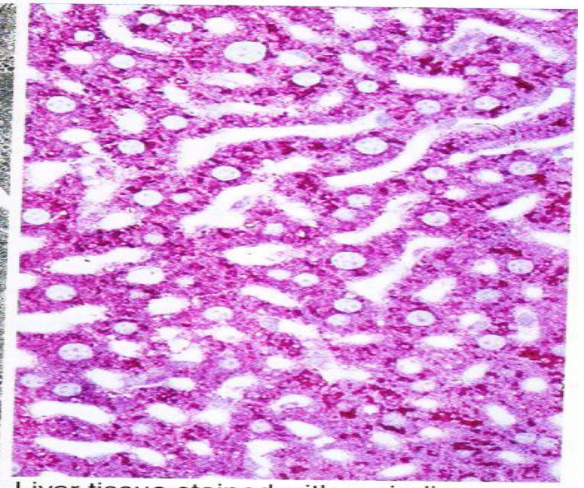
The **rough endoplasmic reticulum** in hepatocytes is involved in the synthesis of plasma proteins: albumin, coagulation factors (fibrinogen and prothrombin in particular), and binding proteins for hormones and growth factors in blood circulation.



The **smooth endoplasmic reticulum** in hepatocytes is highly developed and is always associated with clusters of **glycogen** molecules forming typical rosette-like inclusions.

Stored glycogen in hepatocytes represents a glucose reserve for the maintenance of sugar concentrations in blood. Glycogen is also stored in muscle.





Liver tissue stained with periodic acid–Schiff reagent to demonstrate deposits of glycogen (magenta staining) in the cytoplasm of hepatocytes.

Rough endoplasmic reticulum

Albumin, a major product of the hepatocyte, maintains plasma oncotic pressure. A decrease of albumin in a liver disease causes **edema** and **ascites**.

Blood coagulation depends on **fibrinogen**, **prothrombin**, and **factor VIII** produced in the hepatocyte. **Bleeding** is associated with liver failure. **Complement proteins**, synthesized by hepatocytes, participate in the destruction of pathogens.

Smooth endoplasmic reticulum

The smooth endoplasmic reticulum has an important function in **detoxification**.

Enzymes necessary for the detoxification of drugs (barbiturates), steroids, alcohol, and other toxicants reside in the membrane of the smooth endoplasmic reticulum.

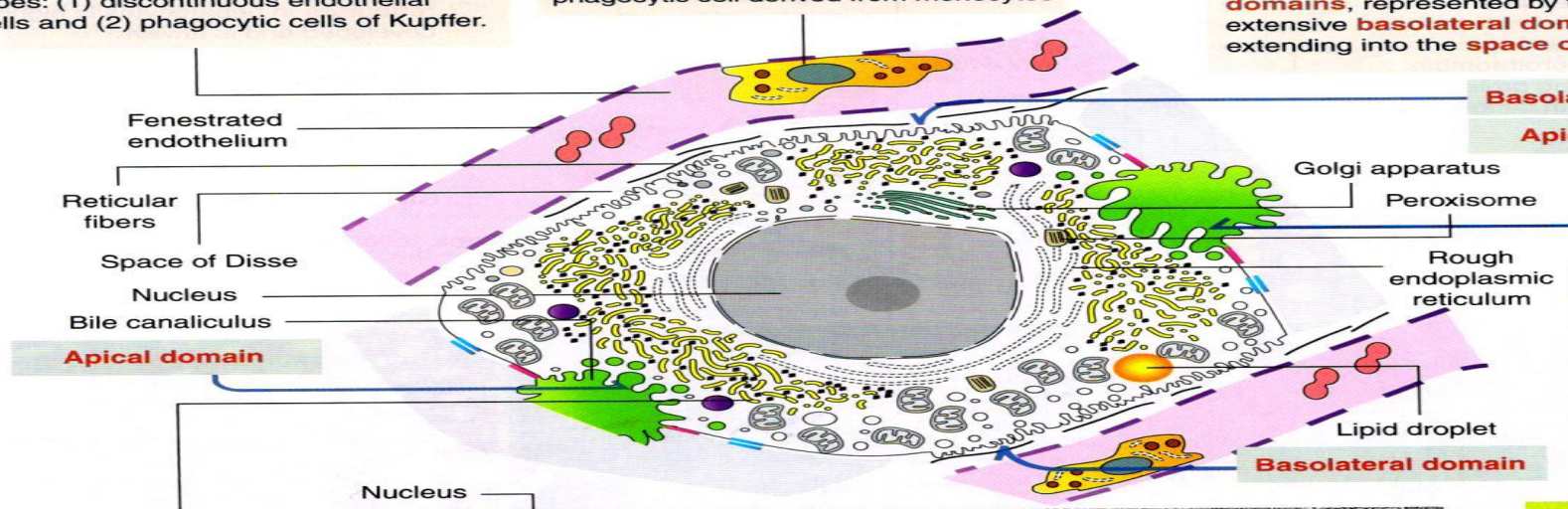
АПИКАЛЬНЫЕ И БАЗОЛАТЕРАЛЬНЫЕ ДОМЕНЫ ГЕПАТОЦИТА

Figure 17-15. Apical and basolateral domains of hepatocytes

Hepatic sinusoids are lined by two cell types: (1) discontinuous endothelial cells and (2) phagocytic cells of Kupffer.

