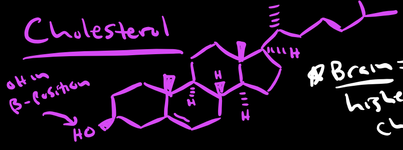
Cholesterol



✪ Brain = organ w/ highest [ ] of cholesterol

- amphipathic
  - polar OH group can form H-bonds w/ phosphate groups of membrane phospholipids
  - rest of molecule = hydrophobic
    - interacts w/ long-chain hydrocarbon moieties of phospholipids
  - ↳ net result = ↓ in liquid-disordered phase in membranes containing cholesterol → ↑ membrane stability & ↓ permeability to other substances

✪ Cholesterol in membranes ↓ passive permeability to solutes across plasma membrane

- ~ 250 g of total cholesterol (free + esterified) present in avg. person
- particularly abundant in nervous tissue (esp. spinal cord)
- most cells synthesize cholesterol from acetyl moieties of acetyl-CoA
  - only synthesized in liver
  - synthesis = energetically expensive
  - ~50% from diet
  - many intermediates in synthesis used in other pathways
- avg. adult requirement ~ 400-500 mg/day
- stored as cholesteryl esters, synthesized by acyl CoA acyl transferase (ACAT)
  - used for synthesis & repair of cell membranes
  - main storage sink = liver
  - free cholesterol released by lysosomal acid lipase or cholesterol ester esterase
  - cholesterol & its esters have limited solubility
    - ↳ transported through circulation in lipoprotein particles

✪ In liver, ↑ cholesterol → ↑ cAMP → ↓ cholesterol synthesis

Adrenal, ↓ cholesterol → ↑ cAMP
↳ ↑ neutral cholesteryl-ester esterase (hydrolase) → ↑ cholesterol → ↑ substrate for hormone synthesis

Cholesterol Synthesis - Endogenous Pathway - Liver only ✪

Carbohydrates, FAs, AAs → Acetyl-CoA

2 Acetyl-CoA → (Thiolase; CoA-SH released) → Acetoacetyl-CoA

HMG-CoA synthesized in: mitochondria → ketones; cytosol → cholesterol

→ (HMG-CoA Synthetase) → HMG-CoA

→ (*RLS* HMG-CoA Reductase) → Mevalonate

Insulin → (+) HMG-CoA Reductase

Statins, Glucagon, Epinephrine, ↑ Cholesterol ⊣ HMG-CoA Reductase

↑ cAMP → ↑ PKA → ↑ PPI-1 → ↓ phosphoprotein phosphatase

Regulation of HMG-CoA Reductase:
- Reductase kinase kinase (ATP → ADP) → (AMP) Reductase kinase–Ⓟ (active)
- (AMP) Reductase kinase (ATP → ADP) → HMG-CoA Reductase–Ⓟ
- Phosphoprotein phosphatase: Reductase kinase–Ⓟ → Reductase kinase–OH
- Phosphoprotein phosphatase: HMG-CoA Reductase–Ⓟ → HMG-CoA Reductase
- cAMP → PKA → Ⓟ Protein phosphatase inhibitor 1 (PPI-1) → (phosphatase) → PPI-1-OH
- Protein phosphatase inhibitor 1 → phosphoprotein phosphatase–Ⓟ

Mevalonate

ATP ↓ (phosphorylation)

isoprene intermediate - geranyl pyrophosphate (10c) → geranylgeranylPP → prenylation of proteins on C-term. cysteine (-SH) residues

CO_2 ↓ (decarboxylation)

isoprene intermediate - farnesyl pyrophosphate (15c) → prenylation; → dolichol, ubiquinone, Heme

↓

Squalene (30-C)

* occurs in ER: squalene epoxidase → cyclization

lanosterol

↓ *1 step uses Cyt P450s; a lot of NADPH; ↳ $FADH_2$ → FMN

7-Dehydrocholesterol → Vitamin D_3

↓ 7-dehydrocholesterol-Δ7-reductase (DHCR7)

Cholesterol

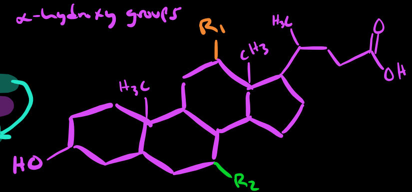
→ Bile acids (Bile acid sequestrants ⊣ bile acid recycling)

→ (Steroids) → Mineralocorticoids, Glucocorticoids, Androgens → Estrogens

Bile Acids

- lipid soluble, cholesterol = precursor
- act as detergents → reversibly form aggregates = micelles → facilitates emulsification of dietary fats
  - ↳ solubilizes the lipids → more easily degraded by intestinal lipases
  - ↳ allows more ready uptake of cholesterol by intestinal cells
- micelles also carry fat-soluble vitamins (A, D, E, K) & riboflavin (B_2) to intestinal cells
- cholesterol-containing micelles contain phosphatidylcholine & bile acid/conjugate anions in specific ratios
- characterized by: ① modified (oxidized) & shortened side chain
  - ② absence of 5,6 double bond
  - ③ presence of 1, 2, or 3 α-hydroxy groups
- examples:

