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Chapter 25: Liver Function

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Introduction

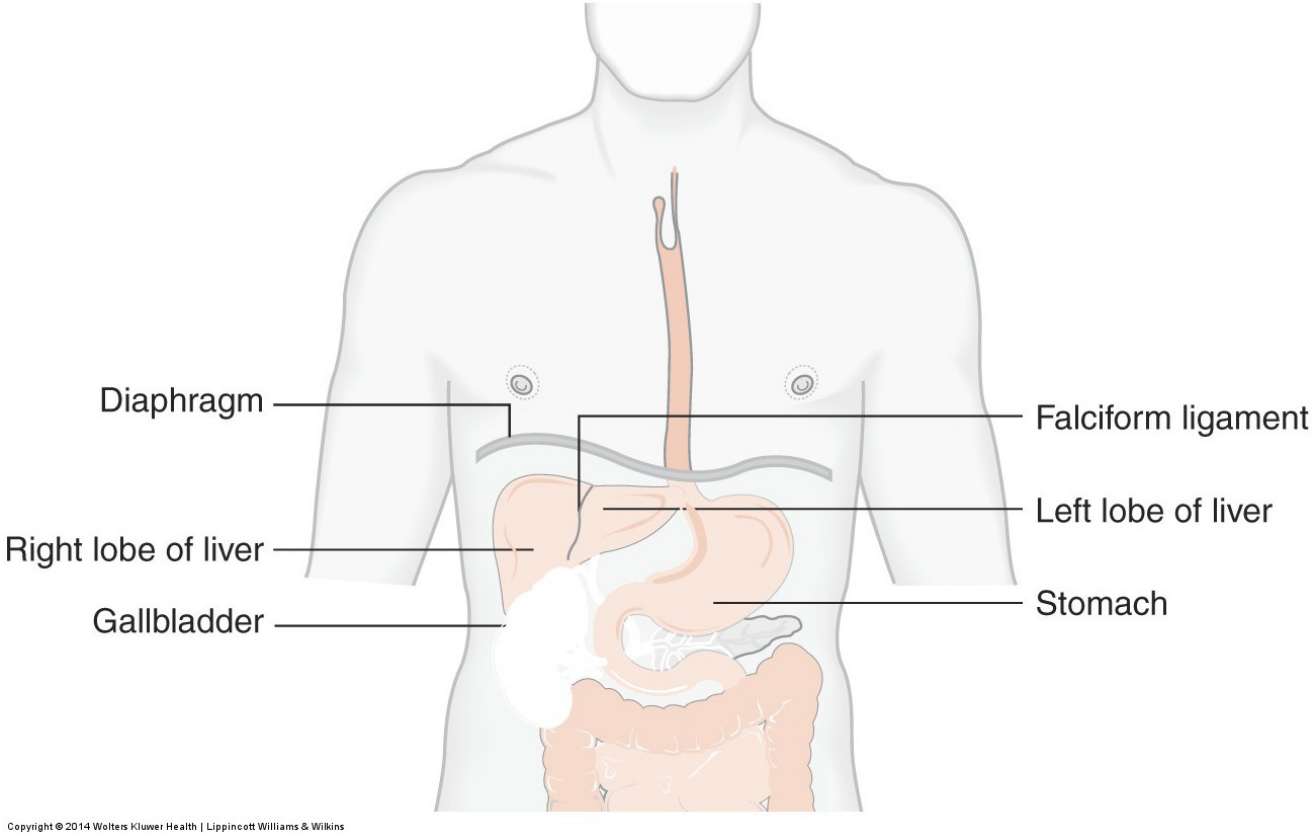
- Liver
  - Largest internal organ; functionally complex
  - Plays critical role in:
    - Metabolism
    - Digestion
    - Detoxification
    - Elimination of substances from body
    - Glycogen storage
  - Unique in resilience, ability to regenerate cells destroyed by short-term injury or disease

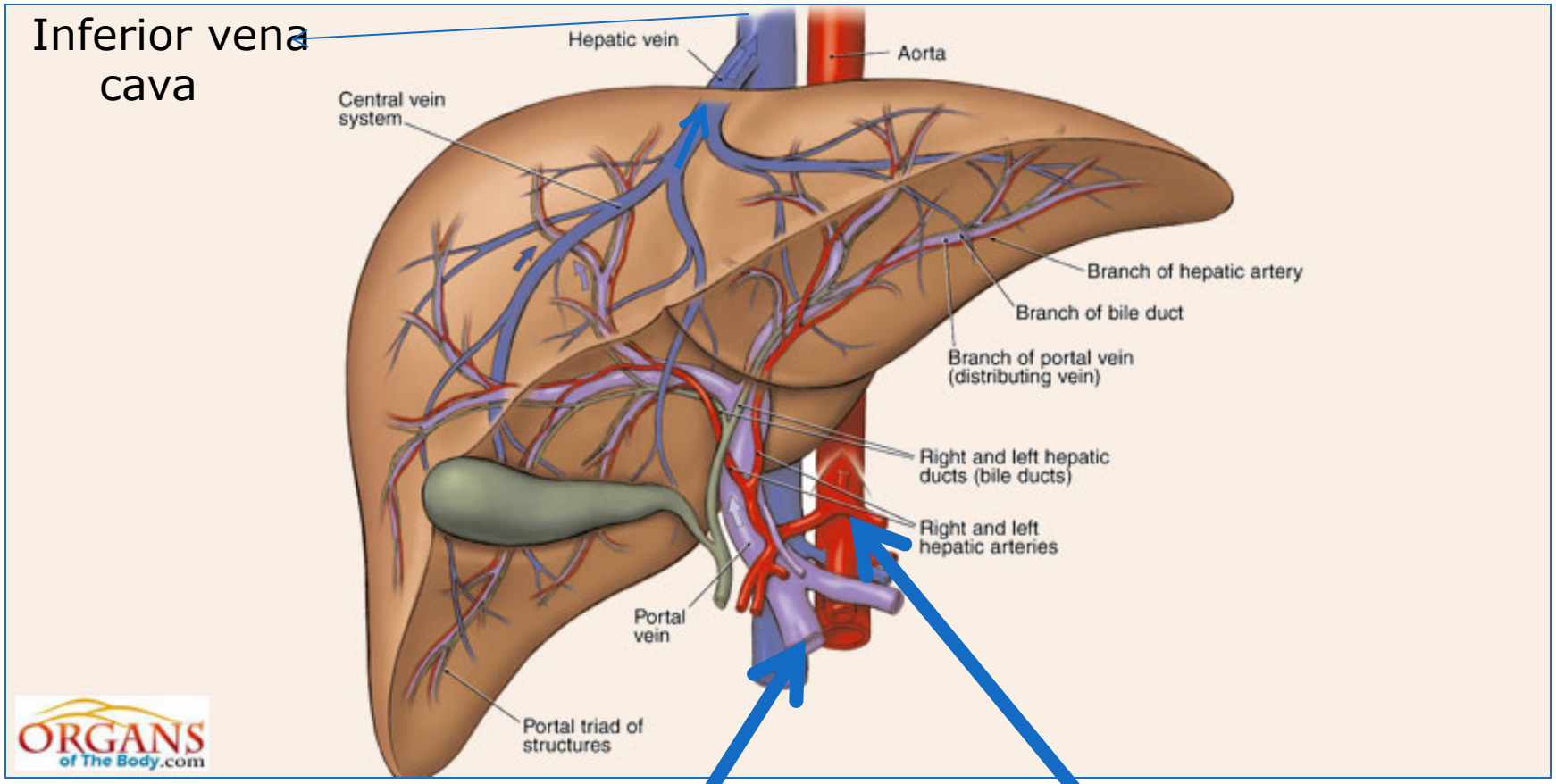
Anatomy

- Gross Anatomy
  - Liver weighs 1.2–1.5 kg in healthy adult
  - Located beneath & is attached to diaphragm, protected by rib cage, held in place by ligamentous attachments
  - Divided unequally into 2 lobes by falciform ligament
  - Extremely vascular; receives blood from 2 sources:
    - Hepatic artery (supplies 25%)
    - Portal vein (supplies 75%)
  - **Bile canaliculi:** small spaces between hepatocytes that form intrahepatic ducts where excretory products of cell can drain