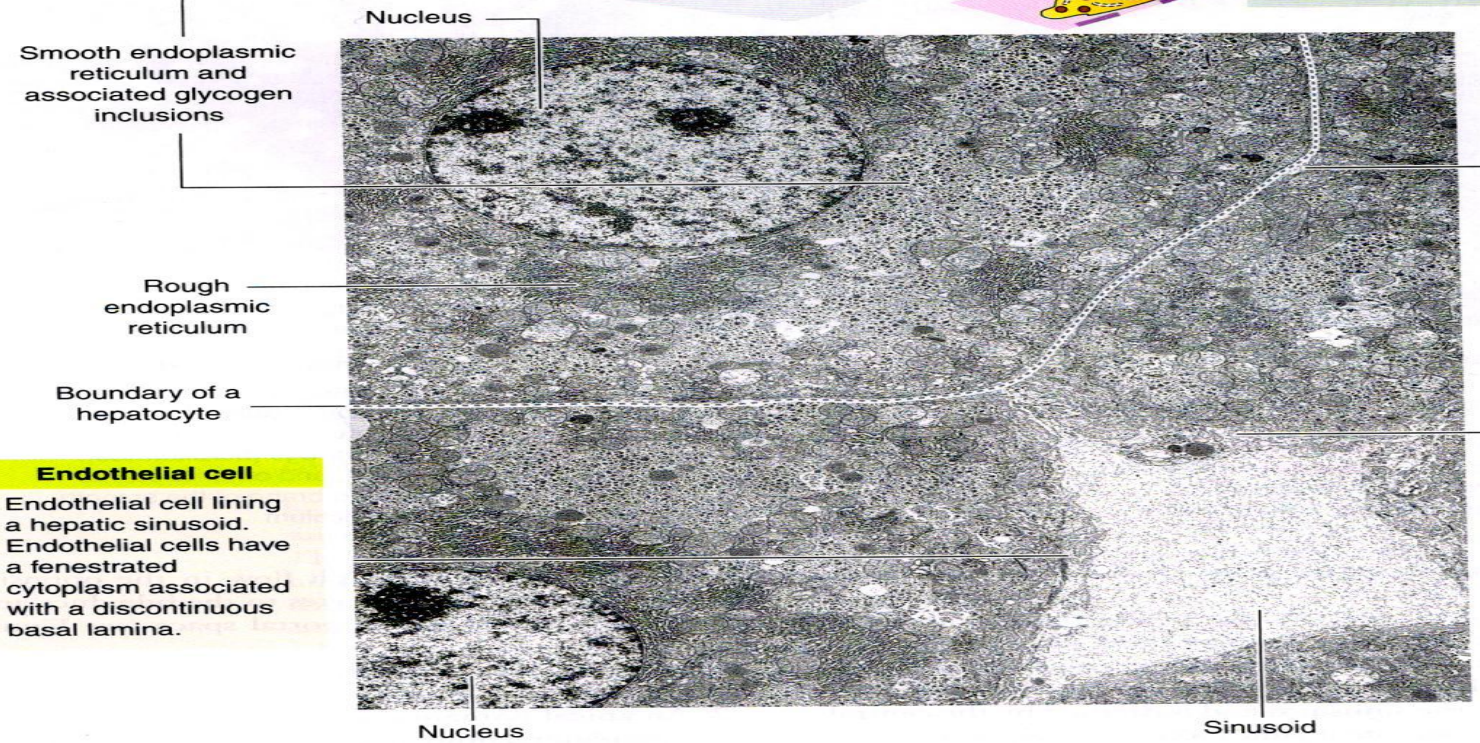
Kupffer cell is a differentiated phagocytic cell derived from monocytes

A hepatocyte has distinct domains: **apical domains**, represented by the **bile poles**, and extensive **basolateral domains** with microvilli extending into the **space of Disse**.



Peroxisome

A membrane-bound structure that contains oxidases and catalase. Oxidases produce H_2O_2. Catalase breaks down H_2O_2 into O_2 and water.



Endothelial cell

Endothelial cell lining a hepatic sinusoid. Endothelial cells have a fenestrated cytoplasm associated with a discontinuous basal lamina.

Bile canaliculus

The bile canaliculus is an **extracellular canal** between adjacent hepatocytes. The surface of this canal displays microvilli.

Bile released into the canaliculus is drained by the **canal of Hering**, or **cholangiole**, an epithelial-lined ductule in the periportal space.

The canal of Hering carries the bile to the bile ductules, one of the three components of the portal space.

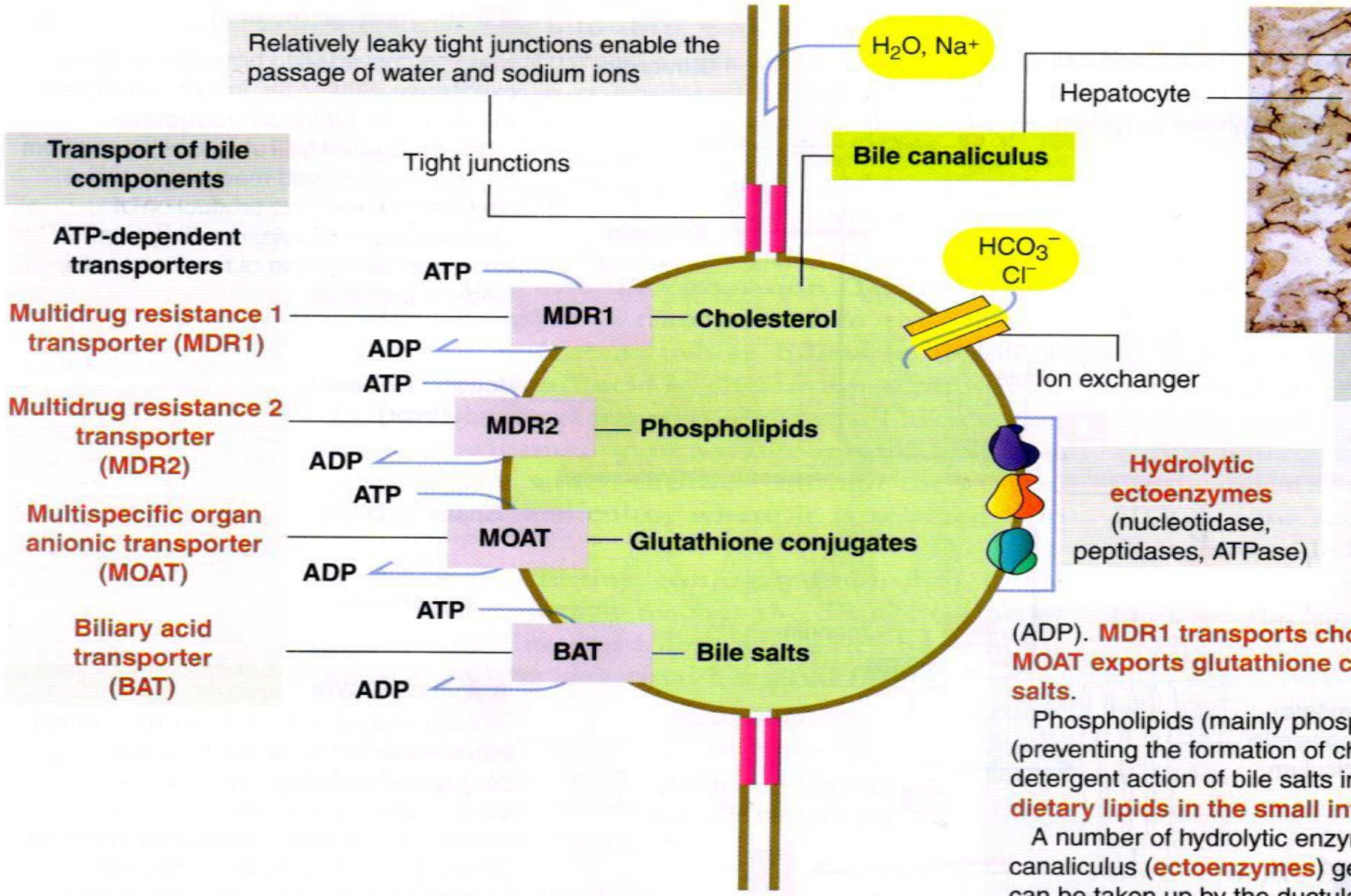
Space of Disse

The space of Disse, between the sinusoid and the basolateral domain of hepatocytes, enables an exchange between blood and hepatocytes.