	Acid	R_1	R_2
Main 1° bile acids	Cholic acid	-OH	-OH
	Chenodeoxycholic acid	-H	-OH
Main 2° bile acids	deoxycholic acid	-OH	-H
	Lithocholic acid	-H	-H



- 1° bile acids synthesized in liver (as taurine or glycine conjugates) and stored in gall bladder
  - concentrated (as hydrophilic taurine or glycine conjugates)
- bacteria in lower intestine & colon contain enzyme that remove (reduce) 7-α-OH group of 1° bile acid conjugates → form conjugates of 2° bile acids
- Taurine & glycine conjugates of both 1° & 2° acids actively reabsorbed via enterohepatic circulation
  - Intestinal bacteria can also deconjugate some taurine/glycine conjugates → free bile acids → passive reabsorption

Sterols in non-mammalian organisms

- plants make many sterols (phytosterols) but no (or very small amounts) of cholesterol, and also make stanols (sterol but double bond reduced to single bond)
  - typical western diet: 100-400 mg/day of phytosterols e.g. (β-sitosterol & campesterol).
  - important yeast sterol = ergosterol → precursor to Vitamin D_2 (ergocalciferol)
- Some margarines, vegetable oil spreads, salad dressings etc. "fortified" w/ free plant sterols & stanols (or esterified conjugates) → inhibits intestinal cholesterol uptake
  - ↳ associated w/ 10% ↓ in serum [LDL]

Bile Acid Synthesis

cholesterol

↓ *RLS* 7-α-hydroxylase (O_2, NADPH, H^+ → $NADP^+$)
- part of CYP7A1, type of Cyt. P450

7-hydroxy-cholesterol

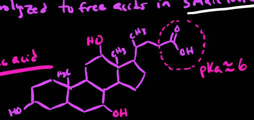
↓ (NADPH, H^+, O_2, (2) CoA-SH; → Propionyl-CoA)

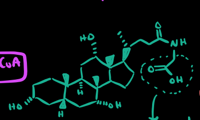
Cholyl-CoA | Chenodeoxycholyl-CoA

Acid Conjugates

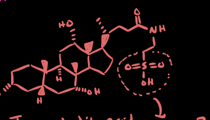
- in bile, most bile acids are in the form of conjugates, NOT as free acids or CoA-esters
  - ↳ CoA-esters enzymatically react w/ taurine & glycine → tauric & glycic acids → hydrolyzed to free acids in small intestine

cholic acid





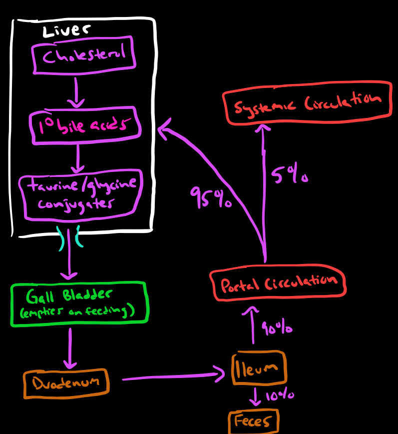
Glycocholic acid



Taurocholic acid

Enterohepatic Circulation

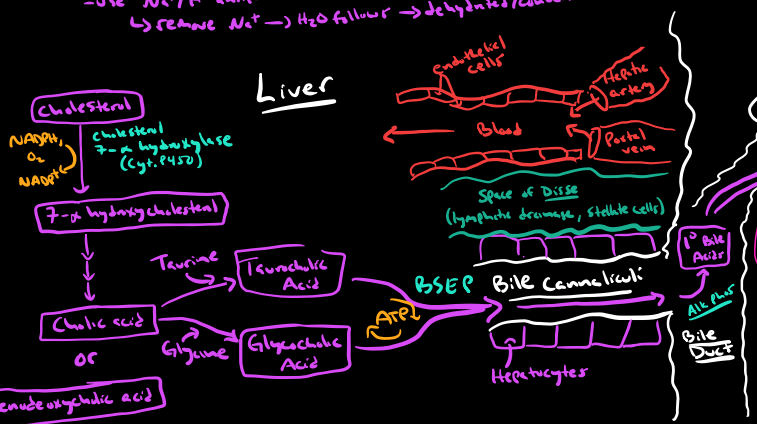
- very efficient → only ~10% of bile acids pool lost in feces/day
  - ↳ accounts for major loss of cholesterol carbon skeleton from body
  - only small fraction of cholesterol lost via conversion to steroid hormones → excretion of steroid hormone derivatives
- in blood, bile salts complexed w/ albumin
  - ↳ prevents micelle formation
  - systemic bile acids reabsorbed by liver via hepatic artery



Gallbladder/Biliary Secretions

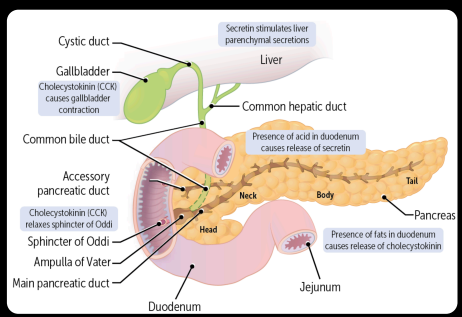
Bile
- Bile salts - necessary for lipid emulsification → absorption (via micelles)
- Bilirubin - necessary for bile salt excretion
- 95% water
- 5%:- conjugated Bile Salts (deoxycholate & lithocholate acid)
  - Cholesterol
  - Phospholipids
  - Bilirubin
  - Electrolytes

