Liver Function

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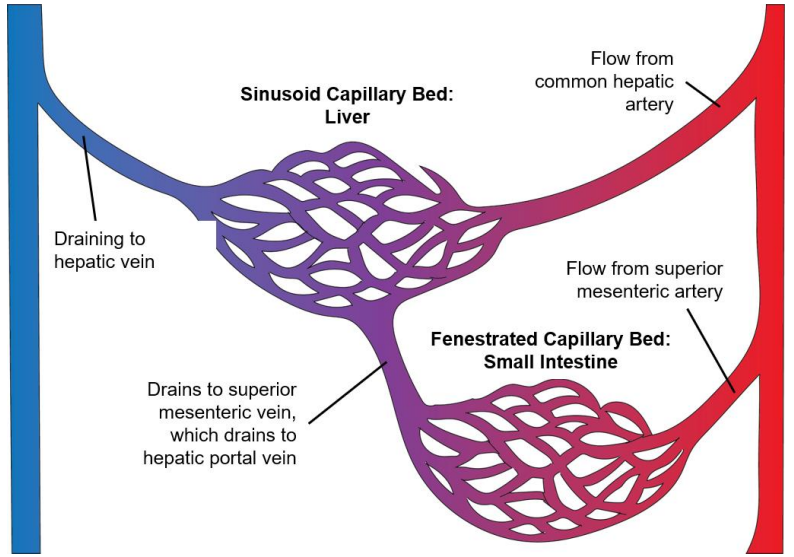
Liver's function

- Liver serves numerous purposes
  - Fetal erythropoiesis
  - Builds serum proteins
  - Energy storage (glycogen)
  - Lipid regulation/construction
  - Digestion
  - Detoxification
    - Outside substances, ammonia, cell breakdown products

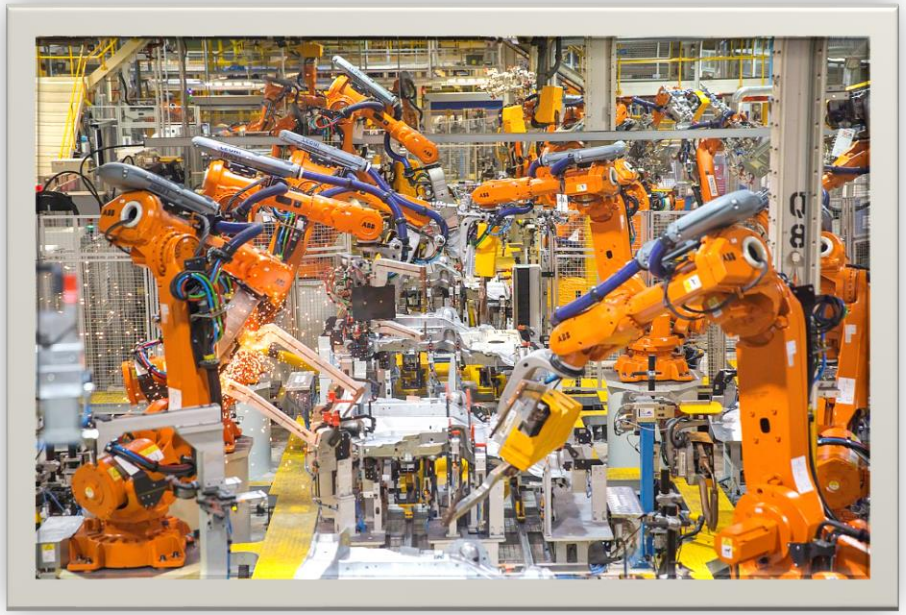
Liver Inputs

- Liver receives 3/4 of blood from hepatic portal VEIN
  - After blood has visited digestive tract, pancreas, and spleen
  - This blood contains:
    - RBCs and their breakdown products
    - nutrients and toxins
    - Endocrine secretions to regulate liver function
- Hepatic artery supplies ¼ blood
  - Mixed with venous to increase oxygenation



