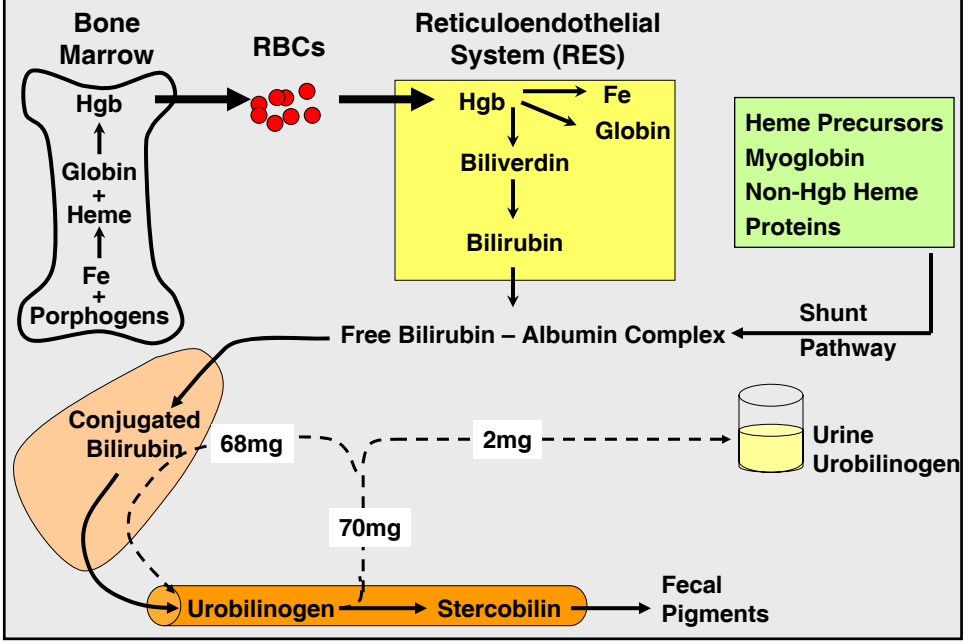
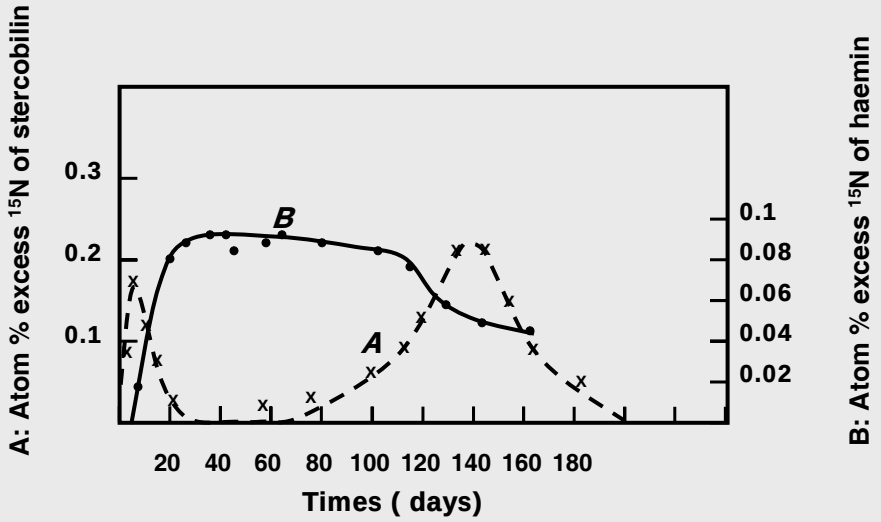
Bilirubin and Jaundice