- 1° bile acids/salts
  - Synthesized by hepatocytes (liver) from cholesterol
  - amphipathic
  - Conjugated w/ Taurine or Glycine (hydrophilic)
    - ↳ better surfactant
    - ↳ water-soluble
  - Transported into bile canaliculus via Bile Salt Export Pump (BSEP)
    - BSEP = ATPase
    - bile canaliculi run parallel & counter to blood in hepatic sinusoids
    - empty into bile duct → duodenum (use)
      - → gallbladder (storage)
  - In gallbladder, 1° bile salts concentrated via gallbladder epithelial cells
    - use Na^+/H^+ antiporter in apical membrane
      - ↳ remove Na^+ → H_2O follows → dehydrated/concentrated bile



Bile functions
1. Emulsification of fats → absorption by ↑ surface area on which pancreatic lipase can act
   - ↳ Bile salts form micelle droplets act as surfactants b/c part of molecule is hydrophilic (can travel through blood to liver) & part lipophilic (to bind lipids)
2. Excretion of cholesterol
3. Antimicrobial
   - ↳ disrupt bacterial cell membrane in small intestine

In intestine
- I cells detect Fats & AAs → secrete CCK
  - CCK → bile duct contraction (bile released from gallbladder → intestine)
    - → Pancreatic enzyme release
      - ↳ relaxes Sphincter of Oddi → ↑ bile & pancreatic juices into duodenum)
- Pancreatic lipases breakdown TAGs emulsified in micelles by 1° bile acids
  - ↳ lipids absorbed into circulation via enterocytes
  - ↳ free bile acids enter Colon
- In Colon
  - Colonic bacteria convert most 1° bile salts → 2° bile salts
  - 95% of bile salts reabsorbed in terminal ileum via active transport
  - 5% bind to bilirubin → excreted in feces



Gallstones
- Delicate balance of cholesterol, Bile Salts, & Bilirubin → keep bile fluid
  - ↳ if balance is upset → excess components precipitate out → Stones
- Gallstones lodged in common bile duct → no bile flow into intestine
  - Cystic duct or gallbladder → still have bile flow directly from liver (just come from gallbladder) → will have normal bilirubin excretion

- Cholesterol stones
  - ↓ [Ca++] → radiolucent → not visible on X-ray
  - caused by Hypercholesterolemia, ↓ bile acids, ↑ estrogen
    - estrogen upregulates HMG-CoA reductase → ↑ cholesterol synthesis
  - Classically occurs in 40 year olds
    - rare in children
    - Elderly pt w/ Gallstone symptoms = Cancer
  - Risk factors:- Female gender, pregnancy (↑ estrogen)
    - Obesity, rapid weight loss (↑ total cholesterol & nucleation)
    - Cirrhosis → ↓ bile salt synthesis in liver
    - Crohn's disease → inflammation in ileum → ↓ reabsorption/recycling
    - Cystic Fibrosis → fat malabsorption → ↑ bile acid excretion
    - Fibrates → ↓ bile acid synthesis
    - Bile acid resins → ↑ bile acid excretion
- Bilirubin Stones
  - ↑ [Ca++] → Calcium Bilirubinate → radiopaque → visualized on X-ray
  - black/brown stones
  - due to ↑ unconjugated bilirubin (not soluble)
    - Can be caused by:
      - extravascular hemolysis → ↑ bilirubin release
      - Cirrhosis or chronic liver disease → impaired conjugation
      - Recurrent biliary tree infections
        - ↳ bacterial glucuronidases → de-conjugate bilirubin
          - ↳ brown (not black) stones
- Gallstone Symptoms
  - RUQ Pain - stone lodged in cystic or common bile duct (choledocholithiasis)
    - ↳ Pain subsides within a few hours → gallstone moved back into gallbladder
      - ↳ Biliary Colic
    - ↳ pain persists → gallstone is stuck in common bile duct
      - ↳ Jaundice - stone lodged in common bile duct → ↓ bile outflow from gallbladder
        - → conjugated bilirubin spills over into blood
        - = obstructive jaundice

Alkaline Phosphatase (Alk.Phos)
- produced by bile duct epithelial cells
- ↑ Alk.Phos in response to cholestasis (obstructed bile flow)

Cholestasis (↓ bile flow from gallbladder)
- bile stasis → ↑ chance of cholesterol precipitating out → stones
- can be caused by many things:
  - ↓ CCK (↓ stimulus to contract)
    - Can be caused by Total Parenteral Nutrition (TPN) (when pt receiving nutrition directly into blood, bypassing entire system → no I-cell stimulation to release CCK

Hepatobiliary (HIDA) Scan
- radioactive tracer injected into venous blood in arm
  - → travels to liver & biliary system
    - ↳ if gallbladder NOT visualized ⇒ acute cholecystitis (inflammation of gallbladder)
    - if gallbladder visualized ⇒ choledocholithiasis (common bile duct obstruction)