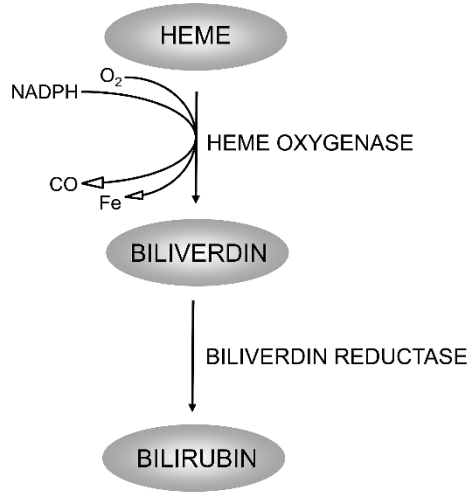
Liver Outputs

- Nutrients
  - Proteins
  - Lipids/lipoproteins
  - Carbohydrates
- Functional serum proteins
- Bile
- Breakdown Products
  - Urea- proteins
  - Bilirubin- RBCs

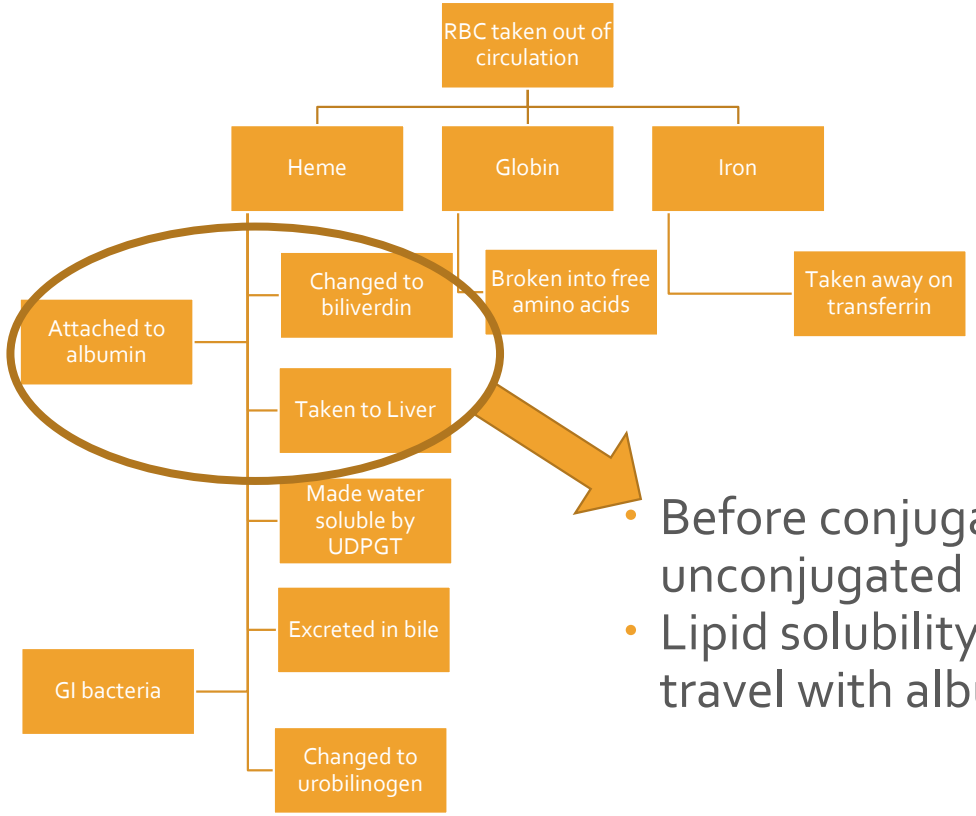


Overview: The Story of Erythrocyte Degradation

- RBCs lifespan of about 120 days ends
  - Reticuloendothelial system (mononuclear phagocyte system)
    - Spleen and liver
  - Iron and globin chains are liberated from hemoglobin and recycled
  - Heme degraded to biliverdin, then bilirubin
    - Lipophilic
  - Transported to liver on albumin
  - Liver conjugates with glucuronic acid
    - Water-soluble
  - Drains out of the liver into bile
  - Intestinal bacteria metabolize to urobilinogen
    - Oxidized to urobilin (stercobilin)