Hepatocyte absorptive function is enhanced by the microvilli extending into the space of Disse. Collagen fibers are found in this space.

ТРАНСПОРТ ЖЕЛЧИ В ЖЕЛЧНЫХ КАНАЛЬЦАХ

Figure 17-20. Transport of bile into the bile canaliculus



Histochemical detection of **ATPase activity** defines the boundaries of bile canaliculi

Bile consists of bile acids, phospholipids, cholesterol, water, and ions.

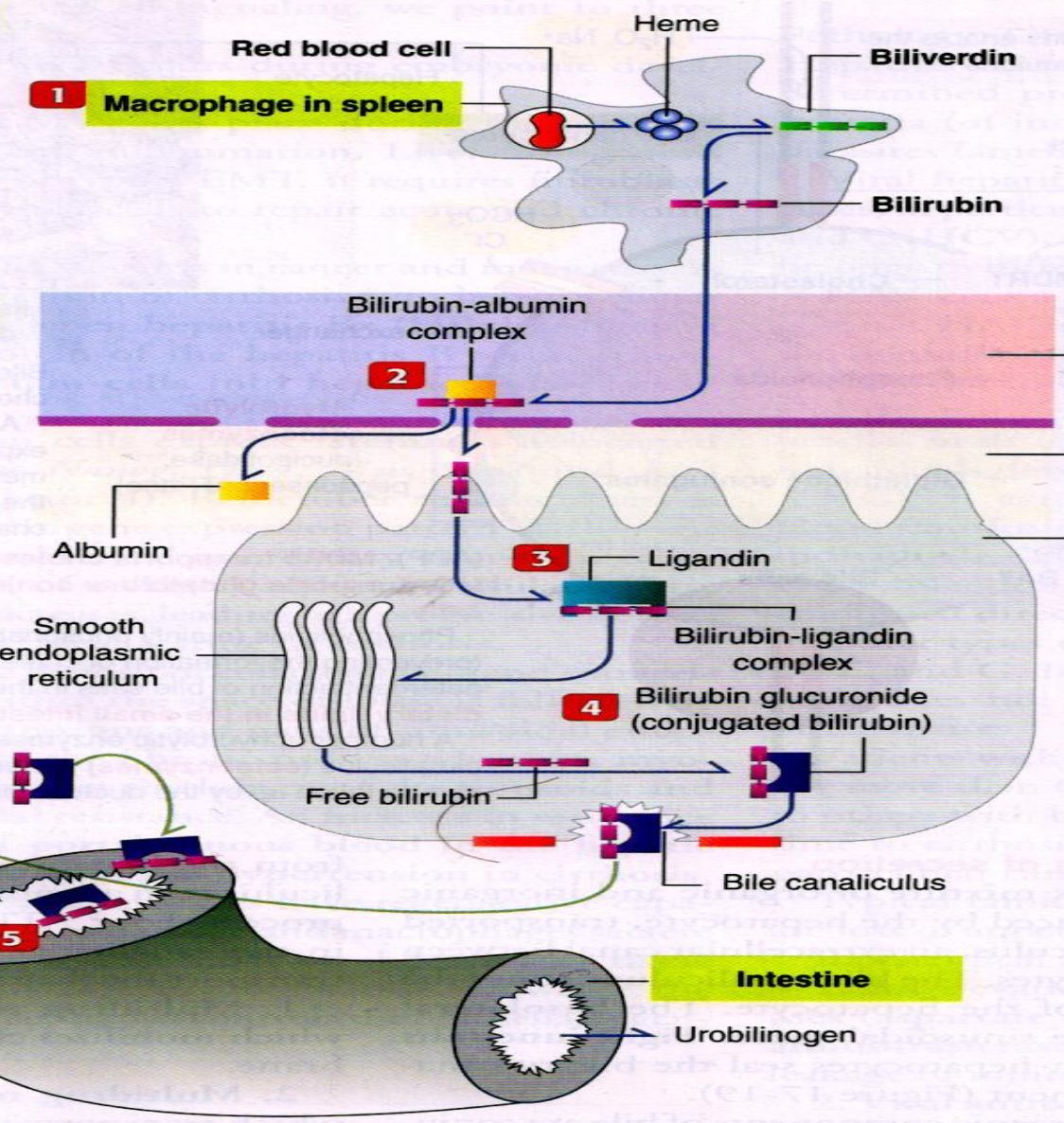
Adenosine triphosphate (ATP)–dependent export pumps located in the plasma membrane of the bile canaliculus enable the transport of bile components. ATP changes into adenosine diphosphate (ADP). **MDR1 transports cholesterol; MDR2 transports phospholipids; MOAT exports glutathione conjugates (bilirubin); BAT exports bile salts.**

Phospholipids (mainly phosphatidylcholine) solubilize cholesterol (preventing the formation of cholesterol gallstones) and reduce the detergent action of bile salts in the small intestine. **Bile salts emulsify dietary lipids in the small intestine.**

A number of hydrolytic enzymes on the luminal surface of the bile canaliculus (**ectoenzymes**) generate nucleosides and amino acids that can be taken up by the ductular epithelial cells.

МЕТАБОЛИЗМ БИЛИРУБИНА

Figure 17-21. Metabolism of bilirubin



2 Blood

In blood, bilirubin forms a complex with albumin. The **bilirubin-albumin complex** is too large to be excreted in urine. This form of bilirubin is water-soluble and can enter the brain to cause severe neurologic disorders (**kernicterus**) in hemolytic disease of the newborn (**erythroblastosis fetalis**).

3 Hepatocyte

Lipid-soluble bilirubin, detached from the albumin carrier, enters the hepatocyte and binds to **ligandin**, an intracellular carrier protein. The **bilirubin-ligandin complex** reaches the smooth endoplasmic reticulum and **free bilirubin** is released into the cytosol by enzymatic action.

5 Intestine

In the intestine, glucuronides are split and bacteria convert bilirubin into **urobilinogens**, which are then excreted in the urine (as **urobilin**), eliminated with feces, or returned to the liver. About 20% of the urobilinogens are reabsorbed in the ileum and colon.

1 Macrophage (spleen)

Heme is converted to biliverdin by heme oxygenase. **Biliverdin**, in turn, is reduced to bilirubin by **biliverdin reductase**.

Unconjugated bilirubin is released from the macrophage and reaches the blood circulation. Excessive production of unconjugated bilirubin, resulting from excessive destruction of red blood cells, leads to **jaundice**.