Bile acid resins
- used as Tx for hypercholesterolemia
- Cholestyramine, colestipol, colesevelam
- bind bile acids → insoluble → ↑ bile acid excretion
- ↑ bile acid excretion → ↓ bile acids in circulation
  - ↳ need to synthesize more → utilize more cholesterol
    - ↳ ↓ [cholesterol] in circulation
- rarely used anymore b/c can cause gallstones

Stellate Cells
- Perisinusoidal cells found in Space of Disse
- Storage site for retinoids (Vit.A metabolites)
- activated in liver disease (cirrhosis)
  - ↳ secrete TGF-β → proliferation & fibrous tissue formation
- Major contributor to cirrhosis

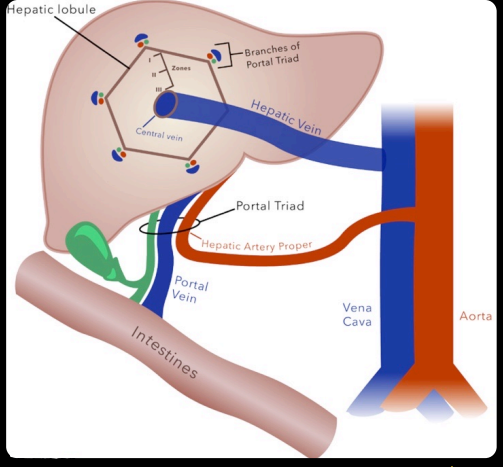
Liver

Anatomy overview

- Portal triad = hepatic artery proper, portal vein, common bile duct
  - branches of portal triad surround liver lobules

- Arterial blood path
  - lobule Zones I → II → III → exits through central vein → vena cava
  - Substances absorbed from intestine travel in same path as arterial blood

- Bile path
  - flows opposite of portal vein & arterial blood → exits via common bile duct



Detoxification

- substances (drugs, toxins, etc.) absorbed by digestive tract enter portal vein for first pass metabolism before entering systemic circulation
- ✱ – NH_3 formed in intestines from protein (AA) breakdown
  → sent to liver → converted to urea via urea cycle
  → systemic circulation → excreted in urine
- ✱ – Estrogen formed in tissues throughout body → hepatic artery proper
  → broken down into metabolites → excreted in urine, feces, bile

Metabolism – Phase I & II

- Phase I – Zone III
  - mediated primarily via Cyt. P450 (CYP) enzymes
  - Redox rxns & hydrolysis → creates slightly Polar Metabolites
    ↳ Potentially leading to formation of metabolic toxins → Zone III damage
  - Drug Metabolism – can convert prodrug to active form of drug

- Phase II – Zone I
  - mediated by transferases
  - Conjugation rxns → creates very Polar Metabolites → renal excretion

Protein Production

- Carrier proteins
  - Albumin ✱
    - fat-soluble substances
  - Transferrin
    - iron
  - Ceruloplasmin
    - Copper
  - Sex-hormone-binding globulin
    - testosterone
- Hemostasis proteins ✱
  - Procoagulation:
    - Factors I – XII
    - Fibrinogen
    - Fibronectin
  - Anticoagulation:
    - Antithrombin III
    - Protein S
    - Protein C
- Immunity & Inflammation
  - Complement proteins (C1–C9)
  - C-reactive protein (CRP)
  - Ferritin (sequesters iron from microbes)
- Hormones
  - Insulin-like growth factor-1 (IGF-1)
    - anabolic growth
  - Thrombopoietin (TPO) ✱
    - Platelet production
  - Angiotensinogen

Carbohydrate Metabolism

- Gluconeogenesis
- Glycogen storage
- Glycogenolysis → Glc released into bloodstream

Lipid Metabolism

- Production of cholesterol & lipoproteins
- Cholesterol metabolism
  - HMG-CoA reductase = RLS in cholesterol synthesis
  - normally converted into bile acid → excreted in feces

✱ Portal Vein Thrombosis
- rare cause of Portal HTN without cirrhosis
- acute onset abdominal pain
- Splenomegaly
- may result in gastric varices w/bleeding
- normal liver biopsy

✱ Varix (pl. varices)
= dilated, tortuous blood vessel
- occur via swelling of collaterals (anastomoses)

Cirrhosis – End stage liver disease = irreversible

- can be caused by chronic liver diseases: – viral Hepatitis (esp. B & C)
  – Alcoholic liver disease
  – Non-alcoholic fatty liver disease

- Cirrhosis = shrunken liver, necrotic tissue replaced by fibrosis & nodules
  - Stellate Cells = major contributor to fibrotic tissue production
    - perisinusoidal cell, storage site for retinoids (wt. A metabolite)
    - activated in liver disease → secrete TGF-β → proliferation & fibrous tissue production
- Hypoglycemia – ↓ gluconeogenesis & ↓ glycogenolysis
- Hyperbilirubinemia → jaundice
- Detoxification impairments
  - Hyperammonemia
    - ↓ urea synthesis → ↑ NH_3 → hepatic encephalopathy
      ↳ Asterixis, confusion, coma
    - Tx: – low protein diet
      – Lactulose – synthetic disaccharide (laxative)
      – broken down by colonic microbiome into FAs → ↓ pH
      ↳ favors formation of NH_4^+ from NH_3
      ↳ NH_4^+ trapped in colon (not absorbed) → excreted in feces
  - ↓ estrogen breakdown → ↑ testosterone
    ↳ Spider angiomas – localized arteriole dilation
    ↳ Gynecomastia
    ↳ Negative feedback on hypothalamus
    ↳ ↓ GnRH, FSH, & LH release
    ↳ testicular atrophy (males)
    ↳ Amenorrhea (females)
- Protein impairments
  - ↓ albumin → ↓ plasma oncotic pressure → edema
- Hemodynamic impairments – Portal Hypertension
  - Cirrhosis obstructs Portal vein flow through liver
    ↳ ↑ pressure in Portal vein → Portal HTN