Pathways of Bilirubin Synthesis and Catabolism

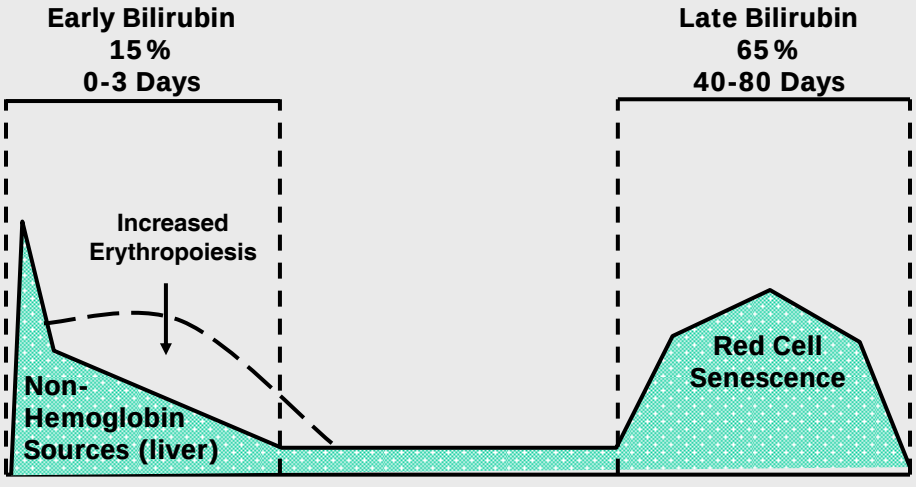


Labeling of RBC hemoglobin and fecal stercobilin

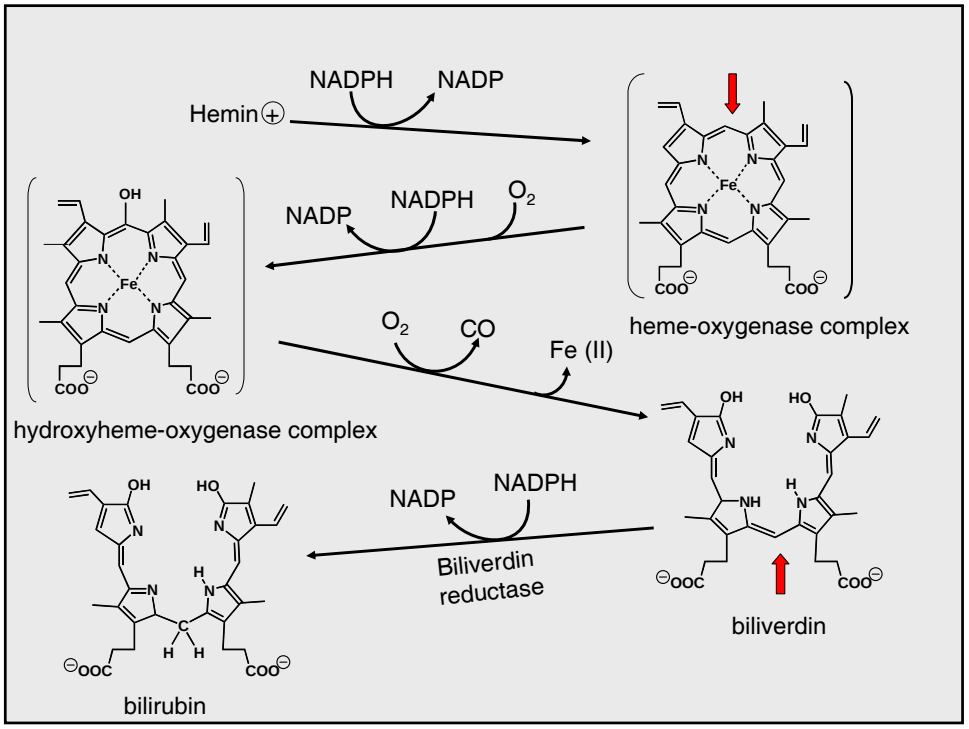


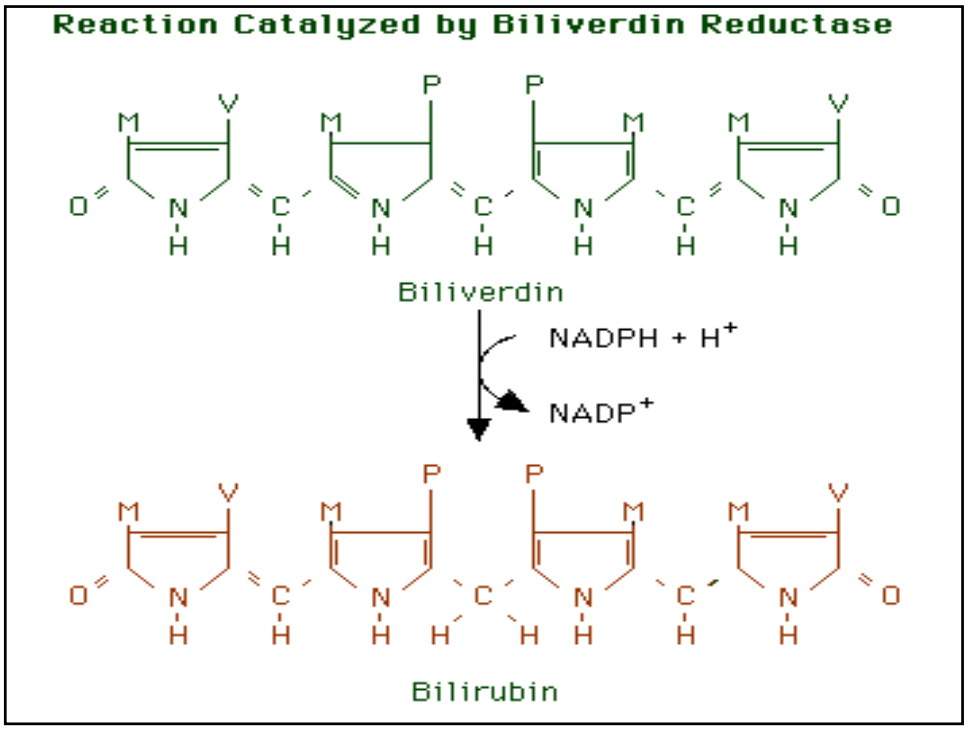
Labeling of red cell hemoglobin and fecal stercobilin in a normal human given ^{15}N orally

