NOTES
LIVER, GALL BLADDER, & PANCREAS

BILE SECRETION & ENTEROHEPATIC CIRCULATION

osms.it/bile-secretion-enterohepatic-circulation

SYNTHESIS OF BILE, BILIRUBIN

- Hemoglobin from old red blood cells taken up by macrophages → biliverdin → unconjugated bilirubin → released into plasma, combines with albumin → unconjugated bilirubin absorbed into hepatic cells, released from albumin → liver conjugates unconjugated bilirubin → conjugated bilirubin excreted from hepatocytes into intestines → some conjugated bilirubin converted by bacteria into urobilinogen (soluble) → some urobilinogen reabsorbed through intestinal mucosa back into blood → re-excreted by liver back into gut/excreted by kidneys into urine → urobilinogen becomes urobilin → stercobilin in feces

RECYCLING OF BILE

- Bile transported from ileum into portal blood after digestion → portal blood delivers bile salts to liver → liver extracts bile salts from portal blood, adds to hepatic bile salt/acid pool → bile returned to gallbladder
- Some bile excreted into feces as stercobilin
- Only excreted bile needs to be replaced

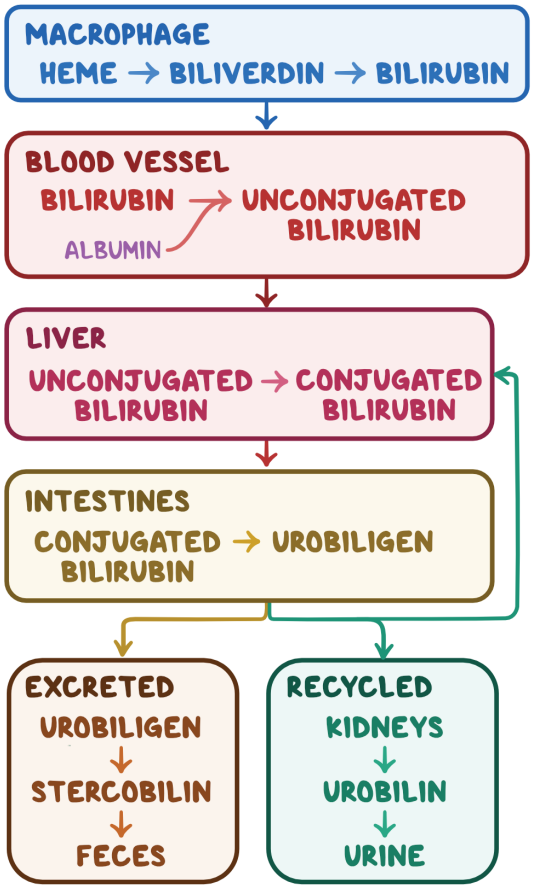

Figure 40.1 Bile synthesis to excretion/recycling pathway.

LIVER ANATOMY & PHYSIOLOGY

osms.it/liver-anatomy-physiology

LIVER ANATOMY

Functions

- Bile production, storage (e.g. glycogen), detoxification, nutrient interconversion, synthesis (e.g. albumin, clotting factors), phagocytosis (Kupffer cells)

Location

- Located in right upper quadrant (RUQ) under diaphragm, almost entirely within rib cage
  - Largest internal organ
- Covered by visceral peritoneum
  - Except superior-most region (bare area), contacts inferior surface of diaphragm
- *Falciform ligament*: mesentery separates right, left lobes; suspends liver from diaphragm, anterior abdominal wall
- *Round ligament/ligamentum teres*: inferior to falciform ligament, remnant of fetal umbilical vein

Four lobes

- Right lobe (largest)
- Left lobe
- Caudate lobe
- Quadrate lobe

Blood supply

- 75% from nutrient rich, oxygen poor portal vein
- 25% from nutrient poor, oxygen rich hepatic artery
- Enterohepatic circulation gives liver first access to nutrients, toxins, medications from gut

Liver lobule

- Functional unit of liver
  - Hexagonal liver lobule made of hepatocytes
- Each liver lobule surrounded by six portal triads on each point withlobes central vein in center