↓ Albumin → ↓ Oncotic Pressure

↑ Nitric Oxide → ↑ Splanchnic vasodilation → ↓ Systemic venous return → ↓ BP

↓ Effective Circulating Volume (ECV)

↑ SNS → ↑ Cardiac Output

↑ RAAS, ↑ ADH → ↑ Na^+/H_2O reabsorption → ↑ Total Body H_2O

✱ Pt's w/ Cirrhosis but without Portal HTN do NOT develop ascites

↑ Total Body H_2O + Portal HTN → Ascites, Edema

↓ albumin

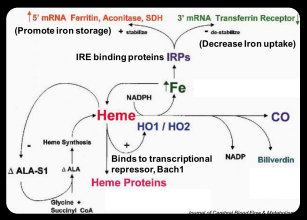
✱ Portal HTN & Heart Failure = 2 major conditions where both ↓ ECV AND ↑ TBW

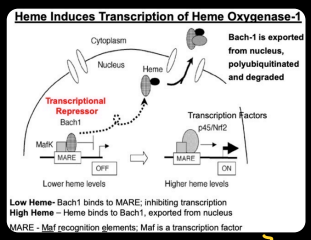
- Ascites – accumulation of fluid in peritoneal cavity
  - in liver disease, due to Portal HTN +/- ↓ albumin
  - Tx: – ↓ dietary Na^+
    – Spironolactone (K^+-sparing diuretic), bitter aftertaste in DCT
    – loop diuretic (not as good as spironolactone)
- Portal HTN → opens venous collateral circulation (links Portal-systemic veins)
  - normally collapsed, but engorged in Portal HTN
  - Umbilicus → caput medusae
  - Esophagus → via left gastric vein → portal vein
    ↳ esophageal varices (→ upper GI bleeding)
  - Stomach: short gastric veins → L. gastric AND splenic vein → Portal
    ↳ Gastric varices (→ upper GI bleeding)
  - Rectum: internal hemorrhoids (→ rectal bleeding)
- Portal HTN → Hypersplenism → ↓ platelets
- Portal HTN Tx: TIPS – Transjugular Intrahepatic Portosystemic Shunt
  – forced shunt through jugular vein → push through hepatic vein → through liver → portal vein
  ↳ shunt connects portal vein → hepatic vein directly
  ↳ blood drained away from portal system

- Coagulation impairments
  - ↓ thrombopoietin (thrombocytopenia) & ↓ clotting factors
    ↳ ↓ platelets & ↑ clotting time (↑ PT/PTT)
    ↳ Easy bruising = purpura (large) & petechiae (tiny)

Bilirubin (Heme Catabolism)

- Heme contributors:
  - Senescent RBCs (~80%)
    - after ~120 days in circulation
  - Heme proteins (~10%)
    - Myoglobin
    - Cytochromes
  - Ineffective erythropoiesis (~10%)
- Occurs in reticuloendothelial cells (macrophages) of liver, bone marrow, spleen
- Heme oxygenase (HO)
  - major source of endogenous CO → excreted in lungs
    - [CO] expelled = direct measurement of HO activity
  - HO1
    - inducible isozyme → ↑upregulated by ↑ [Heme] & oxidative stress
  - HO2
    - constitutively expressed in all cells
    - promotor solely responsive to ↑ glucocorticoids
    - ↳ cannot compensate for deficiency in HO1
- Regulated by [Heme] ⇒ Heme regulates itself
  - Bach1 = transcriptional repressor of HO
  - ↓[Heme] → Bach1 free to bind HO gene → ↓HO txn
  - ↑ [Heme] → Heme binds Bach1 → Bach1 exported from nucleus & ubiquitinated → degradation
    - ↳ allows TFs to bind HO gene → ↑HO txn