4 Hepatocyte

Glucuronic acid is attached by **glucuronyl transferase** to free bilirubin, forming **conjugated bilirubin** (bilirubin glucuronide). Conjugated bilirubin is released into the bile canaliculus and to the extrahepatic biliary system. Impaired excretion of conjugated bilirubin causes cholestatic **jaundice**.

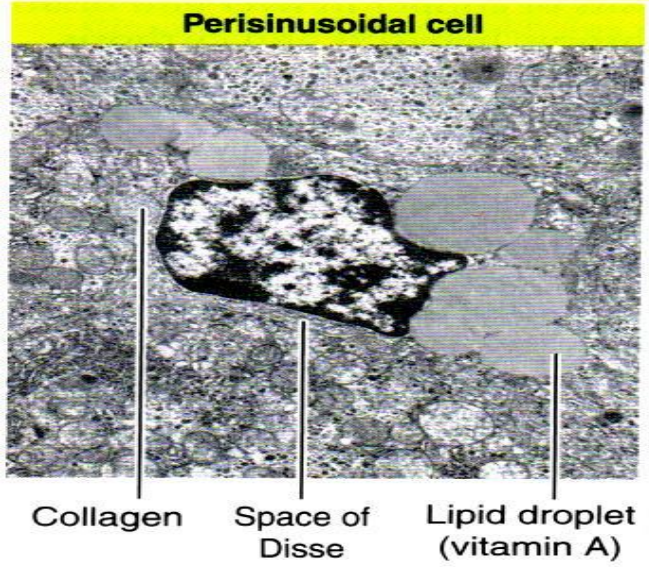
Clinical significance of unconjugated and conjugated bilirubin in jaundice

An increase in plasma levels of **unconjugated bilirubin** indicates excessive production of bilirubin (for example, in hemolytic anemia and Gilbert's syndrome).

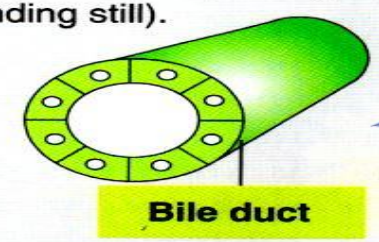
An increase in plasma levels of **conjugated bilirubin** indicates a disorder beyond the hepatic conjugating enzyme system (for example, a biliary tract obstruction).

ПЕРИСИНУСОИДАЛЬНАЯ КЛЕТКА И ХРОНИЧЕСКАЯ БОЛЕЗНЬ ПЕЧЕНИ

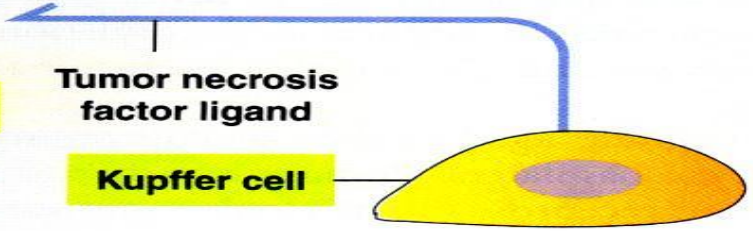
Figure 17-18. Perisinusoidal cell and chronic liver disease



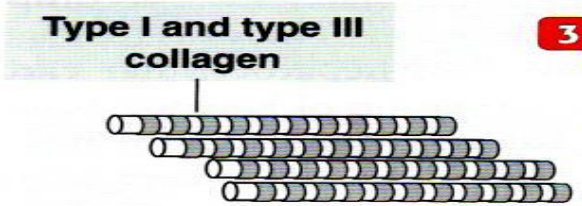
1 Tumor necrosis factor ligand causes a slowdown and arrest of the flow of bile in bile ducts (**cholestasis**: Greek *chole*, bile; *stasis*, standing still).

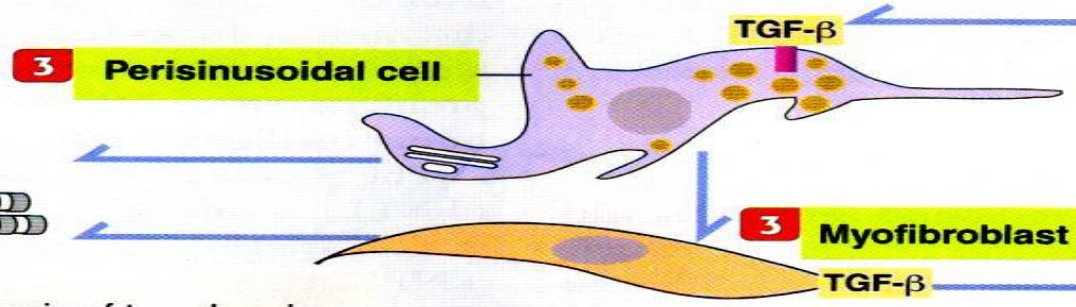


Hepatitis viral infection causes injury of hepatocytes. Persistent virus replication in hepatocytes causes **chronic liver disease**, which may progress to **fibrogenesis**, **cirrhosis** and finally **hepatocellular carcinoma**. During chronic liver disease, proinflammatory cytokines are produced: tumor necrosis factor ligand, secreted by Kupffer cell, and transforming growth factor–β, **TGF-β**, secreted by myofibroblasts. Hepatitis B virus and hepatitis C virus replicate in hepatocytes and promote prolonged inflammation, fibrogenesis and hepatocyte regeneration resulting in chronic liver damage leading finally to hepatocellular carcinoma.

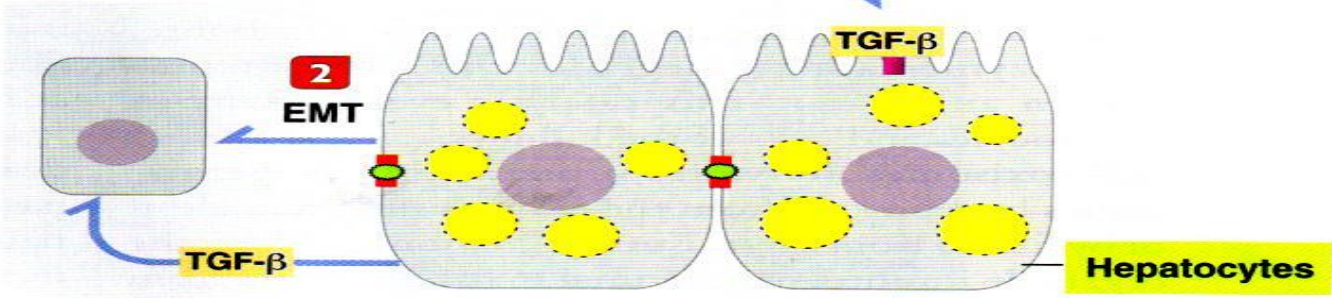


2 TGF-β secreted by myofibroblasts and hepatocytes stimulates **epithelial-mesenchymal transition** (**EMT**) during hepatocyte injury and repair. During EMT, hepatocytes switch from an epithelial phenotype to a permanent fibroblast-like, or mesenchymal stage. TGF-β, secreted by hepatocytes, regulates transcription factors that suppress epithelial characteristics (such as cell junction components) and activates mesenchymal features.