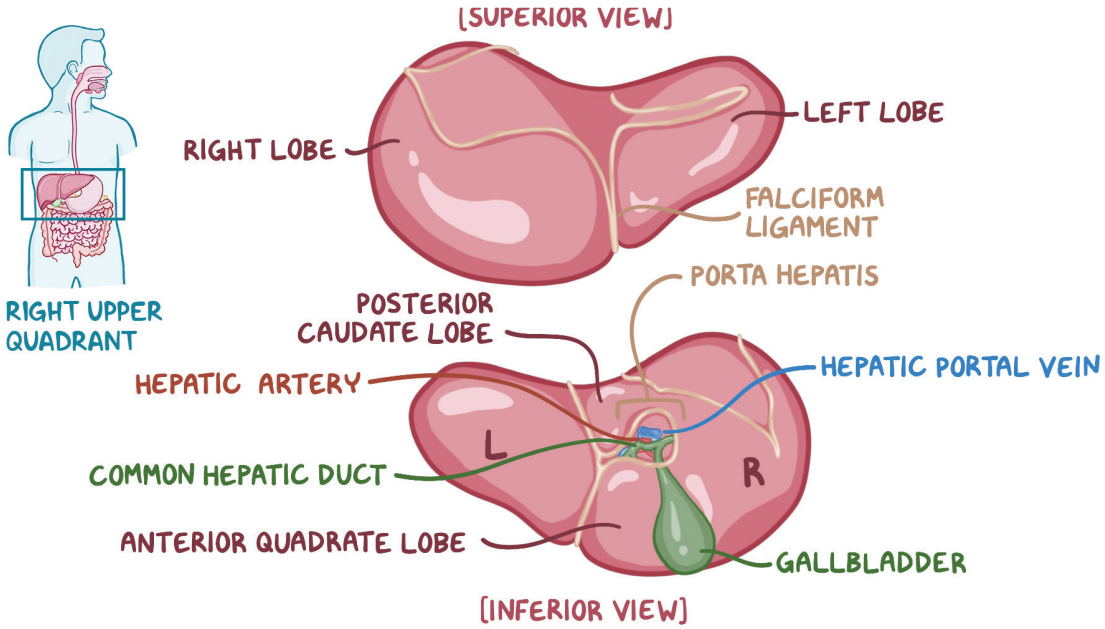

Figure 40.2 Superior and inferior view of liver.

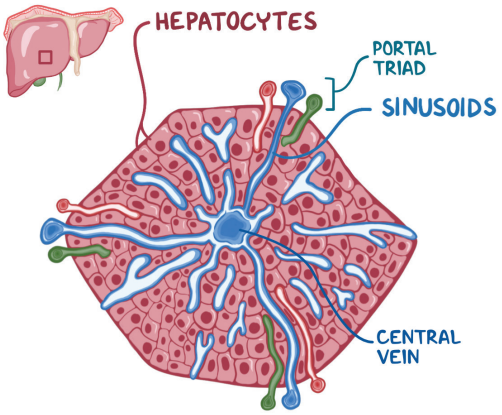

Figure 40.3 Liver lobule.

- Portal triad
  - Portal venule + portal arteriole + bile duct

Sinusoids

- Mixing of portal vein, hepatic arterial blood
- Lined with leaky endothelial cells
- Pathway of blood flow
  - Blood from hepatic portal vein, artery → sinusoids → central vein → hepatic vein → inferior vena cava

Bile

- Produced by hepatocytes, excreted into bile ducts
- Composed of bile salts, bile pigments, cholesterol, triglycerides, phospholipids
  - *Primary bile salts*: cholic, chenodeoxycholic acids (cholesterol derivatives)
  - *Function*: emulsify fat (break into smaller pieces to maximize surface area for digestion); facilitate fat, cholesterol absorption
  - Bile salts conserved via enterohepatic circulation
  - Main bile pigment is bilirubin (waste product of hemoglobin from broken down erythrocytes), stercobilin gives feces dark color
- Bile flow
  - Parallel, opposite direction flow of blood
  - Canaliculi → bile ducts → fusion of multiple bile ducts to form common hepatic duct → fusion with cystic duct draining gallbladder → bile duct → ampulla of vater

Major fuels

- Glucose, fructose, galactose (after meal); fatty acids (after fasting)
  - Amino acids can also be used
  - *Long-chain fatty acids:* major source of fuel during prolonged fasting

Cell types

- Hepatocytes
  - *Function*: carry out most metabolic pathways
  - Majority cell type in liver
  - Contain large amounts of rough, smooth endoplasmic reticulum (ER), Golgi bodies, peroxisomes, mitochondria
- Endothelial cells
  - *Location*: sinusoidal lining
  - *Function*: release growth factors; secrete cytokines, endocytose ligands
  - Contain fenestrations → free diffusion of blood, nutrients between sinusoids, hepatocytes
- Kupffer cells
  - *Location*: sinusoidal lining
  - *Function*: macrophages specific to liver protect against gut-derived pathogens, release cytokines, secrete mediators of inflammatory response, remove damaged erythrocytes from circulation
- Stellate (Ito) cells
  - *Location*: scattered amongst hepatocytes
  - *Function*: primary vitamin A storage site; regulate contractility of sinusoids; control turnover of extracellular matrix, hepatic connective tissue
  - Responsible for tissue cirrhosis
- Pit cells (liver-associated lymphocytes)
  - *Function*: natural killer cells specific to liver