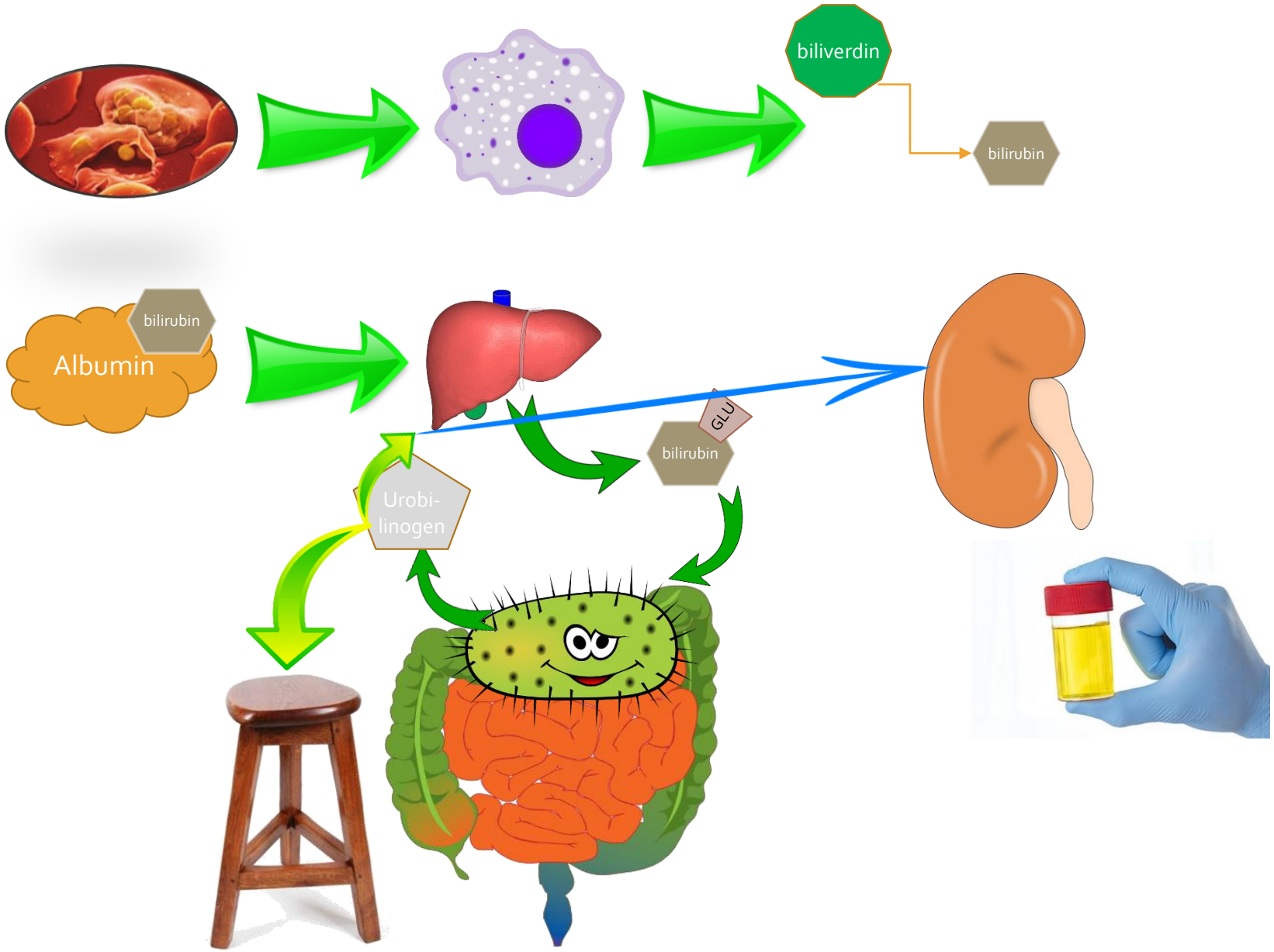


Visual Overview of RBC Degradation



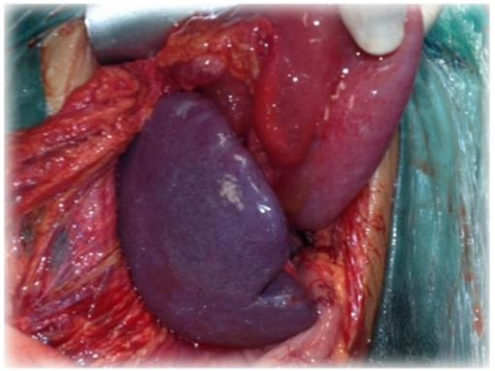
- Before conjugation it is known as unconjugated or indirect bilirubin
- Lipid solubility means it must travel with albumin