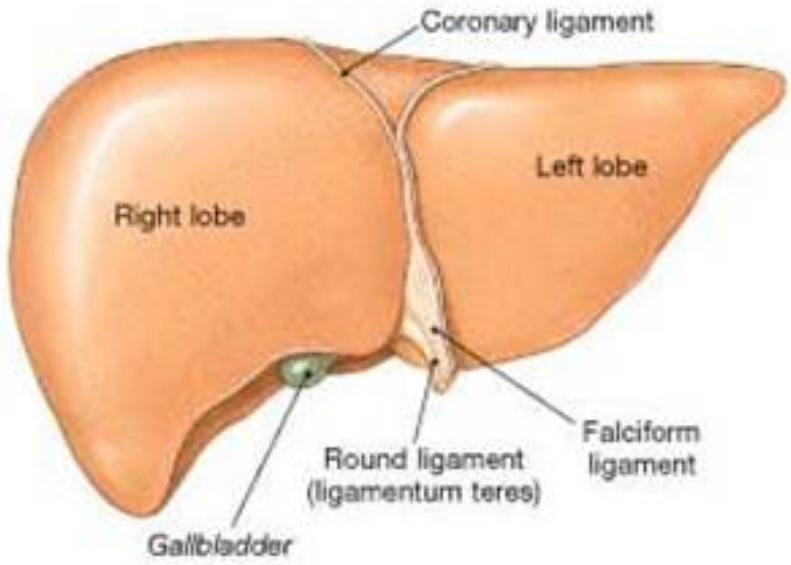
Anatomy (cont'd)

- Gross anatomy of the liver

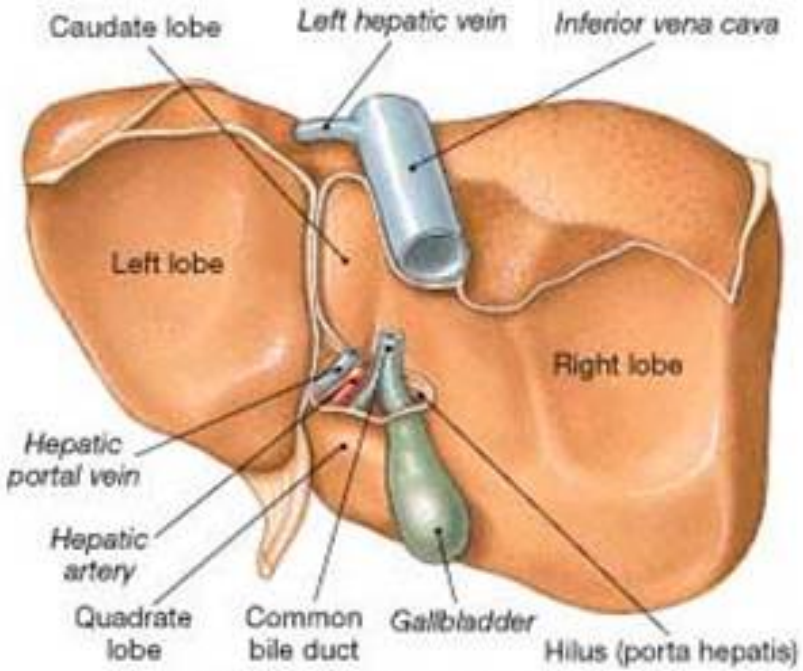




Liver receives blood via portal vein (75%) & hepatic artery (25%)



(b) Anterior (parietal) surface



(c) Posterior (visceral) surface

FIGURE 24-19 Anatomy of the Liver. **(b)** The anterior surface of the liver. **(c)** The posterior surface of the liver.