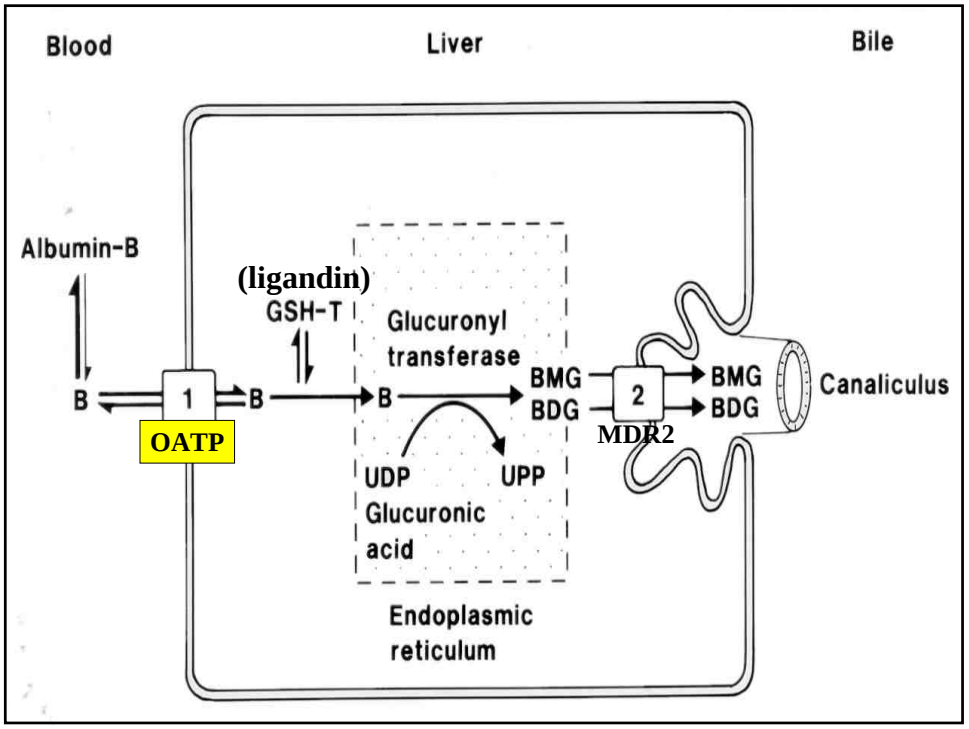
Sources of bilirubin production in the rat