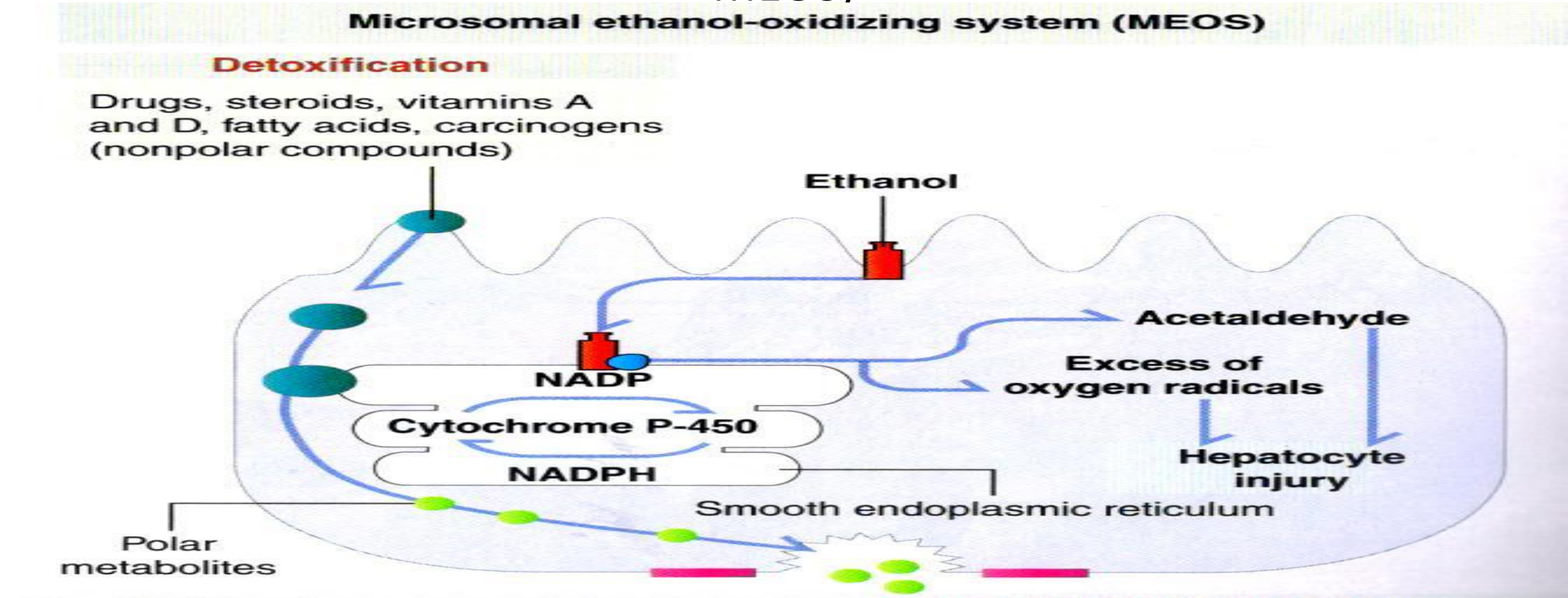




3 TGF-β stimulates the synthesis of type I and type III collagen by **perisinusoidal cells** (also called **hepatic stellate cells**). Persinusoidal cells transdifferentiate into **myofibroblasts** and secrete TGF-β. **Fibrogenesis** follows a period of hepatitis during which hepatocytes are injured and destroyed, a process followed by regeneration. Liver fibrogenesis promotes chronic liver disease in response to continuing inflammation and regeneration.



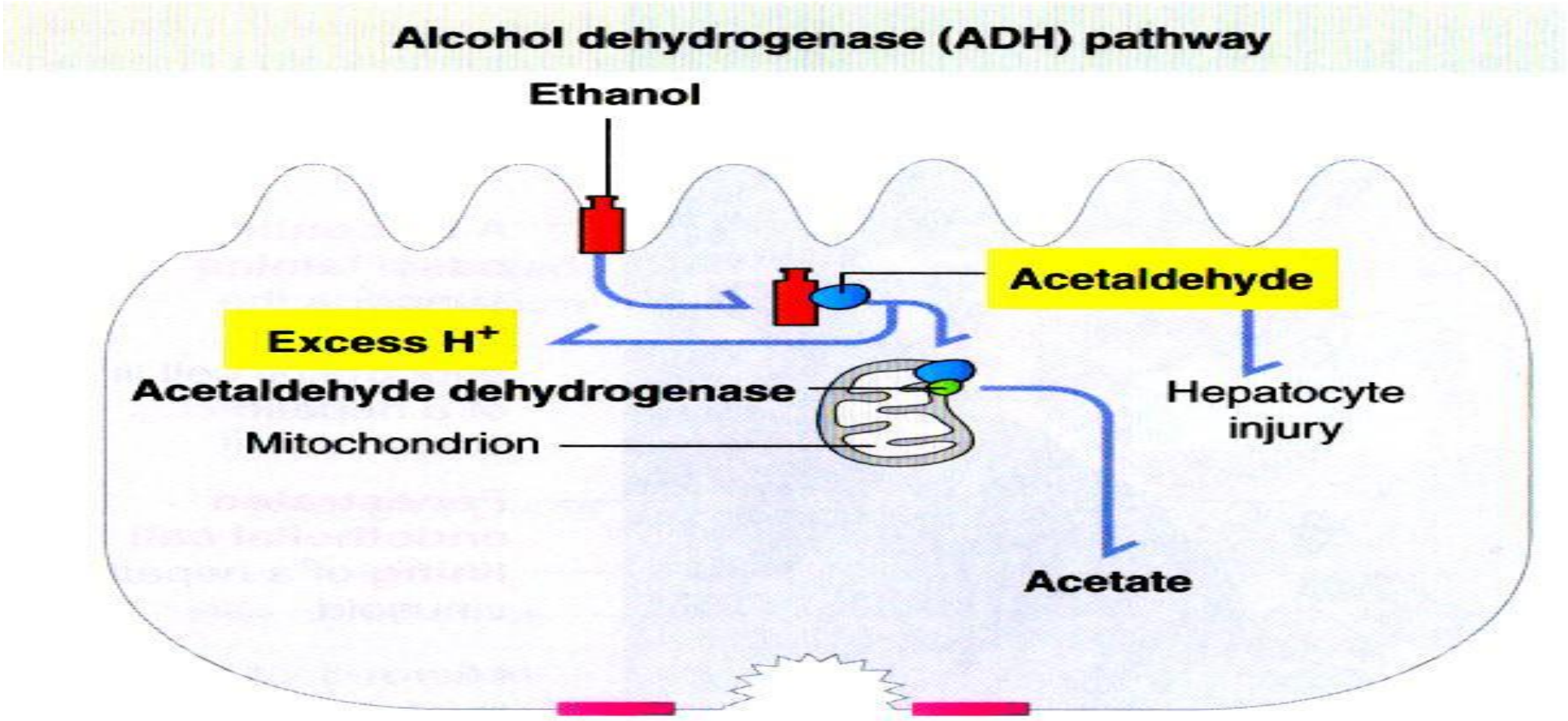
МИКРОСОМАЛЬНАЯ СИСТЕМА, ОКИСЛЯЮЩАЯ ЭТАНОЛ (MEOS)