Ex

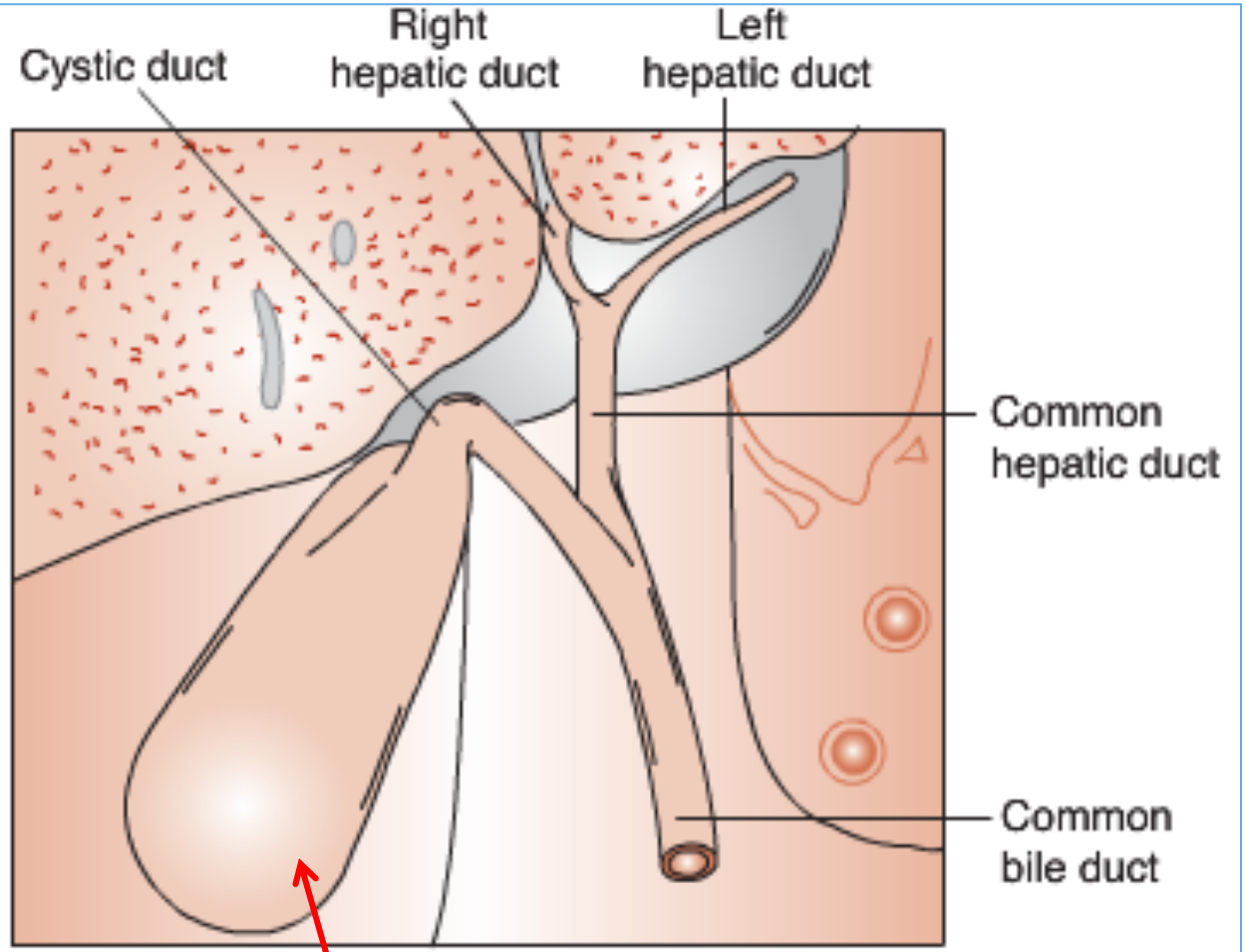


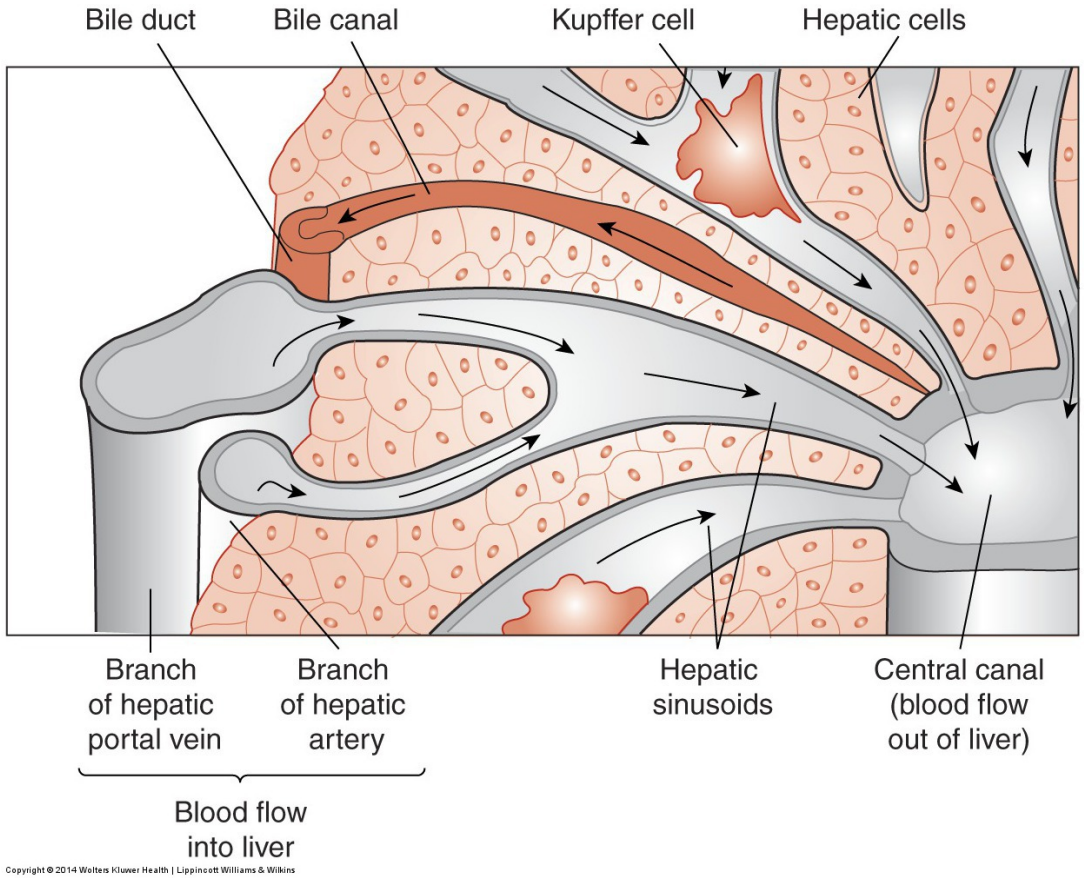
FIGURE 25-3 Excretory system of the liver.

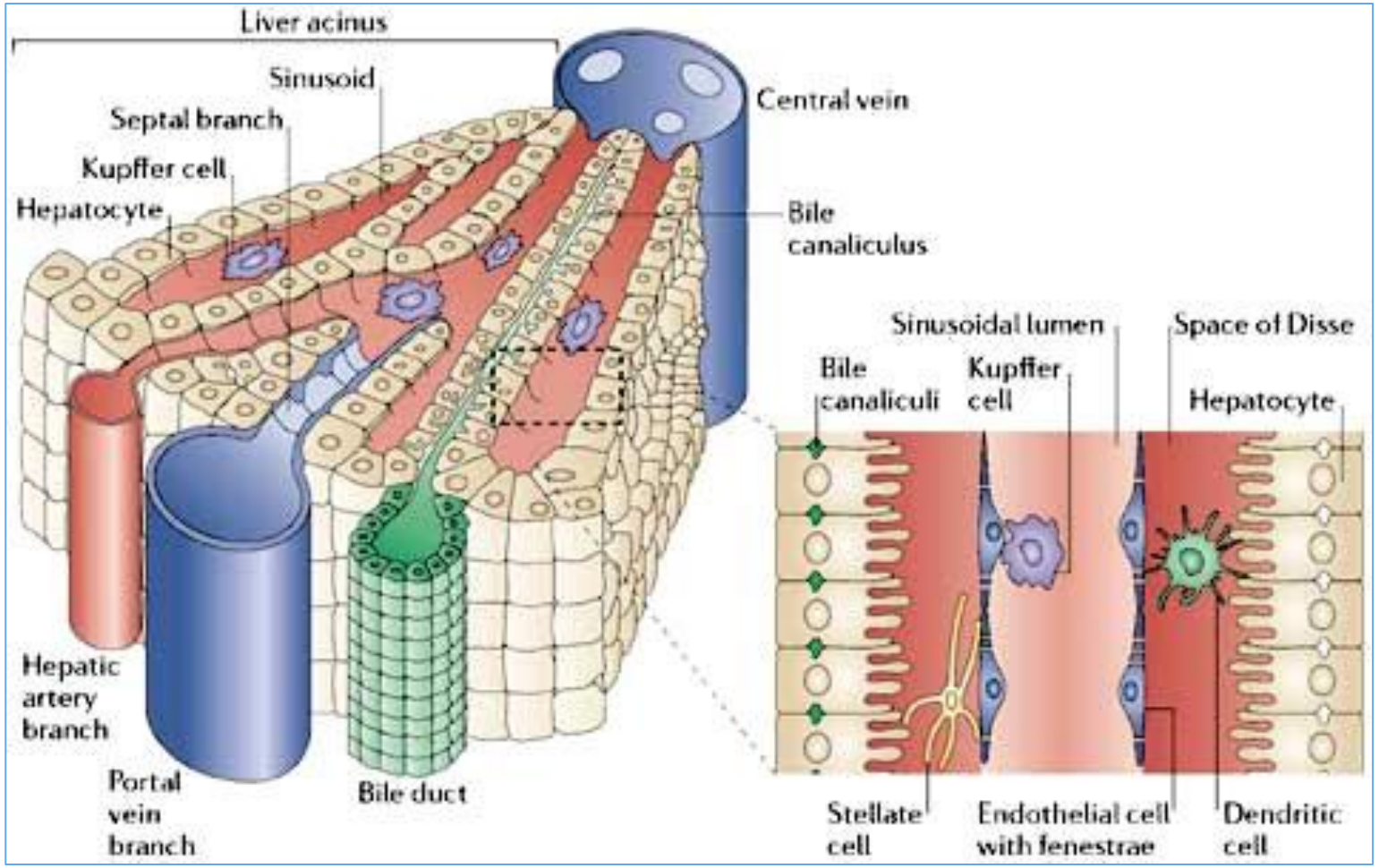
Anatomy (cont'd)

- Microscopic Anatomy
  - Lobules
    - Microscopic units that divide liver
    - Responsible for all metabolic & excretory functions
    - 6-sided structures with centrally located vein & portal triads
    - Portal triad contains hepatic artery, portal vein, bile duct.
  - Two major cell types in liver
    - **Hepatocytes:** large cells radiating outward from central vein
    - **Kupffer cells:** macrophages lining sinusoids; act as phagocytes, engulfing bacteria, debris, toxins