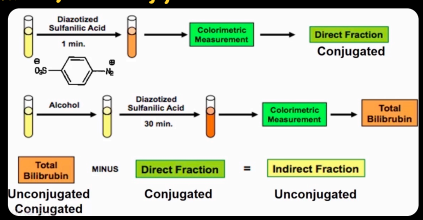


Bruise Color Changes

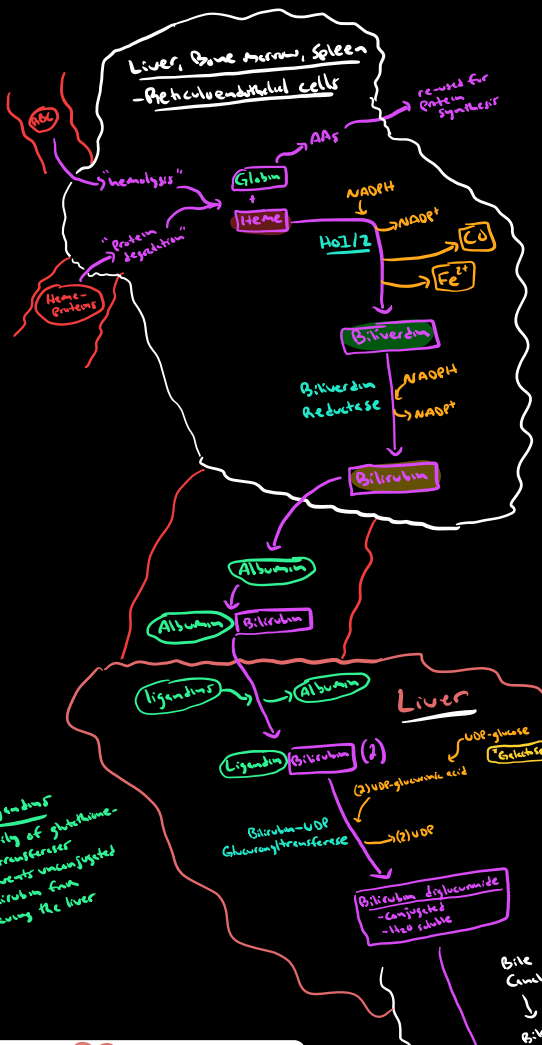
- due to changes in structure of tetrapyrroles in breakdown of RBCs @ wound site
  - Red-Blue - Porphyrins
  - Blue-green - Biliverdin
  - Yellow-Brown - Bilirubin

Test for [Bilirubin]

- Van den Bergh Reaction
  - ① Add Plasma + Diazo reagent (diazotized sulfanilic acid)
    - ↳ Direct Fraction measurement
      - → Conjugated Bilirubin (H_2O-soluble) reacts w/reagent within 1 min
        - ↳ reacted conj. bilirubin → red color (measured w/spectrophotometry)
  - ② Add Alcohol → releases unconjugated bilirubin from albumin
    - ↳ Total Bilirubin (conj. & unconj.) measurement
  - ③ Subtract: (Total Bilirubin) − (Conj. Bilirubin) = Unconjugated Bilirubin (indirect fraction)
    - after 30 min, both conj & unconj. bilirubin react w/dye → red color

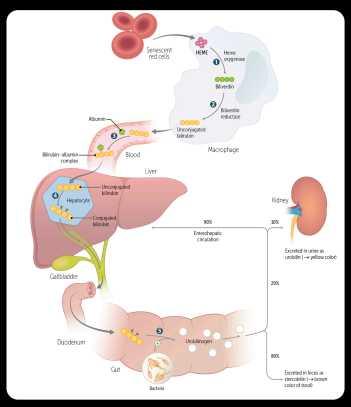


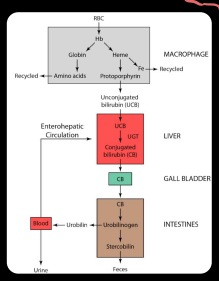
- Transcutaneous Bilirubinometer
  - Estimates bilirubin instantly & noninvasively
    - measures "yellowness" of skin (jaundice) by analyzing spectrum of light reflected off skin



- Ligandins
  - family of glutathione-S-transferases
  - prevents unconjugated bilirubin from leaving the liver

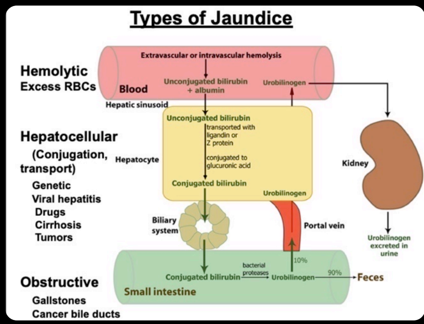
	Unconjugated Bilirubin	Conjugated Bilirubin
Also called	Indirect	Direct
Normal serum level	0.2-1.0 mg/dL	<0.2 mg/dL
Location	Blood (albumin bound)	Liver
Water soluble?	No	Yes
Lipid affinity?	Yes	No
Renal excretion?	No	Yes
Brain tissue affinity	Present (kernicterus)	Absent



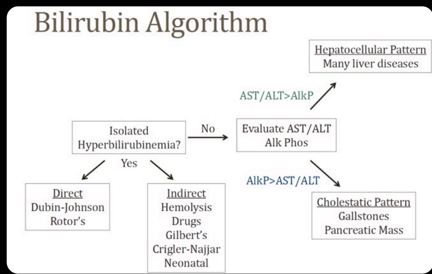


Hyperbilirubinemia – Jaundice

- Bilirubin = yellowish pigment
- ↑ [Bilirubin] in plasma → diffuses into tissues
  - ↳ yellow color of skin, nailbeds, & sclera
- In primary liver diseases... → mixed
  - early disease – ↑↑ [urobilinogen] in urine
    - urobilinogen from intestines reabsorbed as usual
    - cannot be excreted in bile
      - ↳ spills into urine
  - late disease – ↓↓ [urobilinogen] in urine
    - lack of conj. bilirubin to intestines
      - ↳ ↓ formation of urobilinogen