GALLBLADDER ANATOMY

- Muscular sac
  - Stores, concentrates bile produced by liver
- Located under inferior surface of right liver lobe
- Inner mucosa (with rugae) → allows expansion
- Smooth muscle layer → allows contraction

to occur in response to cholecystokinin (produced by duodenum) → bile released into small intestine
    - Also contracts in response to vagal stimulation
- Flow of bile
    - Cystic duct → common bile duct → ampulla of vater → duodenum

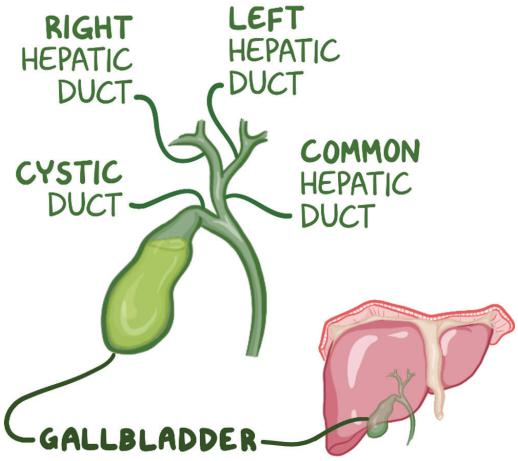

Figure 40.4 Gallbladder.

PANCREAS ANATOMY

- Located retroperitoneal posterior to stomach, duodenum

Four regions

- *Head*: right side nestled into curve of duodenum
- *Neck*: thin portion between head, body
- *Body*: tapered left side
- *Tail*: ends near spleen

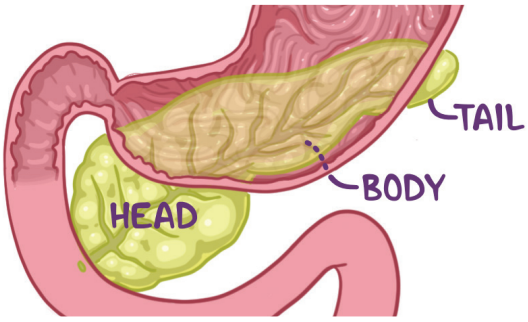

Figure 40.5 Pancreatic location relative to stomach and duodenum.

Acinar gland

- Exocrine gland
- Acinar cells
    - Contain zymogen granules full of proenzymes for digestion
- Stimulated by secretin, cholecystokinin (from duodenum), vagus nerve
- Secretes digestive enzymes into duodenum
    - Amylase, lipase, nuclease secreted as active enzymes
    - Proteases (trypsinogen, chymotrypsinogen, procarboxypeptidase) secreted in zymogen form, must be cleaved to be activated

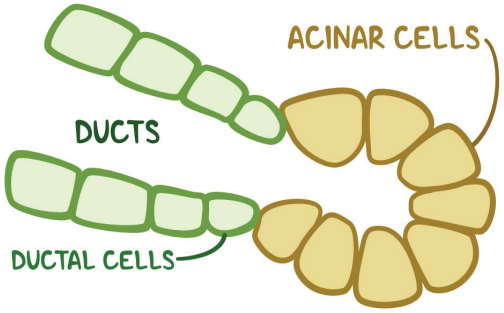

Figure 40.6 Acinar gland.

Islets of Langerhans

- Endocrine gland
- Responsible for glucose homeostasis
    - Beta cells → insulin
    - Alpha cells → glucagon
    - Delta cells → somatostatin → inhibits insulin, glucagon secretion

Ducts

- *Main pancreatic duct*: located centrally, fuses with bile duct to drain into duodenum
- *Accessory pancreatic duct*: smaller duct; empties directly into duodenum
- *Ductal cells*: responsible for aqueous secretions (water, HCO_3^-, sodium)
    - Secretion of bicarbonate ions neutralizes acidic chyme entering duodenum, provides optimal pH for activation of digestive enzymes

LIVER PHYSIOLOGY

Efficient exchange of compounds between sinusoidal blood, hepatocytes

- Fenestrated endothelial cells
- Lack of basement membrane between endothelial cells, hepatocytes
- Slow blood flow

Biotransformation of xenobiotics

- Principal site for processing xenobiotics, toxins
- *Phase I reactions*: oxidation, reduction, hydroxylation, hydrolysis
  - Introduces reactive functional groups to increase compound polarity
- *Phase II reactions*: conjugation, sulfation, glucuronidation, methylation
- *Detoxification*: xenobiotic → phase I reaction → primary metabolite → phase II reaction → secondary metabolite → excretion
- *Cytochrome P450 system*: major xenobiotic metabolizer in body; oxidizes substrates, adds oxygen to structures
  - First pass effect for pharmaceuticals