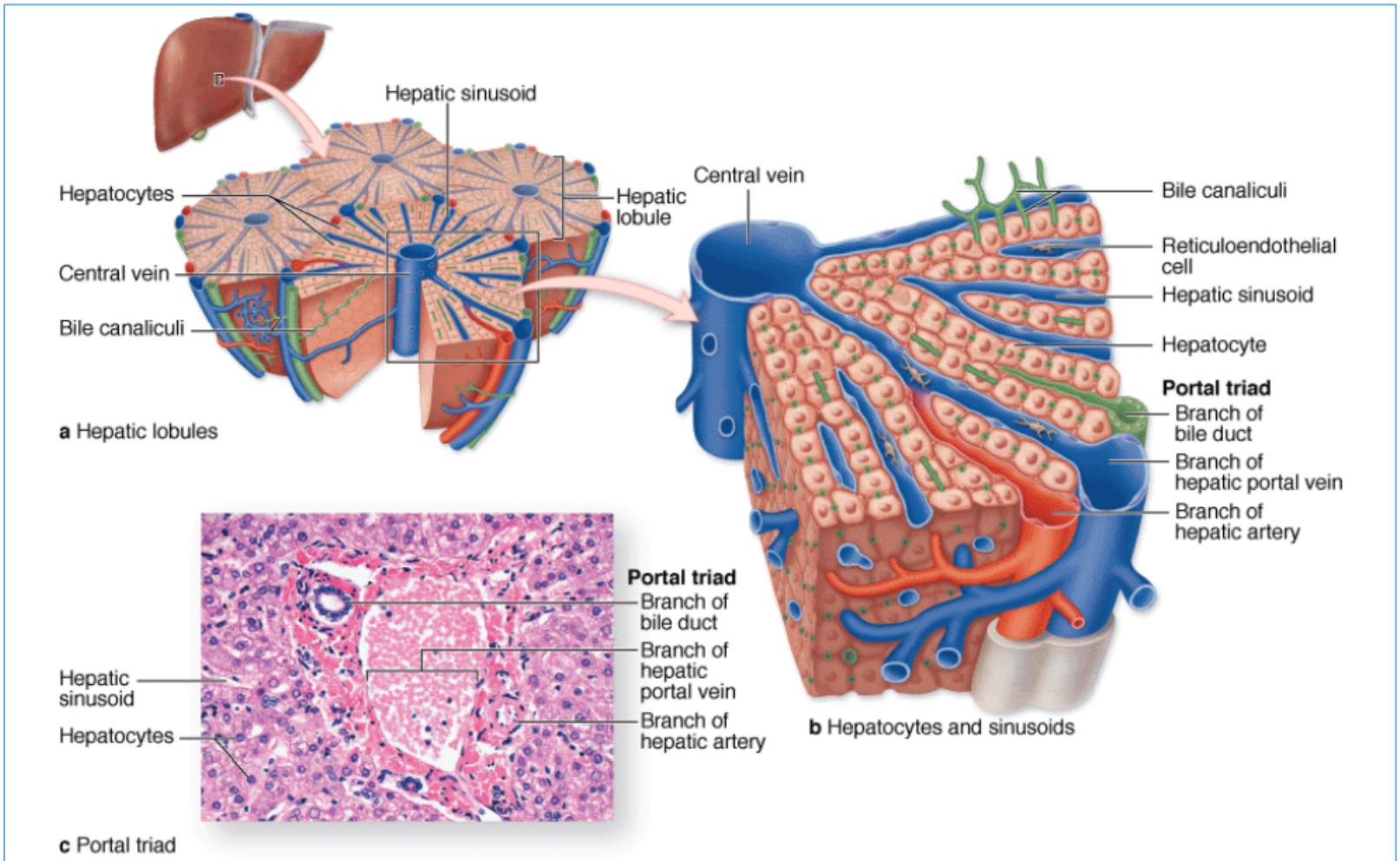
Anatomy (cont'd)

- Microscopic anatomy of the liver





The liver contains thousands of lobules, which are the structural & functional units of liver. Lobules contain hepatocytes.



Biochemical Functions

- Excretory and Secretory
  - Liver is only organ with capacity to rid body of heme waste.
  - Bile
    - Made up of bile acids or salts, bile pigments, cholesterol
    - Body produces 3 L of bile per day & excretes 1 L.
  - Bilirubin
    - Principal pigment in bile, derived from breakdown of heme in red blood cells
    - 200–300 mg produced per day
    - Bilirubin is transported by albumin & transferred to liver
    - Most is eliminated in feces, some in urine.

- Hepatocytes converts it to conjugated bilirubin
- Ligandin in hepatocytes transport unconjugated bilirubin
- Conjugation of bilirubin requires the enzyme UDPGT
- Conjugated bilirubin is secreted into bile canaliculi … Bile duct >> intestine
- Intestinal bacteria convert conjug bilirubin to mesobilirubinogen, further reduced to urobilinogen (colorless)
- Most urobilinogen (80%) is oxidized to urobilin or stercobilin (orange-colored) and excreted in feces
- Ref range for bilirubin in serum is 0.2-1.0 mg/dL, mostly conjugated bilirubin