Types of Jaundice
Hemolytic
Excess RBCs
Extravascular or intravascular hemolysis
Blood
Unconjugated bilirubin + albumin
Urobilinogen
Hepatic sinusoid
Hepatocellular
(Conjugation, transport)
Genetic
Viral hepatitis
Drugs
Cirrhosis
Tumors
Hepatocyte
Unconjugated bilirubin
transported with ligandin or Z protein
conjugated to glucuronic acid
Conjugated bilirubin
Urobilinogen
Kidney
Biliary system
Portal vein
Urobilinogen excreted in urine
Obstructive
Gallstones
Cancer bile ducts
Small intestine
Conjugated bilirubin
bacterial proteases
Urobilinogen
10%
90%
Feces



Bilirubin Algorithm
Hepatocellular Pattern
Many liver diseases
AST/ALT>AlkP
Isolated Hyperbilirubinemia?
No
Evaluate AST/ALT Alk Phos
Yes
AlkP>AST/ALT
Direct
Dubin-Johnson
Rotor's
Indirect
Hemolysis
Drugs
Gilbert's
Crigler-Najjar
Neonatal
Cholestatic Pattern
Gallstones
Pancreatic Mass

- * Cholestasis → ↑ Alk Phos
  - ↳ will also see minor ↑ AST/ALT b/c bile duct epithelial damage/obstruction → bile backs up into hepatocytes
  - → hepatocytes ↑ AST/ALT in response to damage, but ↑ Alk Phos >> ↑ AST/ALT
- * w/ Hepatocellular damage → ↑ ALT/AST >> ↑ Alk Phos
  - ↳ ↑ Alk Phos due to secondary effect on bile duct cells, but ↑ not as drastic as liver enzymes b/c 1° problem is in liver = Hepatocellular pattern

Conjugated (Direct Hyperbilirubinemias)

- causes:
  1. Deficiency in canalicular bilirubin transport system
     - * ↳ w/o glucuronidation, bilirubin cannot be excreted w/ bile
     - Circulating albumin-bound bilirubin that is not excreted is taken up by liver
     - In liver, Bilirubin UDP-glucuronyl transferase 1A1 (UGT1A1) converts conjugated bilirubin → two isomeric monoglucuronides & 1 diglucuronide
       - → water-soluble glucuronides excreted in bile via transport protein (MRP2) Multi-drug resistance-associated
       - MRP2 deficiency → Dubin-Johnson Syndrome
         - Rotor Syndrome
  2. Cholestasis (Impaired/obstructed Bile flow) → ↑ Alk Phos
     - Extrahepatic
       - Choledocolithiasis (gall stones)
       - Tumors pressing on/obstructing biliary tree
       - Biliary Strictures
     - Intrahepatic
       - Parasite (clonorchis sinensis)
       - Alcoholic liver disease
       - Viral hepatitis

Symptoms

- Conj. bilirubin = water-soluble → will stay in blood, bile, & urine
  - ↳ will not diffuse into skin & brain
- ↳ dark-brown urine
  - b/c conj. bilirubin can pass through glomerular barrier
- if cause is obstruction
  - ↳ pale, clay-colored stools
    - b/c conj. bilirubin can't travel to intestine where it gets converted to stercobilin by microbial enzymes
      - stercobilin gives poop brown color
  - ↳ Absent Urobilinogen
    - b/c no bilirubin to intestine

* Dubin-Johnson Syndrome, Rotor Syndrome
CBD obstruction – Gallstones, Pancreatic tumor, cholangiocarcinoma, Schistosomiasis
Diffuse Biliary obstruction – Primary sclerosing cholangitis, Ascending cholangitis

Unconjugated (Indirect Hyperbilirubinemia)

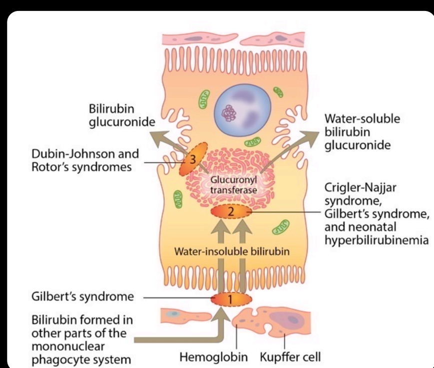
- buildup of unconj. (lipid-soluble) bilirubin in blood
- causes:
  1. ↑ Hemolysis (RBC breakdown)
  2. ↓ Conjugation
     - due to liver diseases w/ significant hepatocyte damage
       - Chronic hepatitis
       - Advanced Cirrhosis
- * Unconjugated bilirubin diffuses into blood & urine but b/c not water-soluble → diffuses into tissues
  - ↳ especially skin & brain
    - skin
      - ↳ jaundice in skin, sclera (scleral icterus), dorsum of tongue
    - brain
      - easily crosses BBB when ↑↑↑↑ [bilirubin]
      - ↳ neurotoxic to Basal Ganglia & Brainstem nuclei
    - placenta
      - can cross placental barrier
- No urine bilirubin detected b/c unconj. bilirubin cannot cross glomerular barrier
  - ↳ urine & stool color will be normal b/c unconj. bilirubin does not get filtered by kidney & is not excreted in stool

* Hemolysis, physiologic newborn disease, Portal Hypertension?
Gilbert Syndrome, Crigler-Najjar Syndrome