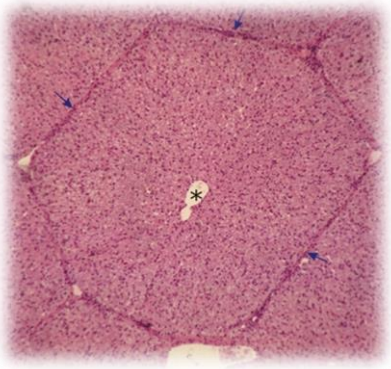
Visual Overview of RBC Degradation



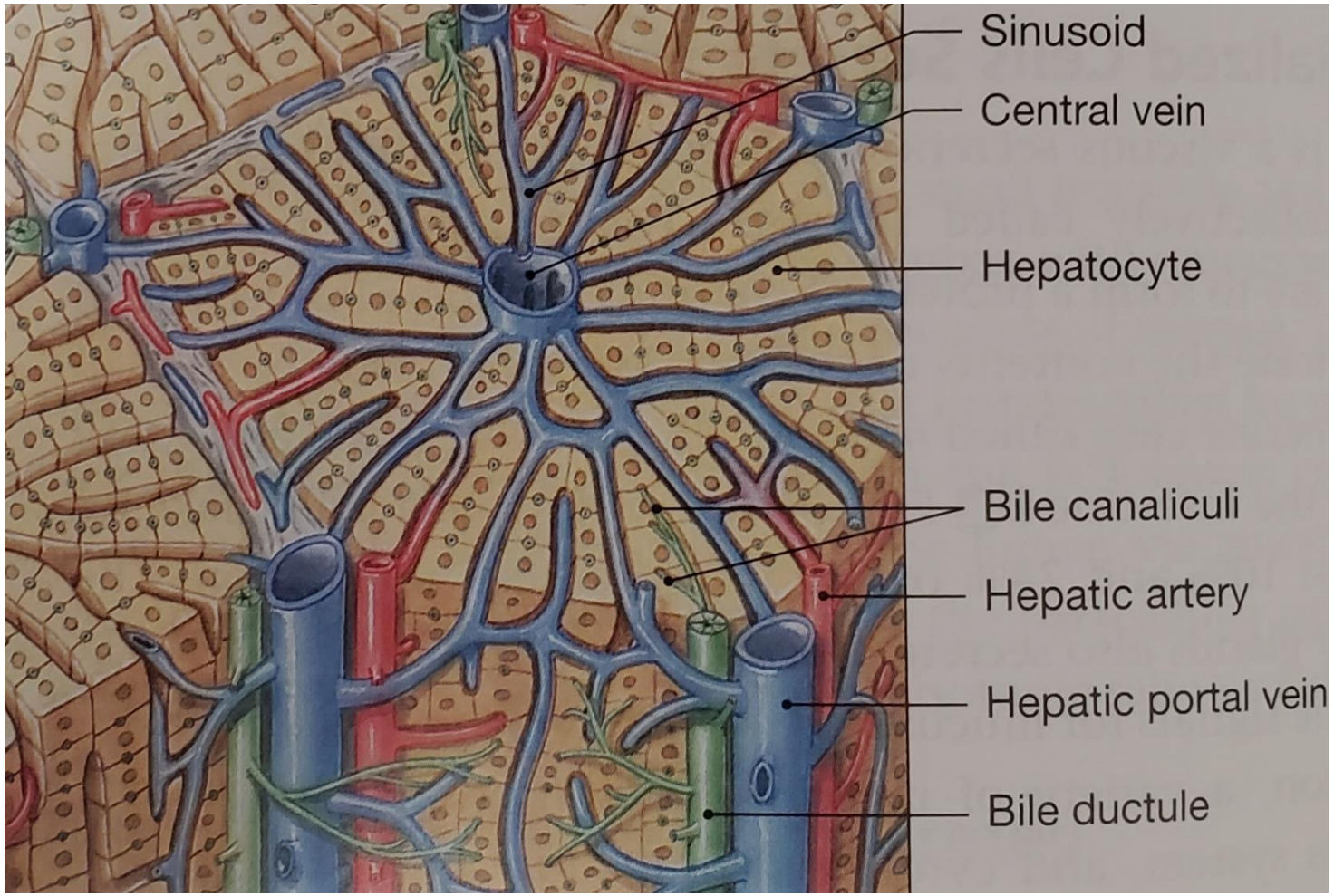
The Liver's Role in RBC Degradation

- UDP-glucuronyl transferase (UDPGT)
  - Slow to come up to full levels in newborns (PJNB)
- Glucuronic acid makes bilirubin water soluble
  - Now conjugated bilirubin or direct bilirubin (C. Bili or D. Bili)
  - Main pigment in bile
- Bile is excreted into bile duct, gall bladder, GI tract
  - Intestinal bacteria act on bilirubin to make urobilinogen (colorless)
    - Some reabsorbed and goes right back to liver
    - *Some* makes it to general circulation, kindeys
  - Urobilinogen further oxidized to urobilin (urochrome) and stercobilin





Form Follows Function



Testing For Bilirubin

- Evelyn Malloy- bilirubin combines with diazotized sulfanilic acid to form azobilirubin (purple)
  - Jendrassik-Grof modifies this by shifting pH at end to make azobilirubin blue
  - Only able to combine with water soluble bilirubin (direct)
  - Measuring all bilirubin requires solubilizing
    - Accelerant

Direct Bilirubin	Indirect bilirubin	Total Bilirubin
Water-soluble	Lipid-soluble	Assay with diazo and accelerant
Reacts readily with diazo reagent	Reacts with diazo after adding accelerant	After doing total and direct, can calculate indirect