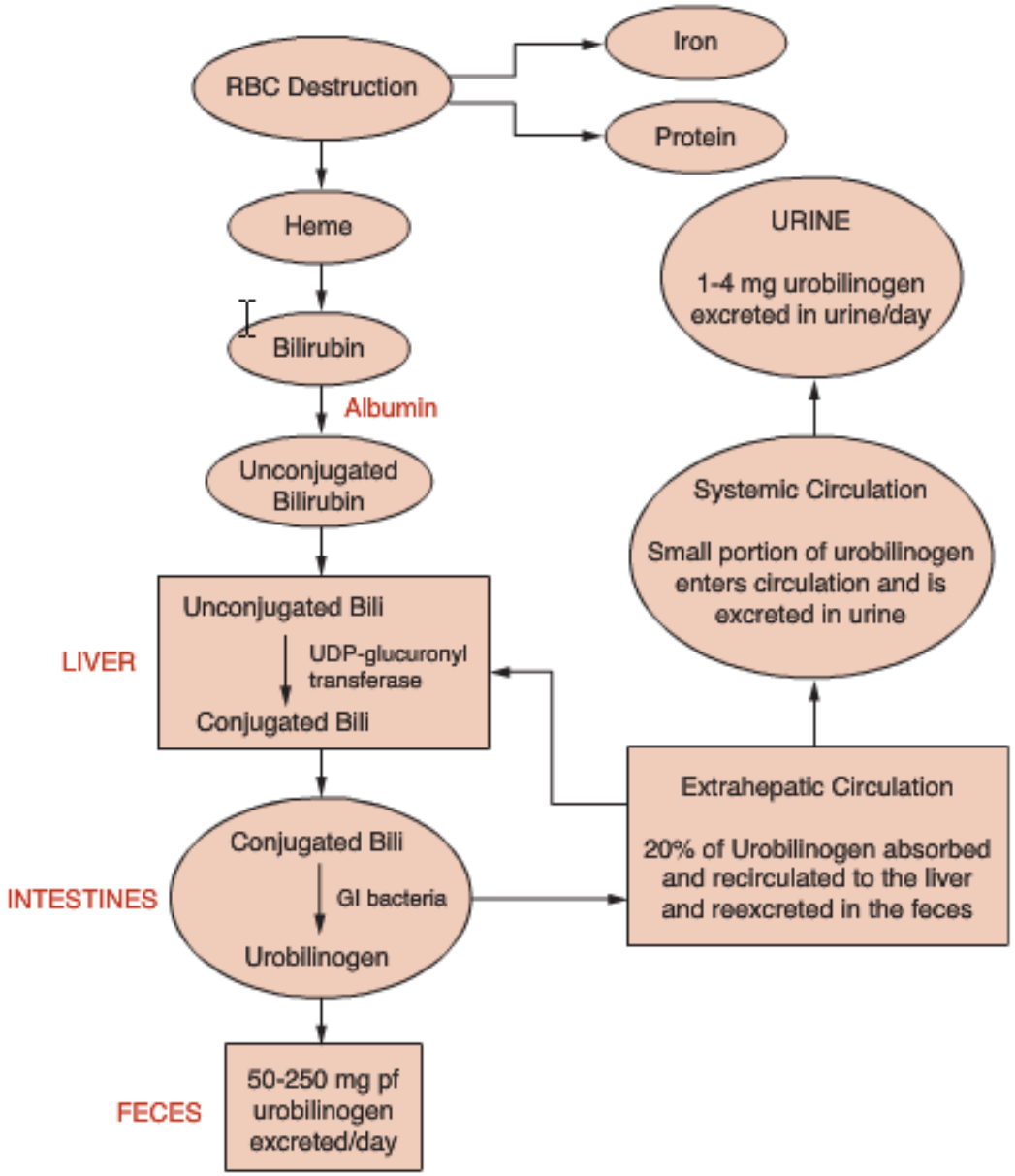
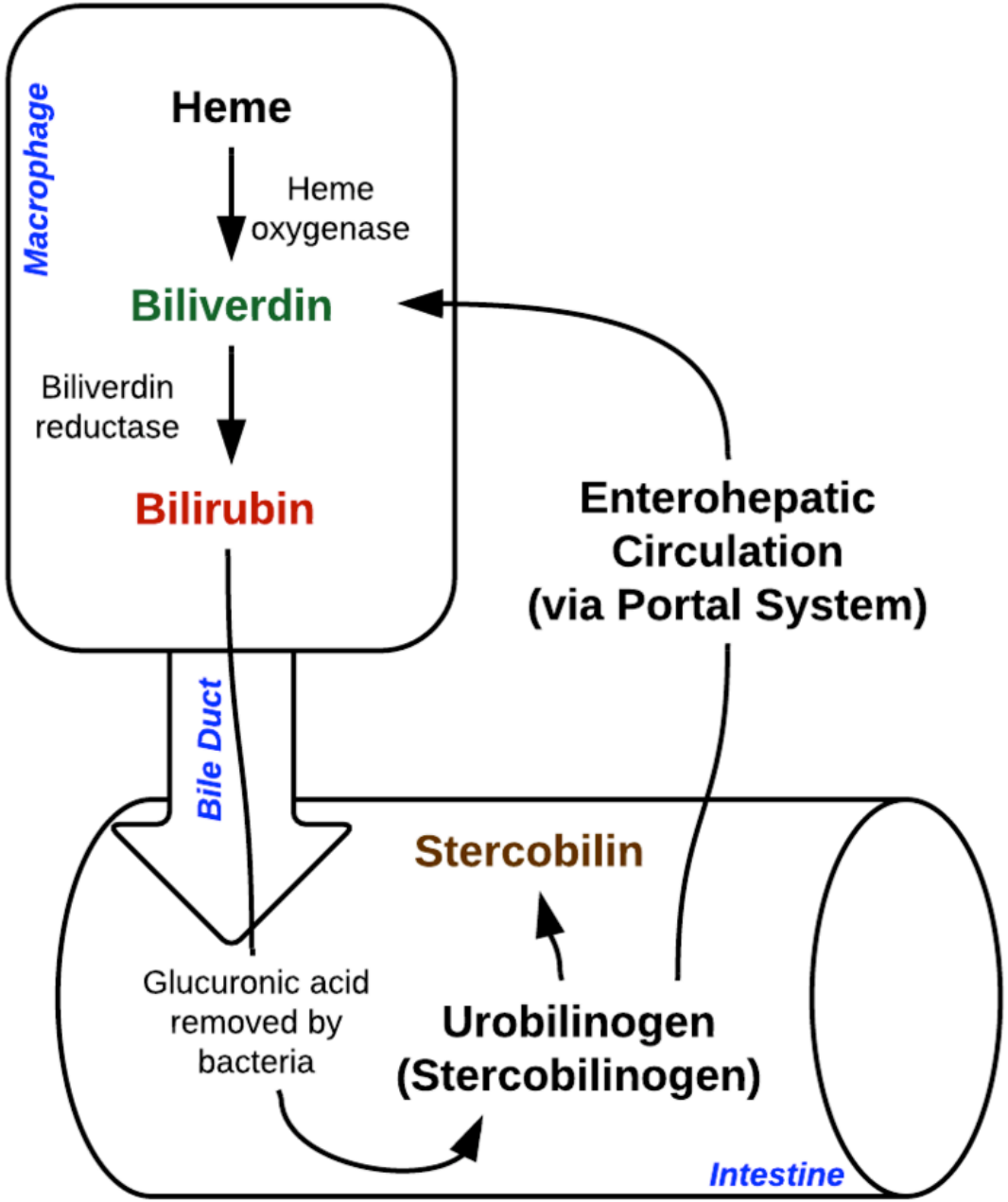
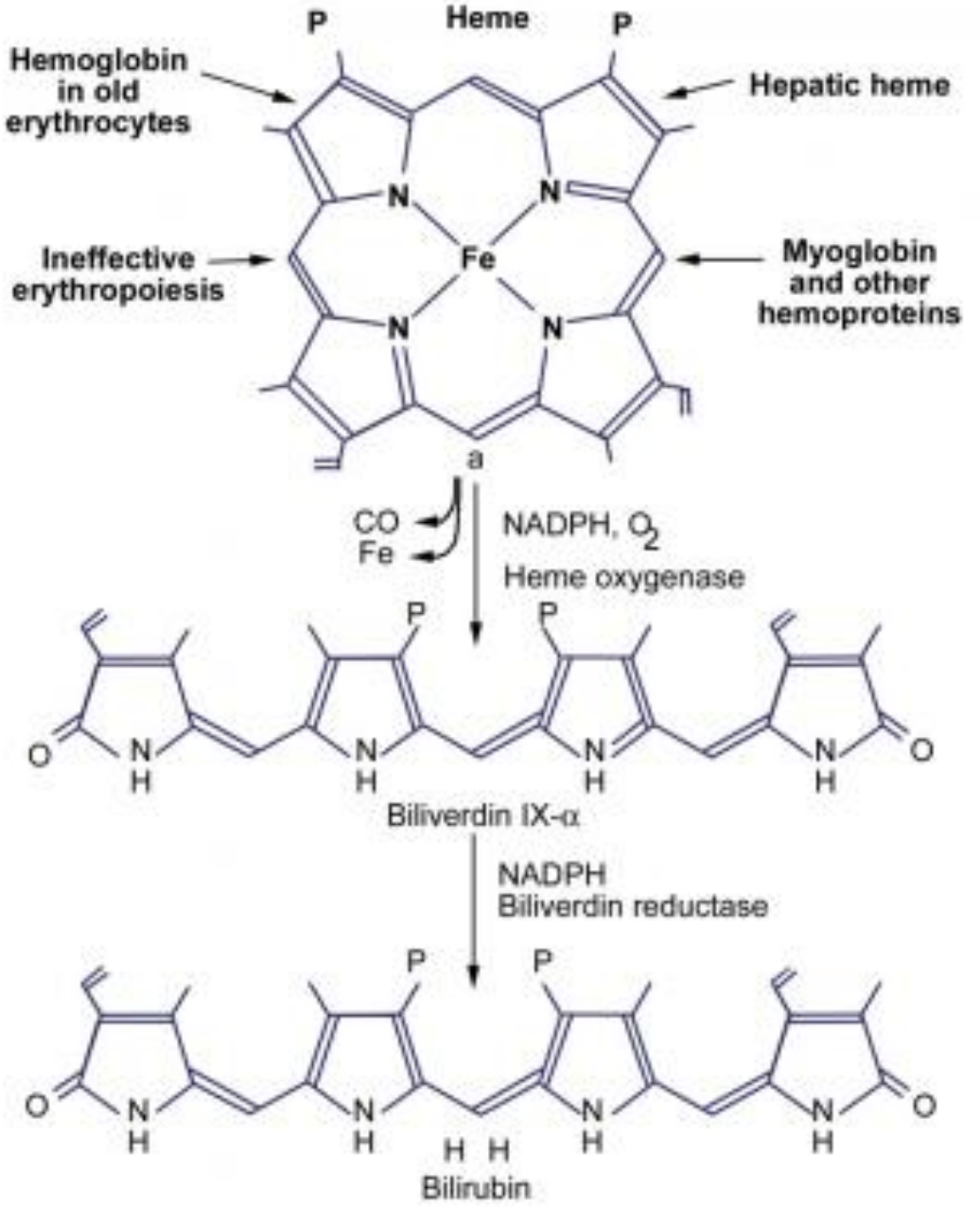
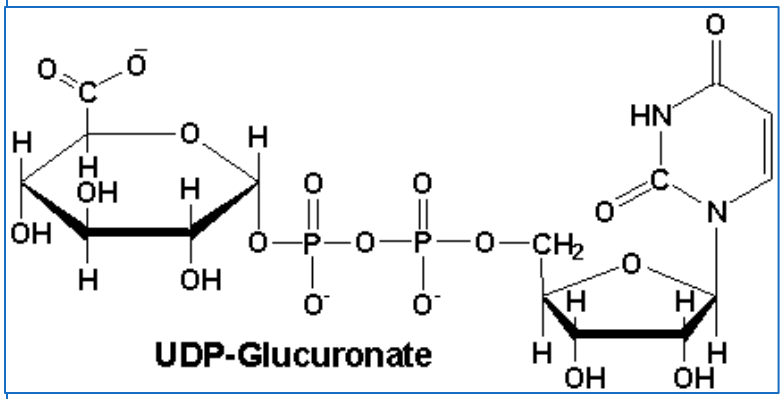


FIGURE 25-5 Metabolism of bilirubin. Reprinted by permission of Waveland Press, Inc. from Anderson SC, Cockayne S. *Clinical Chemistry/Concepts and Applications/2003.* Long Grove, IL: Waveland Press, Inc.; 2007. All rights reserved.