Special Cases of Hyperbilirubinemia

Neonatal Jaundice (common)

- Several mechanisms:
  - ↑ hemolysis in newborns → ↑ bilirubin synthesis
    - can be due to hemolytic disease of newborn (common)
      - Rh- or ABO incompatibility between baby & maternal blood
        - Rh(-) mother exposed to Rh(+) baby @ birth → antibodies
        - Rh – once Rh(-) mother exposed to Rh(+) baby @ birth → antibodies formed → attack RBC's of future babies if Rh(+).
          - ↳ not problem w/ first-pregnancy b/c no antibodies formed yet
        - ABO – maternal IgG's specific to fetal ABO type → hemolysis
          - less severe than Rh b/c fetal RBCs have fewer antigens & not entirely developed in utero
  - ↓ UGT1A1 activity in newborns → ↓ conjugation
    - UGT1A1 not mature (functional levels) until ~ 4 weeks old
  - ↓ microbial enzymes that aid in bilirubin metabolism
    - have not grown any gut bacteria yet since all nutrition from mother
  - ↑ [unconjugated bilirubin] → lipophilic → skin & brain
    - skin → severe jaundice
    - brain → kernicterus – fatal w/o Tx
- Tx: phototherapy
  - expose skin to specific wavelengths that converts bilirubin → lumirubin (isomer)
    - ↳ lumirubin = more H_2O-soluble
      - ↳ ↑ excretion w/o conjugation
  - only effective until ~ 4 y/o → then skin is too thick to permit adequate light absorption



Bilirubin glucuronide
Dubin-Johnson and Rotor's syndromes
3
Glucuronyl transferase
2
Water-soluble bilirubin glucuronide
Crigler-Najjar syndrome, Gilbert's syndrome, and neonatal hyperbilirubinemia
Water-insoluble bilirubin
Gilbert's syndrome
1
Bilirubin formed in other parts of the mononuclear phagocyte system
Hemoglobin
Kupffer cell

	Gilbert Syndrome	Crigler-Najjar Syndrome Type 1	Crigler-Najjar Syndrome Type 2	Dubin-Johnson and Rotor Syndrome
Metabolism defect	Mildly reduced UDPGT	Absent UDPGT	Reduced UDPGT	Reduced excretion of conjugated bilirubin
Liver pathology	Normal	Normal	Normal	Grossly black (D-J only)
Clinical course	Short flares of benign jaundice	Severe disease, fatal in neonates	Moderate disease, occasional kernicterus	Clinically benign jaundice
Treatment	No required treatment	Plasmapheresis, phototherapy, potential liver transplant	Phenobarbital	No required treatment

Dubin-Johnson Syndrome

- Conjugated hyperbilirubinemia
- Autosomal recessive
- Defective MRP2 transporter gene
  - → ↓ secretion from hepatocytes → bile
    - ↳ ↑ [conjugated bilirubin]
- May or may not see bilirubin in urine
- No pruritis (itching due to bile salts in skin)
- Liver turns black
- Benign condition, no Tx required
- typically asymptomatic until condition exacerbated by stress

Rotor's Syndrome

- Similar to Dubin-Johnson but milder → No black liver

Gilbert's Syndrome

- Hepatic Jaundice
- Deficient UGT1A1
- Typically due to defective promoter in UGT gene
  - b/c only affects promoter → only affects txn (~30 reduced), but whatever is translated is fully functional
- Mild ↓ UGT1A1 levels
  - ↳ mild ↑ [total] & [unconjugated] bilirubin
- Jaundice can occur w/ ↑ bilirubin w/:
  - exertion
  - stress
  - fasting
  - infection
- * No serious clinical consequences

Rifampin / Probenecid

- Rifampin = antibiotic used for TB
- Probenecid = treats gout/gouty arthritis
- Compete w/ bilirubin for uptake into liver
  - ↳ ↓ hepatic uptake of UNCONJUGATED bilirubin
- ↳ mild ↑ [unconjugated] & [total] in Van den Bergh rxn
  - all other LFT's normal

Crigler-Najjar Syndrome

- Hepatic Jaundice

Type I – usually incompatible w/ life
- Autosomal recessive
- Severely reduced/absent UGT1A1, mutation cause complete misfolding
  - ↳ ↓↓↓ hepatic uptake → cannot conjugate → ↑ [unconj. bilirubin]
- usually presents in infancy
  - Jaundice
  - Kernicterus – often fatal
    - ↑ [unconj. bilirubin] = small, lipophilic → crosses BBB
      - ↳ neurotoxic to basal ganglia & brain stem nuclei
    - newborns (esp. Preterms) particularly vulnerable
- Tx: liver transplant

Type II
- autosomal DOMINANT
- partial deficiency of UGT1A1
  - only capable of forming monoglucuronated bilirubin
    - ↳ ↓ neurological damage
  - only major consequence is skin jaundice
- Tx:
  - phototherapy w/ bilirubin lights until age 4
  - Blood transfusions
  - phenobarbital or clofibrate → CYP-inducers
    - phenobarb = AED/sedative
    - clofibrate = lipid-lowering agent
  - both ↑ liver glucuronidation → ↓ [bilirubin] by up to 25%