Bilirubin Pathologies

- Jaundice- Not a disease
  - Yellowing due to high amounts of bilirubin, eye sclera/conjunctiva first
    - Pre-hepatic- overwhelm liver processing
    - Hepatic- liver function impaired
    - Post-hepatic- plumbing backs up
- Kernicterus
  - Unconjugated bilirubin overwhelms albumin
  - Lipid soluble, makes it to brain, damages newborn brain
  - Results in developmental disability, can be fatal

Prehepatic Jauncidce

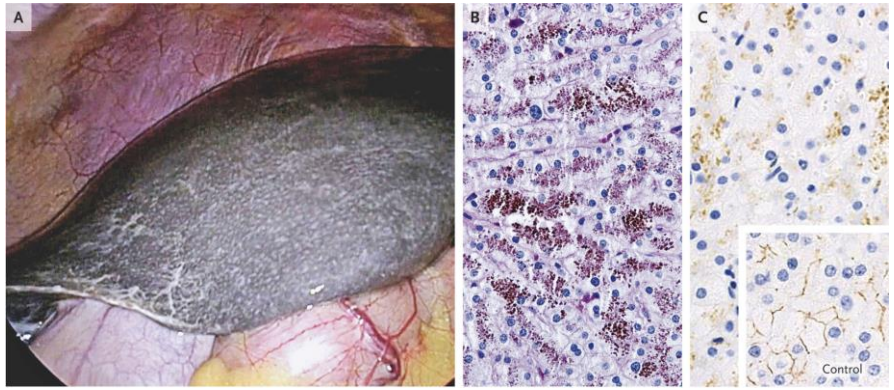
- Due to increased RBC turnover
  - Hemolytic anemias

mg/dL	0	50	150	250
g/L	0	0.50	1.50	2.50

- Liver usually able to keep up
  - Keeps levels below harmful levels, <5 mg/dL
- Circulating bilirubin is unconjugated (indirect)

Hepatic Jaundice

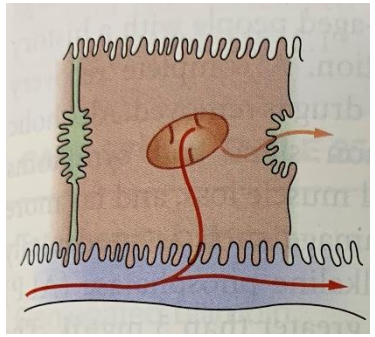
- Bilirubin metabolism or transport is impaired
  - Bilirubin builds up, unconjugated (usually)
- Gilbert's disease
  - Partial loss of UDPGT
- Crigler-Najjar
  - Total loss of UDPGT
- Dubin-Johnson syndrome
  - Cannot secrete into canaliculi
- Rotor syndrome
  - Unknown etiology, similar to D-J
- Other- hepatitis, cirrhosis, liver cancer, Reye's syndrome, autoimmune attacks on liver, Wilson's disease