Macrophage
Heme
Heme oxygenase
Biliverdin
Biliverdin reductase
Bilirubin
Enterohepatic Circulation (via Portal System)
Bile Duct
Stercobilin
Glucuronic acid removed by bacteria
Urobilinogen (Stercobilinogen)
Intestine





Biochemical Functions (cont'd)

- Metabolism
  - Carbohydrate synthesis
    - Liver maintains stable glucose concentrations by storing it as glycogen & degrading glycogen when needed by body.
  - Lipid synthesis
    - Liver breaks down fatty acids to form triglycerides, phospholipids, or cholesterol.
  - Protein synthesis

Detoxification & Drug Metabolism

- It is a gatekeeper between substances absorbed and those released into systemic circulation
- Every substance that is absorbed in the GIT must first pass through the liver (**first pass**).
- This allows important substances to reach the circulation and prevent toxic or harmful substances from reaching the circulation
- Mechanism of drug detoxification:
  - Bind material irreversibly to inactivate the drug
  - Chemically modify the substance so that it is excreted

Liver Function Alterations During Disease

- Jaundice or Icterus
  - Yellow discoloration of skin, eyes, & mucous membranes
  - Usually the concentration of bilirubin in the blood must exceed 2–3 mg/dl for the coloration to be easily visible
  - Results from retention of bilirubin or other substances
  - Classified based on site of disorder

Reference ranges

• Total Bilirubin (conjugated + unconjugated)	0.2 - 1.0	mg/dl
• Conjugated bilirubin	0.0 - 0.2	mg/dl
• Full-term newborns	2.0 – 6.0	mg/dl

General classifications of jaundice

1. Prehepatic

- Excess RBC destruction
- Excessive amounts of bilirubin is presented to the liver (**Not** impaired liver function)
- Increased unconjugated bilirubin
- Unconjugated bilirubin is water insoluble and is bound to albumin
- It is not filtered by the kidney and will not appear in urine.

2. Hepatic

- Defective liver function
- May result from:

1. **Hepatocellular injury or destruction**
2. **Neonatal physiologic jaundice**
3. **Gilbert syndrome**
   - Reduced activity of UDPGT enzyme (20%-30% of normal)

   mutations in the UGTA1A1 gene encoding the UDPGT enzyme
4. **Crigler-Najjar Syndrome**
   - Type 1, complete absence of enzyme
   - Type II, severe deficiency of the enzyme
5. **Dubin-Johnson syndrome**
   - Removal of conjugated bilirubin from the liver cell and the excretion into the bile is defective
   - *Rare autosomal recessive inherited disorder caused by a deficiency of the canalicular multidrug resistance/multispecific organic anionic transporter protein (MDR2/cMOAT)*

TABLE 25-1 CHANGES IN CONCENTRATION OF BILIRUBIN IN THOSE WITH JAUNDICE

	SERUM		
TYPE OF JAUNDICE	**TOTAL BILIRUBIN**	**CONJUGATED BILIRUBIN**	**UNCONJUGATED BILIRUBIN**
Prehepatic	↑	↑	↑
Hepatic			
• Gilbert's disease	↑	↔	↑
• Crigler-Najjar syndrome	↑	↓	↑
• Dubin-Johnson	↑	↑	↔
• Rotor syndrome	↑	↑	↔
• Jaundice of newborn	↑	↔	↑
Posthepatic	↑	↑	↑

Adapted from Table 27-3 of Kaplan LA, Pesce AJ, Kazmierczak S. *Clinical Chemistry: Theory, Analysis, Correlation*. 4th ed. St. Louis, MO: Mosby; 2003.

3. Posthepatic

- Impaired ability of liver to excrete bile into the GI tract due to physical obstruction or biliary obstructive disease
  - gallstones, tumors
- Rise in serum level of conjugated bilirubin but normal to elevated unconjugated bilirubin.
- Conjugated bilirubin appears in urine
- Serum enzymes that indicate biliary obstruction, including alkaline phosphatase and GGT, are also often elevated

Physiological Jaundice of the newborn

- Immature liver at birth
- Temporary deficiency of UDPGT
- Small / moderate elevated unconjugated bilirubin lasting a few days.
- If not processed it is deposited in the brain and nerve cells, causing cell damage and death in the newborn >> called kernicterus

5’-Nucleotidase

- **5’-Nucleotidase** is an enzyme which catalyzes the phosphorylytic cleavage of 5'nucleotides
- In mammalian cells the enzyme is predominantly located in the plasma membrane and its primary role is in the conversion of extracellular nucleotides (e.g. 5'-AMP), which are generally impermeable, to the corresponding nucleoside (e.g. adenosine) which can readily enter most cells.
- Consequently, the enzyme plays a key role in the metabolism of nucleotides.
- The enzyme has a wide substrate specificityfor nucleotides and has been shown to hydrolyze 5’-nucleotides rapidly, ribose-5-phosphate slowly, and other phosphate esters extremely slowly (if at all)

5’-Nucleotidase: clinical significance

- The concentration of 5’-nucleotidase protein in the blood is often used as a liver function test in individuals that show signs of liver problems.
- The combined assays of serum 5’-nucleotidase and alkaline phosphatase (ALP) activities are extremely helpful in differential diagnosis since serum 5’-nucleotidase activity is increased in
  - *Obstructive hepatobiliary disorders*, but not in bone disorders, whereas serum ALP activity is generally increased in both categories of disease

CASE STUDY 25-1

The following laboratory test results were obtained in a patient with severe jaundice, right upper quadrant abdominal pain, fever, and chills (Case Study Table 25-1.1).

Questions

1. What is the most likely cause of jaundice in the patient?

CASE STUDY TABLE 25-1.1
LABORATORY RESULTS

Serum alkaline phosphatase	Four times normal
Serum cholesterol	Increased
AST (SGOT)	Normal or slightly increased
5′-Nucleotidase	Increased
Total serum bilirubin	25 mg/dL
Conjugated bilirubin	19 mg/dL
Prothrombin time	Prolonged but improves with a vitamin K injection

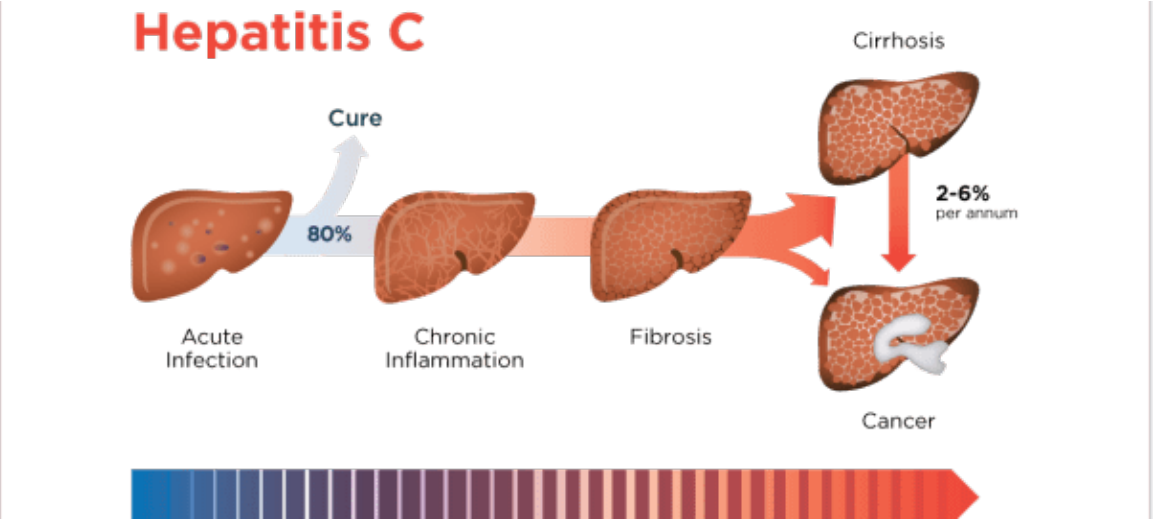
1. *The laboratory test results suggest jaundice as a result of extrahepatic obstruction from a stone in the common bile duct, carcinoma of the head of the pancreas.*

Liver Function Alterations During Disease (cont'd)

- Cirrhosis
  - Condition in which scar tissue replaces healthy liver tissue
  - Scar tissue blocks blood flow & prevents proper functioning.
  - Commonly caused by chronic alcoholism & hepatitis C infection
    - Also: chronic Hep B and D; fatty liver disease; autoimmune disorders, inherited
- Tumors
  - 90–95% of hepatic malignancies are metastatic, not originating in liver cells (primary).
  - **Benign:** hepatocellular adenoma, hemangiomas
  - **Malignant:** hepatocellular carcinoma, hepatocarcinoma, hepatoma
  - Whether primary or metastasic, any malignant tumor in the liver carries a poor prognosis, with survival times measured in months.