Regulation and maintenance of blood glucose levels

- ↑ *blood glucose:* → secretion of insulin by pancreas → ↑ uptake of glucose, amino acids by cells; inhibition of glycolysis, activation of glycogen synthesis, inhibition of gluconeogenesis, inhibition of glycogenolysis, inhibition of fatty acid oxidation → ↓ blood glucose
- ↓ *blood glucose:* ↑ breakdown of glycogen → secretion of glucagon, activation of glycolysis, inhibition of glycogen synthesis, activation of gluconeogenesis, activation of glycogenolysis, activation of fatty acid oxidation → ↑ blood glucose

Elimination of ammonia via urea cycle

- Liver
  - Main organ responsible for eliminating ammonia via urea cycle
- Ammonia transported to liver on glutamine, alanine → converted by liver into urea for excretion in urine

Amino acid metabolism/protein synthesis and regulation

- Liver produces plasma proteins (mainly albumin), coagulation factors, metal-binding proteins (transferrin, ceruloplasmin), lipid transporters (apoproteins), protease inhibitors (antitrypsin), glycoproteins, proteoglycans
- Can convert amino acids into glucose, fatty acids, ketone bodies
- Sugars produced by liver O-linked

Formation of ketone bodies

- Liver
  - Only organ that can produce ketone bodies
- Cannot use ketone bodies for energy
- Ketone bodies formed when glucose levels low, high rates of fatty acid oxidation
- Ketone bodies major fuel source for central nervous system (CNS) under starvation

Cholesterol and triacylglycerol synthesis

- Liver synthesizes very low-density lipoprotein (VLDL) to be secreted into blood
- Food plentiful → liver activates synthesis of fatty acid, triacylglycerol, cholesterol → reduces hepatic cholesterol synthesis
- Also sends excess dietary cholesterol to peripheral tissue

Nucleotide biosynthesis

- Liver can synthesize, salvage nucleotides for use by other cells
- Salvage pathway
  - Liver converts free bases to nucleotides for secretion into circulation as needed by peripheral tissues

Lipid metabolism

- Long-chain fatty acids
  - Liver's major fuel source during fasting
  - Triacylglycerols from adipose tissue → fatty acids bound to albumin → liver → activated via fatty Acyl-coenzyme A (acyl-CoA) synthetases → fatty-acyl-CoA → fatty-acyl-carnitine → carnitine crosses inner mitochondrial membrane → fatty-acyl-carnitine → carnitine, fatty-acyl-CoA → beta oxidation
  - Enzymes in beta oxidation, fatty-acid activation specific for length of fatty acid carbon chains

- Medium-chain-length fatty-acid oxidation
  - 4–12 carbons
  - Liver, kidney is site of oxidation
  - Activating enzyme is medium-chain-length fatty acid-activating enzyme (MMFAE)
  - Oxidation begins with medium-chain-length acyl-CoA dehydrogenase
- Very-long-chain fatty-acid oxidation
  - > 20 carbons
  - Oxidized by peroxisomes to octanoyl-Coa
  - Generates hydrogen peroxide instead of flavin adenine dinucleotide (FADH2), in contrast to mitochondrial beta-oxidation
- Long-chain fatty acids
  - 12–20 carbons
  - Most common type of lipid used for oxidation by liver

PANCREATIC SECRETION

osms.it/pancreatic-secretion

FLOW RATE, COMPOSITION OF PANCREATIC JUICE

High flow rate

- High HCO_3^- concentration, low Cl^- concentration

Low flow rate

- High Cl^- concentration, low HCO_3^- concentration

REGULATION OF BILE, PANCREATIC SECRETION

- Hormones, neural stimuli regulate secretion of bile, pancreatic juice into duodenum

Hormones

- Secretin
  - Released by intestinal cells in response to acidic chyme; stimulates secretion of bile, pancreatic juice
- Cholecystokinin (CCK)
  - Major stimulus for gallbladder to release bile into duodenum; stimulates secretion of enzyme-rich pancreatic juice

Neural stimuli

- Parasympathetic stimulation by vagus nerve stimulates secretion
  - Bile from gallbladder, pancreatic juice

Bile salt

- Major stimulus for more bile secretion via stimulation of secretin release

ACTIVATION OF PANCREATIC PROTEASES

- Enteropeptidase cleaves, activates trypsinogen to trypsin → trypsin activates chymotrypsinogen into chymotrypsin, procarboxypeptidase into carboxypeptidase