The MEOS pathway is significant during the **chronic intake of alcohol**. In contrast to the ADH pathway that produces acetaldehyde and excess H^+, **the MEOS pathway produces acetaldehyde and an excess of oxygen radicals.**

Reactive oxygen produces injury to hepatocytes by causing lipid peroxidation, resulting in cell membrane damage. In addition, an up-regulated MEOS affects detoxification activities of the hepatocyte that require cytochrome P-450 for the oxidation of various drugs, toxins, vitamins A and D, and potential carcinogens. The accumulation of these products is often toxic.

АЛКОГОЛЬДЕГИДРОГЕНАЗА



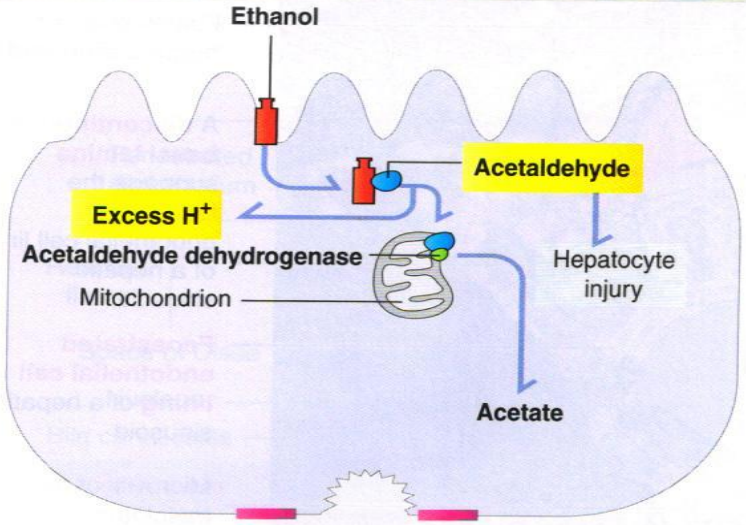
The ADH is the major pathway. **Alcohol is oxidized to acetaldehyde** in the cytoplasm and **acetaldehyde is converted to acetate** in mitochondria.

An excess of H^+ and acetaldehyde causes mitochondrial damage, disrupts microtubules, and alters proteins that can induce autoimmune responses leading to hepatocyte injury.

МЕТАБОЛИЗМ ЭТАНОЛА В ГЕПАТОЦИТЕ

Figure 17-17. Ethanol metabolism in hepatocytes

Alcohol dehydrogenase (ADH) pathway



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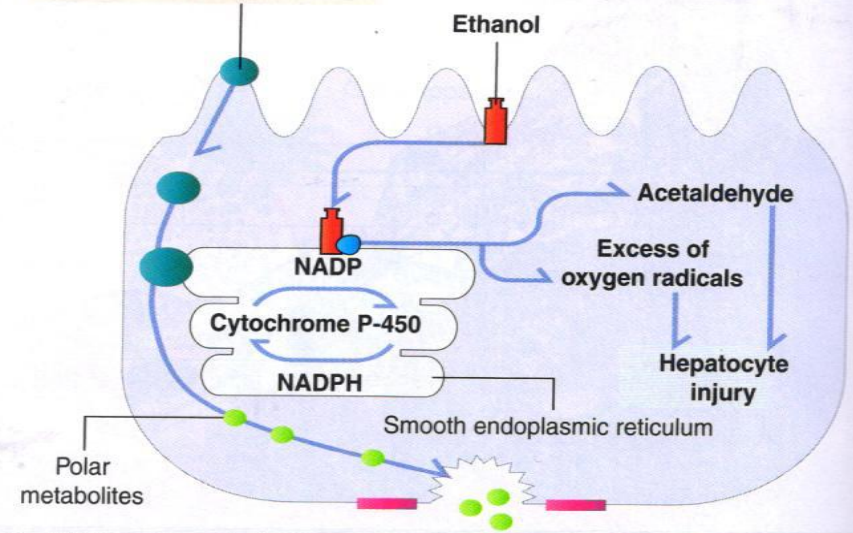
Microsomal ethanol-oxidizing system (MEOS)

Detoxification

Drugs, steroids, vitamins A and D, fatty acids, carcinogens (nonpolar compounds)



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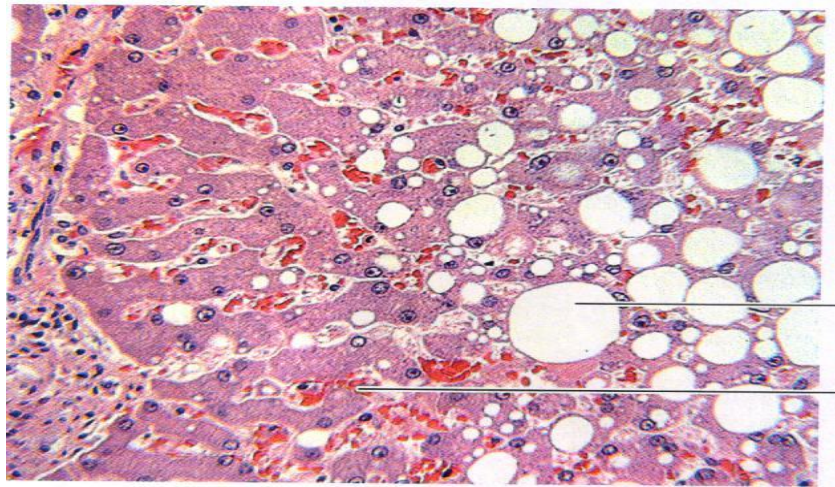