Liver Function Alterations During Disease (cont'd)

- Hepatitis
  - Injury to liver characterized by inflammation in liver tissue
  - **Causes:** viral, bacterial, & parasitic infections, radiation, drugs, chemicals, autoimmune diseases and toxins
  - **Symptoms:** jaundice, dark urine, fatigue, nausea, vomiting, abdominal pain



- Hepatitis
  - **Hepatitis A**
    - Most common form of viral hepatitis worldwide
    - Caused by infection with the hepatitis A virus (HAV) via contaminated or improperly handled food (oral–fecal route)
  - **Hepatitis B**
    - Can cause both acute & chronic hepatitis
    - Caused by infection with hepatitis B virus (HBV) via parenteral, perinatal, & sexual transmission
    - Serologic markers of HBV infection: HBcAg, HBsAg, HBeAg
  - **Hepatitis C**
    - Caused by infection with hepatitis C virus (HCV) via parenteral transmission (primarily by blood transfusion)

- Hepatitis
  - **Hepatitis D**
    - A unique subvirus satellite virus infection
    - Requires HbsAg of HBV for replication; can only occur in patients who already have hepatitis B
  - **Hepatitis E**
    - Caused by infection with hepatitis E virus (HEV): a nonenveloped RNA virus that is only 27–34 nm in diameter
    - Transmitted primarily by fecal–oral route
    - Characterized by water-borne epidemics in developing countries

TABLE 25-3 THE HEPATITIS VIRUSES

	NUCLEOTIDE	INCUBATION PERIOD	PRIMARY MODE OF TRANSMISSION	VACCINE	CHRONIC INFECTION	SEROLOGIC DIAGNOSIS AVAILABLE
Hepatitis A	RNA	2–6 wk	Fecal–oral	Yes	No	Yes
Hepatitis B	DNA	8–26 wk	Parenteral, sexual	Yes	Yes	Yes
Hepatitis C	RNA	2–15 wk	Parenteral, sexual	No	Yes	Yes
Hepatitis D	RNA	—	Parenteral, sexual	Yes	Yes	Yes
Hepatitis E	RNA	3–6 wk	Fecal–oral	No	?	Yes

Liver Function Alterations During Disease (cont'd)

- Reye Syndrome
  - A group of disorders caused by infectious, metabolic, toxic, or drug-induced disease found predominantly in children
  - Often preceded by viral syndrome such as varicella, gastroenteritis, or upper respiratory tract infection (influenza)
  - Associated with ingestion of aspirin during viral syndrome
  - Acute illness characterized by:
    - Noninflammatory encephalopathy
    - Fatty degeneration of liver
    - Clinical presentation of profuse vomiting
    - Neurologic impairment

Liver Function Alterations During Disease (cont'd)

- Drug- and Alcohol-Related Disorders
  - Drug-induced liver disease accounts for 1/3 to 1/2 of all reported cases of acute liver failure in U.S.
  - Most common mechanism of injury is adverse immune response to drug directed against liver.
  - Ethanol (alcohol) is most significant cause of hepatic toxicity.
  - Acetaminophen, excessive doses
  - Three stages of liver injury due to excessive alcohol consumption
    - 1. **Alcoholic fatty liver:** mild; recovery with removal of drug
    - 2. **Alcoholic hepatitis:** evidence of liver damage
    - 3. **Alcoholic cirrhosis:** most severe; poor prognosis

Assessment of Liver Function

- Liver function tests (LFT) are a group of blood tests that give an indication of whether the liver is functioning properly.
- The tests are also very useful to see if there is active damage in the liver (hepatitis) or slow bile flow (cholestasis).
- Because the liver is the site for the conjugation of bilirubin, the liver may be assessed by measurement of total and conjugated bilirubin

Assessment of Liver Function/Liver Function Tests

- Bilirubin
  - Analysis
    - All commonly used methods for measuring bilirubin stem from technique described by Malloy & Evelyn in 1937.
    - Based on reaction of bilirubin with a diazotized sulfanilic acid solution with a 50% methanol solution as an accelerator
    - Also quantified by bilirubinometry in neonatal population
    - **Three fractions: 1)** conjugated (direct), **2)** unconjugated (indirect), & **3)** delta

Assessment of Liver Function/Liver Function Tests (cont'd)

- Bilirubin
  - Specimen Collection and Storage
    - May be performed on serum (preferred) or plasma
    - Fasting sample is preferred; hemolyzed should be avoided.
    - Is sensitive to light & should be protected
  - Methods
    - Most commonly used are Jendrassik-Grof or Malloy Evelyn.

- **Evelyn-Malloy Reaction**

Bilirubin + diazotized sulfanilic acid + accelerator ⟶ 2 azobilirubin (Total bilirubin)

Bilirubin + diazotized sulfanilic acid ⟶ 2 azobilirubin (Conjugated bilirubin)

Total bilirubin – Conjugated bilirubin = Unconjugated bilirubin (Indirect bilirubin)

FIGURE 25-7 Methods to measure different fractions of bilirubin.

Rxn is performed at pH 1.2 where the azobilirubin produced is red-purple in color with a maximal absorption of 560 nm.
The most commonly used accelerator is methanol

Assessment of Liver Function/Liver Function Tests (cont'd)

- Urobilinogen in Urine and Feces
  - Urobilinogen is a colorless end product of bilirubin metabolism that is oxidized by intestinal bacteria to brown pigment urobilin.
  - Increased levels in urine are found in hemolytic disease & defective liver cell function.
  - Absence from urine & stool is seen with complete biliary obstruction.
  - Most quantitative methods involve reaction of urobilinogen with p-dimethylaminobenzaldehyde (Ehrlich's reagent) to form a red color.
- Sample:
  - fresh 2-hour urine specimen
  - Aqueous extract of feces

TABLE 25-2 REFERENCE RANGES FOR BILIRUBIN IN ADULTS AND INFANTS

POPULATION	TYPE OF BILIRUBIN	REFERENCE RANGE
Adults	Conjugated bilirubin	0.0–0.2 mg/dL (0–3 µmol/L)
	Unconjugated bilirubin	0.2–0.8 mg/dL (3–14 µmol/L)
	Total bilirubin	0.2–1.0 mg/dL (3–17 µmol/L)
Premature infants	Total bilirubin at 24 h	1–6 mg/dL (17–103 µmol/L)
	Total bilirubin at 48 h	6–8 mg/dL (103–137 µmol/L)
	Total bilirubin 3–5 d	10–12 mg/dL (171–205 µmol/L)
Full-term infants	Total bilirubin at 24 h	2–6 mg/dL (34–103 µmol/L)
	Total bilirubin at 48 h	6–7 mg/dL (103–120 µmol/L)
	Total bilirubin 3–5 d	4–6 mg/dL (68–103 µmol/L)

Assessment of Liver Function/Liver Function Tests (cont'd)

- Serum Bile Acids
  - Rarely performed because methods are very complex
  - Patterns of individual bile acids & their state of conjugation are examined.
- Enzymes
  - Are released into circulation after an injury that results in cytolysis or necrosis
  - Used to differentiate hepatocellular from obstructive liver disease

Assessment of Liver Function/Liver Function Tests (cont'd)

- Enzymes
  - Aminotransferases
    - Aspartate aminotransferase (AST)
    - Alanine aminotransferase (ALT)
  - Phosphatases
    - Alkaline phosphatase
    - 5'-Nucleotidase
    - Gamma-glutamyltransferase
    - Lactate dehydrogenase

Tests measuring hepatic synthetic ability

- **Protein Synthesis**
- Because the liver is the site for the synthesis of many proteins, the liver may be assessed by measurement total protein and albumin
  - Decreased levels of albumin usually develop only in severe hepatic dysfunction
- Plasma proteins
  - Prothrombin time (PT): due to decreased synthesis of clotting factors or decreased absorption of vitamin K due to disruption of bile flow
  - Commonly increased in liver disease
- Serum γ-globulin levels are transiently increased in acute liver disease and remain elevated in chronic liver disease.