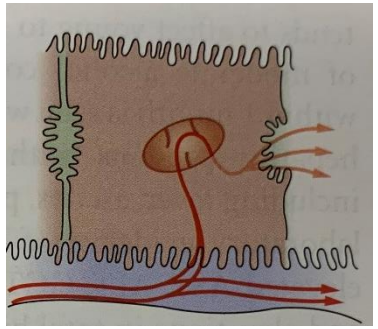
Post-Hepatic Jaundice

- Also known as obstructive jaundice
  - Gallstones, tumors, inflammation, even liver flukes may block bile duct
- Liver able to conjugate and secrete but it never gets past gallbladder
  - No pigments in feces = clay colored stool
- Backup causes regurgitation into bloodstream
  - Lots of conjugated/direct bilirubin present

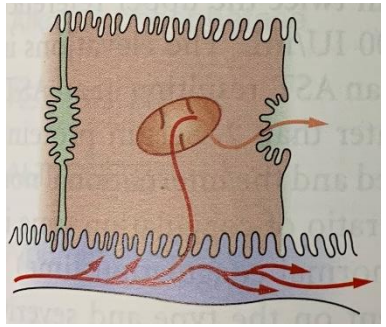
Jaundice Causes Diagrams



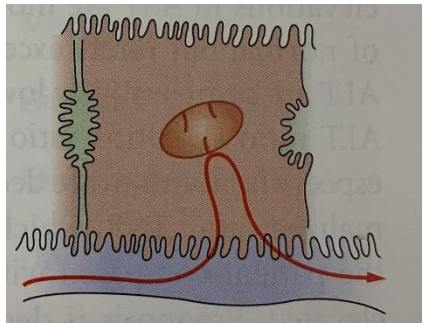
normal



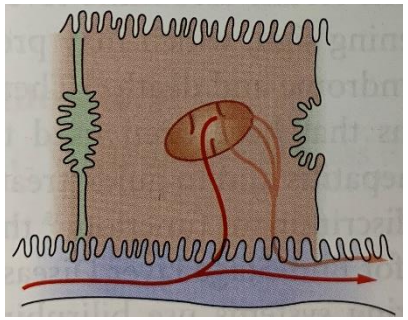
Pre-hepatic



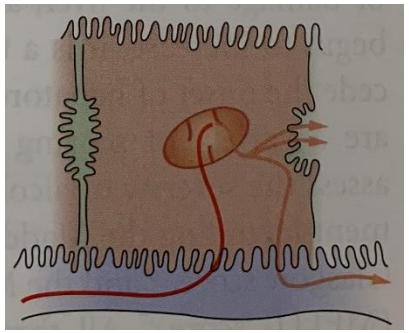
Gilbert's



PNJB/Criggler-Najjar



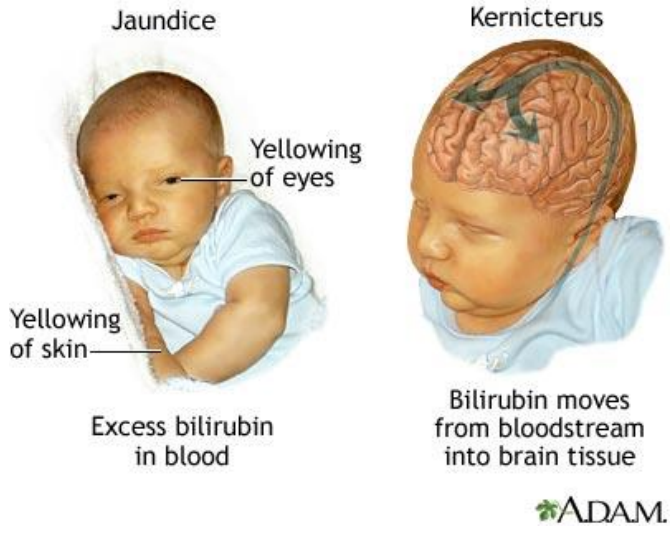
Dubin-Johnson and Rotor's



Obstructive

Treatments

- When is bilirubin a problem?
  - Where does it come from?
  - What type?
  - Why can't the body get rid of it?
- Phototherapy