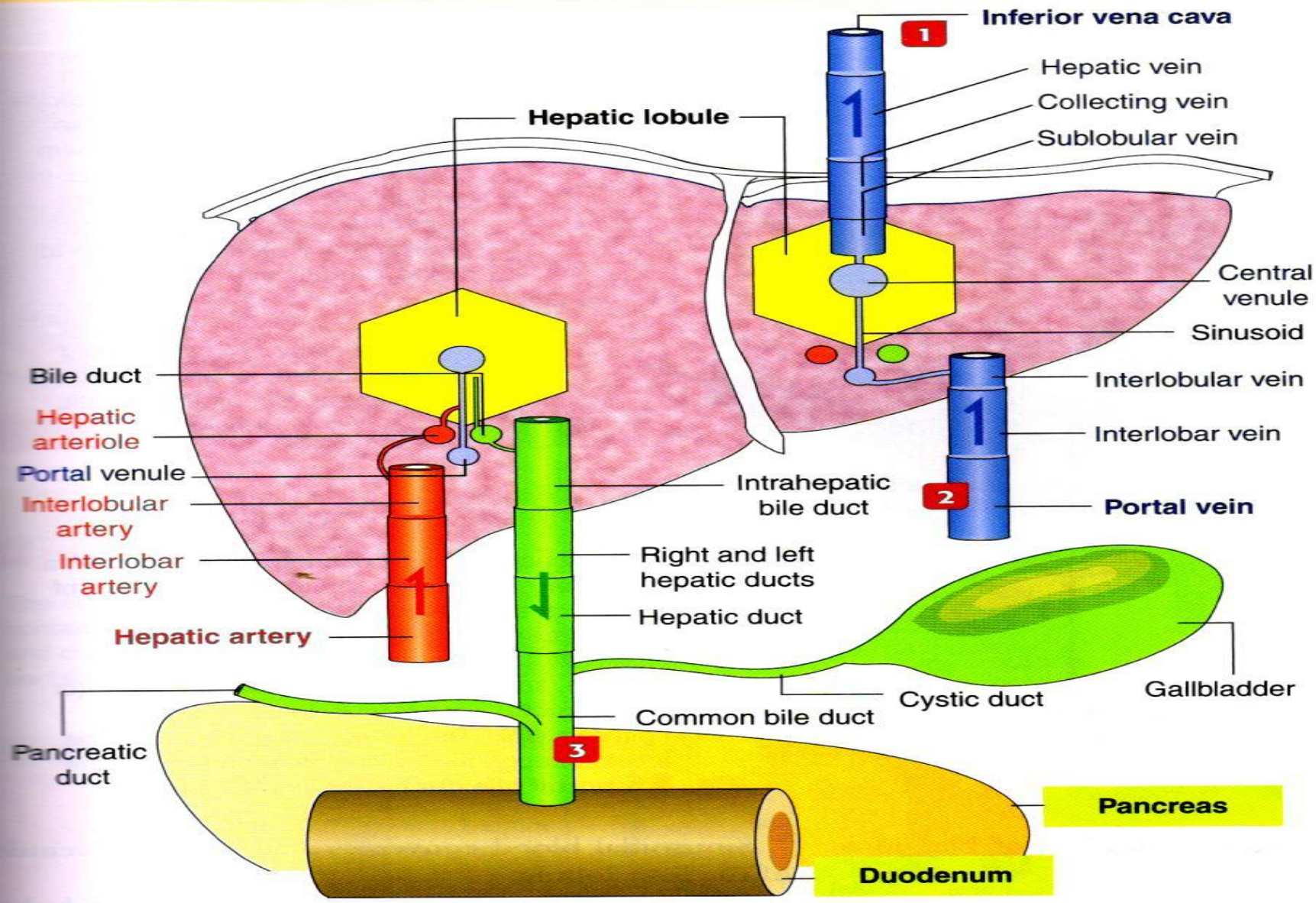
Large fat deposits in the cytoplasm of hepatocytes are observed in **fatty liver (steatosis)** following long-term consumption of alcohol.

Sinusoid

ПЕЧЕНЬ: КРОВЕНОСНЫЕ СОСУДЫ И ПРОТОКИ. БОЛЕЗНИ

(1 – застойная сердечная недостаточность. 2 – портальная гипертензия. 3 – карцинома панкреас.)

Figure 17-10. Liver inflow and outflow (blood vessels and ducts) in clinical disease



1 Congestive heart failure

Valves are not present in the inferior vena cava and hepatic veins.

An increase in central venous pressure (as in congestive heart failure) causes an enlargement of the liver due to blood engorgement.

2 Portal hypertension

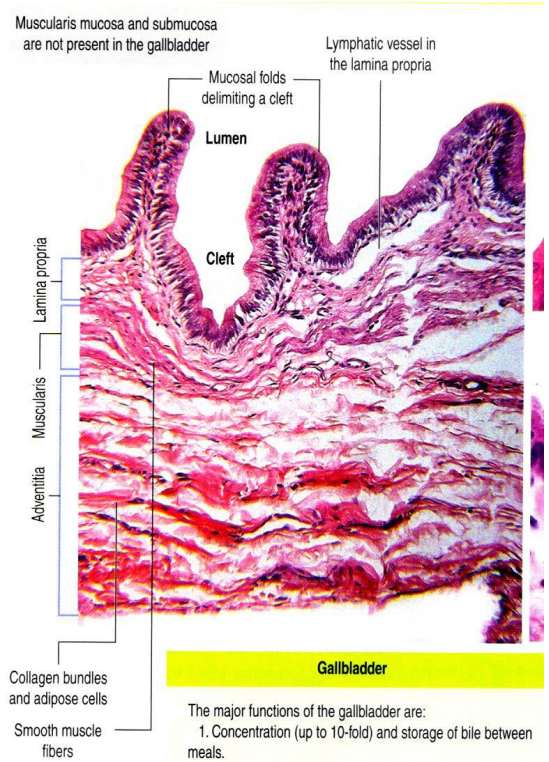
An obstruction to blood flow in the liver during **cirrhosis**, together with failure of hepatocytes to produce plasma proteins, in particular albumin, result in **portal hypertension**.

Portal hypertension increases the hydrostatic pressure in the portal vein and its intrahepatic branches and fluid accumulates in the peritoneal cavity (**ascites**). The loss of fluid is aggravated by reduced plasma oncotic pressure due to a reduction in plasma albumin.

Cirrhosis may develop following chronic hepatitis or alcoholic liver disease.

3 Carcinoma of the pancreas

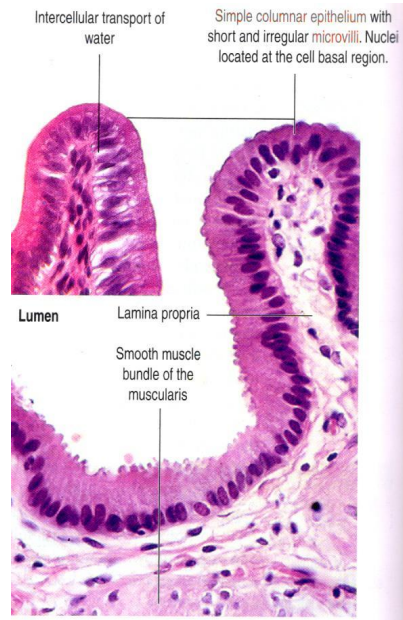
A carcinoma of the head of the pancreas (60% of pancreatic tumors) obstructs by compression the outflow of bile through the ampullary region.