Assessment of Liver Function/Liver Function Tests (cont'd)

- Tests Measuring Nitrogen Metabolism
  - Plasma ammonia level
    - The liver plays a major role in removing ammonia from the bloodstream and converting it to urea so that it can be removed by the kidneys
    - In liver failure, ammonia and other toxins increase in the bloodstream

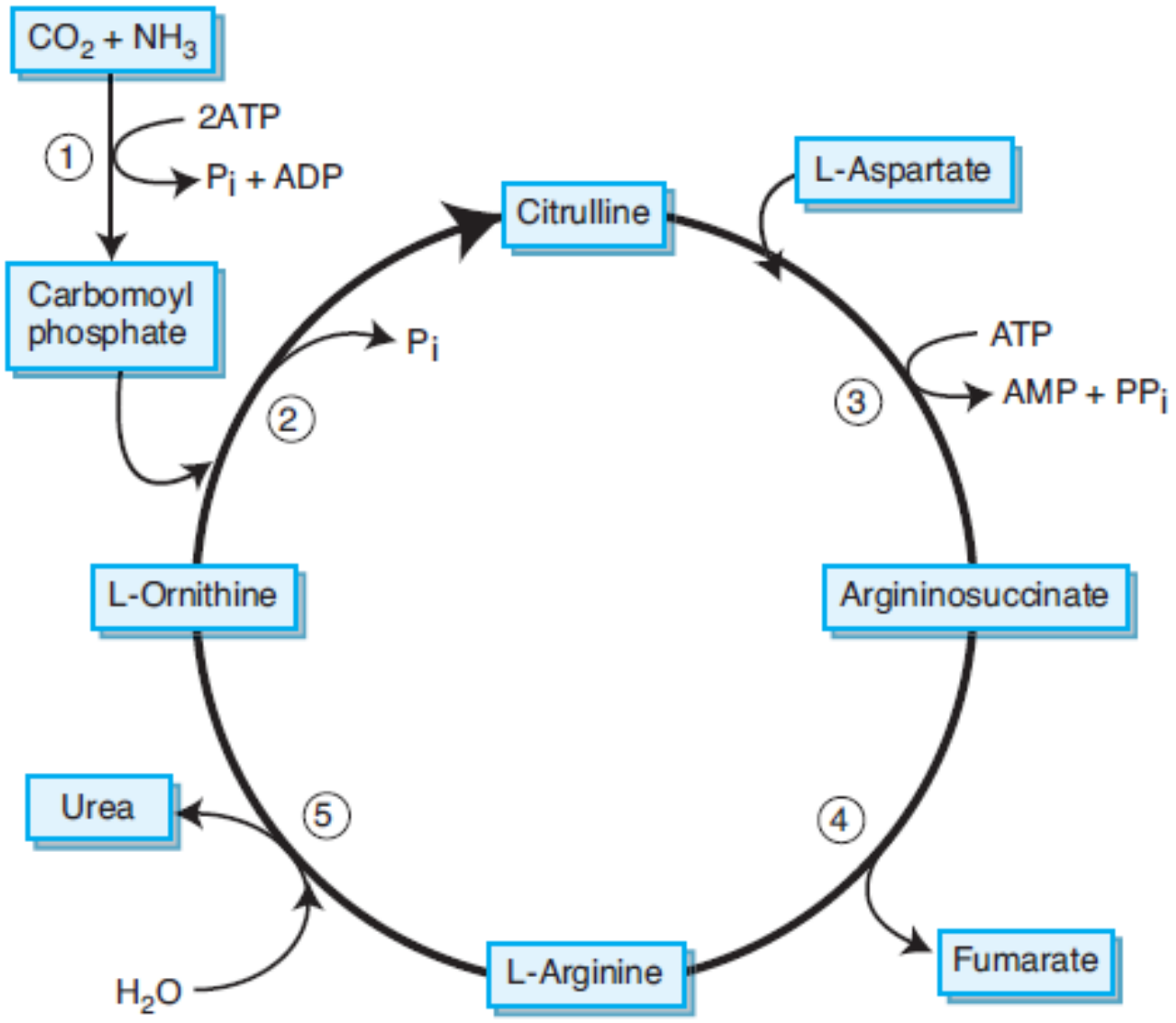


Figure 7–7. Ornithine cycle.

Ref: Clinical chemistry: a laboratory perspective. By Wendy Arneson & Jean Brickell, ©2007. Publisher: F.A. Davies. Chap7 /Page 260

CASE STUDY 25-2

The following laboratory test results were found in a patient with mild weight loss and nausea and vomiting, who later developed jaundice and an enlarged liver (Case Study Table 25-2.1)

Questions

1. What disease process is most likely in this patient?

CASE STUDY TABLE 25-2.1
LABORATORY RESULTS

Total serum bilirubin	20 mg/dL
Conjugated bilirubin	10 mg/dL
Alkaline phosphatase	Mildly elevated
AST (SGOT)	Significantly elevated
ALT (SGPT)	Moderately elevated
Albumin	Decreased
γ-Globulin	Increased

CASE STUDY 25-4

The following results were obtained in the patient from Case Study 25-2 (Case Study Table 25-4.1).

Questions

1. What is the most likely diagnosis?
2. What is the prognosis?
3. What complications may develop?

CASE STUDY TABLE 25-4.1
LABORATORY RESULTS

Hepatitis A antibody (IgG)	Positive
Hepatitis A antibody (IgM)	Negative
Hepatitis B surface antigen	Positive
Hepatitis B surface antibody	Negative
Hepatitis core antibody (IgM)	Positive
Hepatitis C antibody	Negative

CASE STUDY 25-3

The following laboratory results were obtained from a 19-year-old college student who consulted the Student Health Service because of fatigue and lack of appetite. She adds that she recently noted that her sclera appears somewhat yellowish and that her urine has become dark (Case Study Table 25-3.1).

Questions

1. What is the most likely diagnosis?
2. What additional factors in the patient's history should be sought?
3. What is the prognosis?

CASE STUDY TABLE 25-3.1
LABORATORY RESULTS

ALT (SGPT)	Elevated
AST (SGOT)	Elevated
Alkaline phosphatase	Minimally elevated
Lactate dehydrogenase	Elevated
Serum bilirubin	5 mg/dL
Urine bilirubin	Increased
Hepatitis A antibody (IgG)	Negative
Hepatitis A antibody (IgM)	Positive
Hepatitis B surface antigen	Negative
Hepatitis B surface antibody	Negative
Hepatitis C antibody	Negative

CASE STUDY 25-5

A 36-year-old man consulted his family physician because of liver function abnormalities, which had been noted initially during a preinsurance physical examination 6 months earlier. The following laboratory results were obtained, which were identical to those obtained 6 months ago (Case Study Table 25-5.1).

Questions

1. What is the most likely diagnosis?
2. What is the prognosis?
3. What complications may develop?
4. What additional tests should be done?

CASE STUDY TABLE 25-5.1
LABORATORY RESULTS

Hepatitis A antibody (IgG)	Positive
Hepatitis A antibody (IgM)	Negative
Hepatitis B surface antigen	Positive
Hepatitis B surface antibody	Negative
Hepatitis B core antibody (IgM)	Positive
Hepatitis C antibody	Negative