Typical Testing Patterns

	Pre-hepatic Jaundice	Hepatic Jaundice	Post-hepatic Jaundice
Total bilirubin	Normal / Increased	Increased	Increased
Conjugated bilirubin	Normal	Normal / Increased* / ?Decreased?	Increased
Unconjugated bilirubin	Increased	Increased	Normal
Urobilinogen	Increased	Normal	?Decreased? / Negative
Urine Colour	Normal	Dark	Dark
Stool colour	Normal	Normal	Pale
Alkaline phosphate levels	Normal	Slight elevation	Increased
AST & ALT levels	normal	Increased	Normal

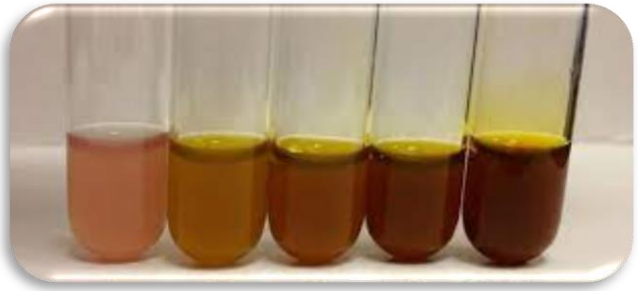
* Increase due to D.bil in case of Dubin-Johnson/Rotor/Cirrhosis type hepatic jaundices

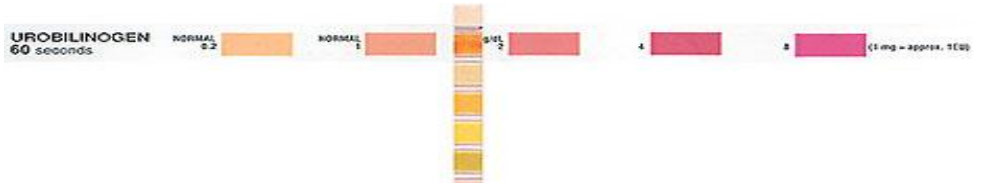
Case Study #1

- 65 YO female reports to ED, complains of:
  - Abdominal pain
  - Chills
  - Fever
  - Loss of appetite
  - 'Whiteish' stools
- Yellow eyes
- Labs are ordered….