Gallbladder

The major functions of the gallbladder are:

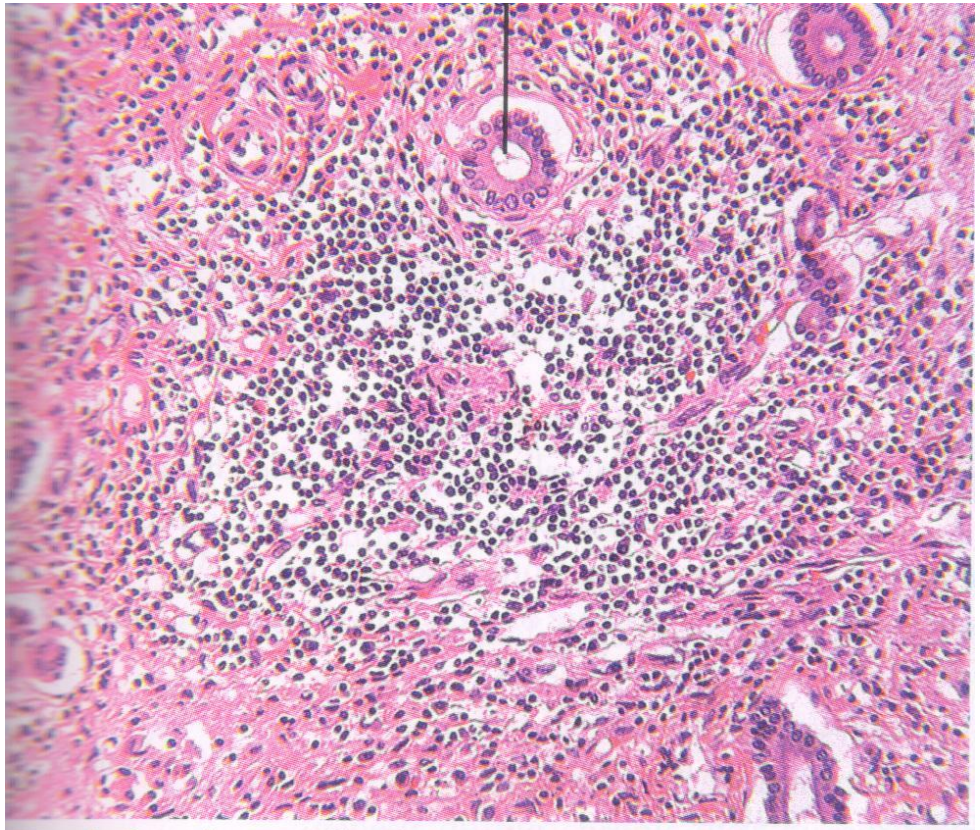
1. Concentration (up to 10-fold) and storage of bile between meals.
2. Release of bile by contraction of the muscularis in response to **cholecystokinin** stimulation (produced by enteroendocrine cells in the duodenum) and **neural stimuli**, together with **relaxation of the sphincter of Oddi** (a muscular ring surrounding the opening of the bile duct in the wall of the duodenum).
3. Regulation of hydrostatic pressure within the biliary tract.



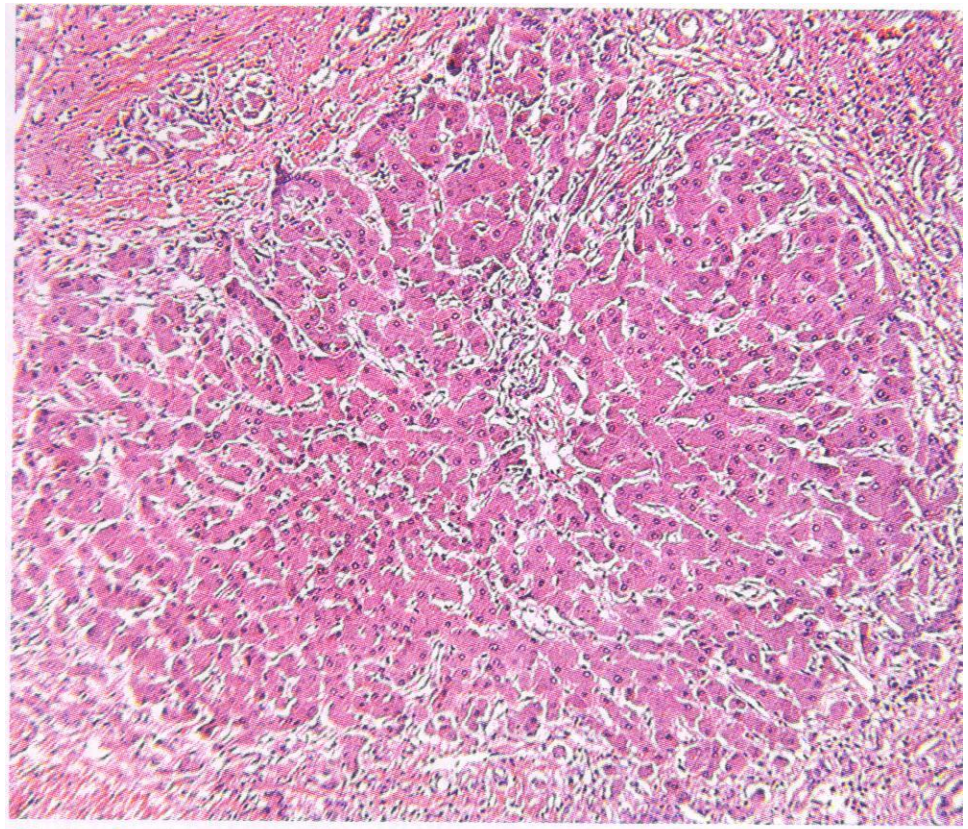
Clinical significance

Cholestasis defines the impaired formation and excretion of the bile at the level of the hepatocyte (**intrahepatic cholestasis**) or a structural (tumor of the pancreas or biliary tract, cholangiocarcinoma) or mechanical (**cholelithiasis**, produced by gallstones) perturbation in the excretion of bile (**extrahepatic cholestasis**).

Clinically, cholestasis is detected by (1) the presence in blood of **bilirubin** and bile acids, secreted into bile under normal conditions; (2) elevation in serum of **alkaline phosphatase** (an enzyme associated with the plasma membrane of the bile canaliculus); and (3) **radiologic examination** (many gallstones are radiopaque and can be detected on a plain radiograph).



Chronic liver disease. Fibrosis and inflammatory cells, mainly lymphocytes and macrophages, are seen in the distorted portal space.



Cirrhosis. Regenerated hepatocyte nodule surrounded and infiltrated by connective tissue containing collagens and extracellular matrix material.