Case Study #1

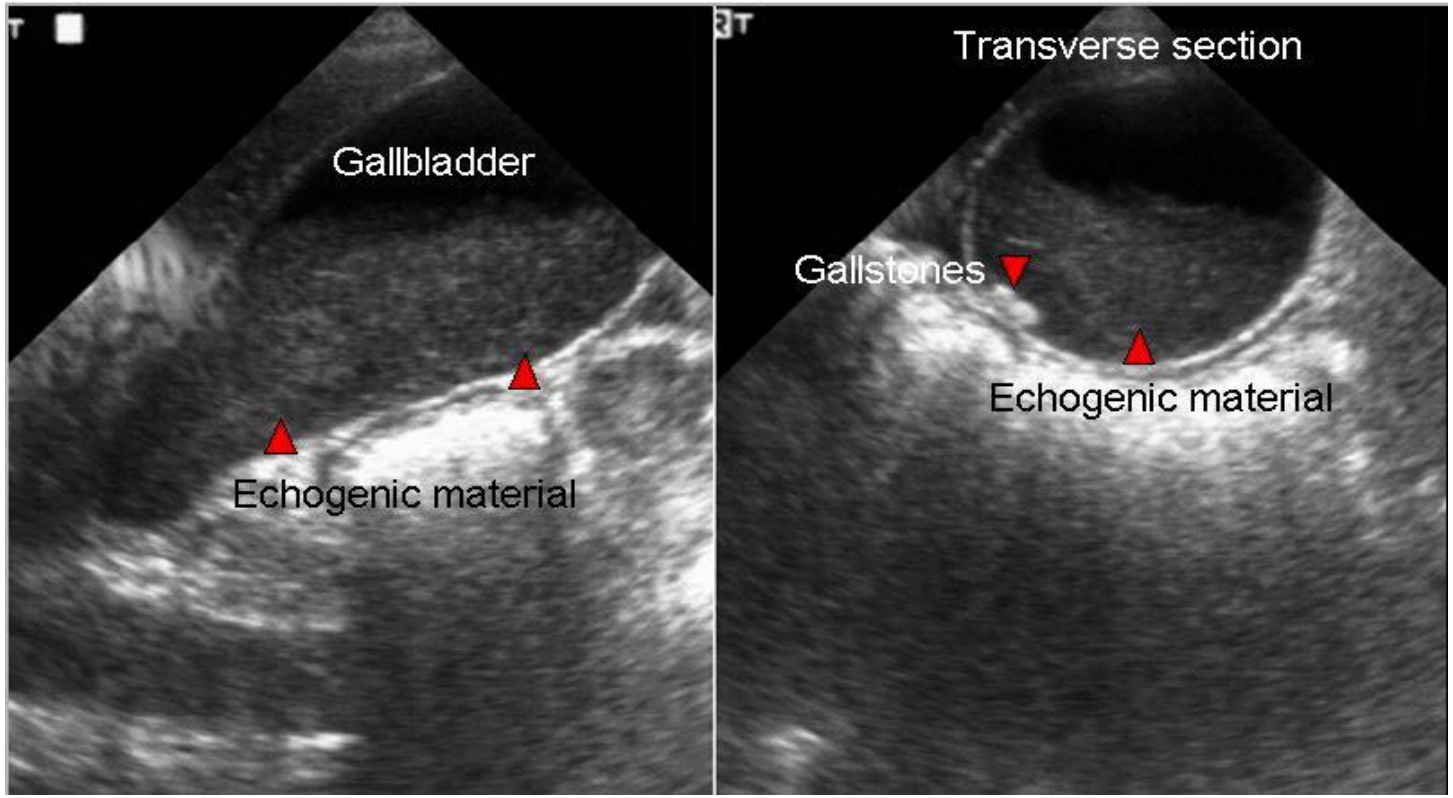
- AST:38 U/L (7-40 U/L)
- ALT:28 U/L (0-30 U/L)
- Alk Phos: 452 U/L (20-120 U/L)
  - What does this mean?
- Bilirubin
  - Total: 6.0 mg/dL (0.1-1.5 mg/dL)
  - Direct: 5.4 mg/dL (0.1-0.4 mg/dL)
  - Indirect: ____ mg/dL (0.1-1.1 mg/dL)
  - What does this mean?
- Urine
  - Dark yellow
  - Bilirubin ++
  - Urobilinogen- Norm
- Ultrasound ordered…





Case Study #1 Conclusion

- Multiple gallstones obstructing bile duct



Case Study #2

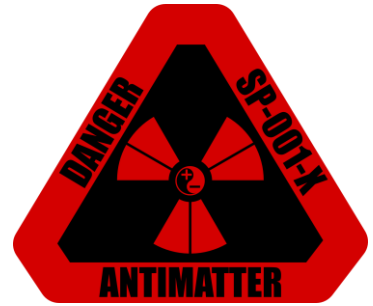
- 49 Y.O. patient on Ribavirin and interferon alpha for control chronic hepatitis C that has been well controlled up to this point.
- They present with:
  - Abdominal pain
  - Fever
  - Yellow eyes

Case Study #2

- Serum bilirubin is 5.5 mg/dl
- Serum unconjugated bilirubin is raised
- Albumin is normal
- Liver enzymes are slightly elevated, but consistent with previous values

Case Study #2 Conclusion

- Blackbox warning for Ribavarin:
  - RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS
    - […]The primary clinical toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as 6 months[…]



Case Study #3

- A 54 year old man presents with vomiting, epigastric pain, and nausea. He admits to a history of heavy drinking. Labs are as follows:
  - Alk Phos: **175** U/L (20-120 U/L)
  - AST: **158** U/L (7-40 U/L)
  - ALT: **92** U/L (0-30 U/L)
  - GGT: **284** U/L (0- 50 U/L)
  - LD: 136 U/L (100-220 U/L)
  - T Bili: **16.7** mg/dL (0.1-1.5 mg/dL)
  - C Bili: **8.9** mg/dL (0.1-0.4 mg/dL)
  - Albumin: *1.7* g/dL (3.5-5.0 g/dL)
  - T Protein: 6.0 g/dL (6.0-8.0 g/dL)
  - PT: **19** sec (9-13 sec)