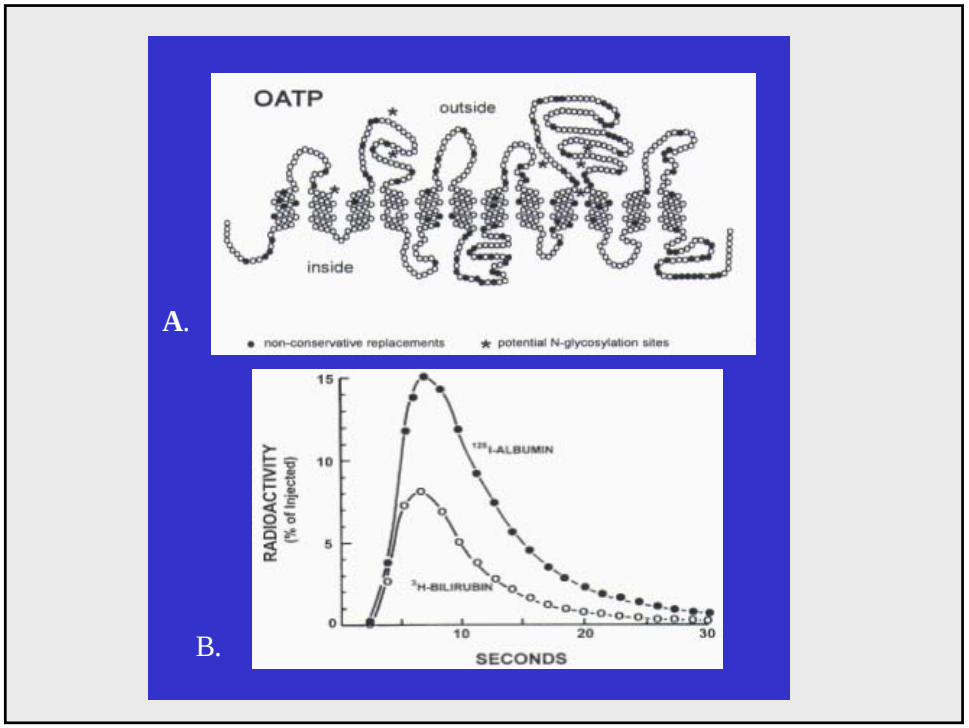


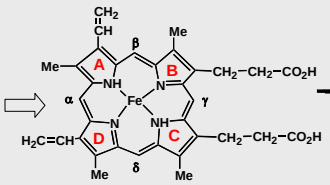
Sources of bilirubin production in the rat, as adduced from studies of the labeling of plasma bilirubin in Gunn rats and bile bilirubin in normal rats.


NADPH
NADP
Hemin
heme-oxygenase complex
NADP
NADPH
O_2
hydroxyheme-oxygenase complex
O_2
CO
Fe (II)
biliverdin
NADP
NADPH
Biliverdin reductase
bilirubin


Reaction Catalyzed by Biliverdin Reductase
Biliverdin
NADPH + H+
NADP+
Bilirubin


Blood
Liver
Bile
Albumin-B
(ligandin)
GSH-T
Glucuronyl
transferase
B
1
B
B
BMG
BDG
2
BMG
BDG
Canaliculus
OATP
MDR2
UDP
UPP
Glucuronic
acid
Endoplasmic
reticulum

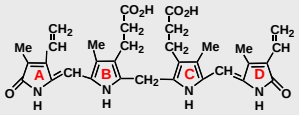

A.
OATP
outside
inside
non-conservative replacements
potential N-glycosylation sites
B.
RADIOACTIVITY
(% of Injected)
15
10
5
0
^{125}I-ALBUMIN
^{3}H-BILIRUBIN
10
20
30
SECONDS



CO (excreted via lungs)

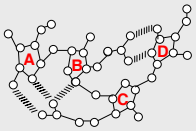
Fe (reutilized)

A.



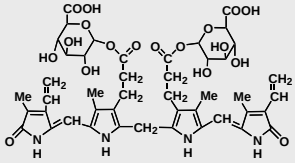
BILIRUBIN – IX α (planar structure)

B.



BILIRUBIN – IX α (convoluted structure)

C.



BILIRUBIN - IX α DIGLUCURONIDE

BILIRUBIN CONJUGATION IN MICROSOMES INVOLVES TWO STEPS, MEDIATED BY ONE BILIRUBIN-UDPGA TRANSFERASE

BILIRUBINS:

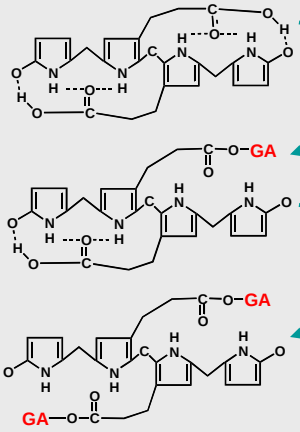
UNCONJUGATED (UCB)

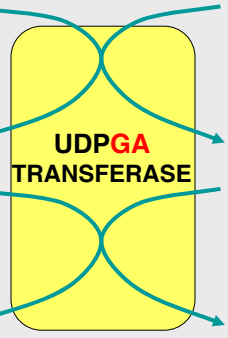
(1)

MONO-GLUCURONIDE (BMG)

(2)

DIGLUCURONIDE (BDG)





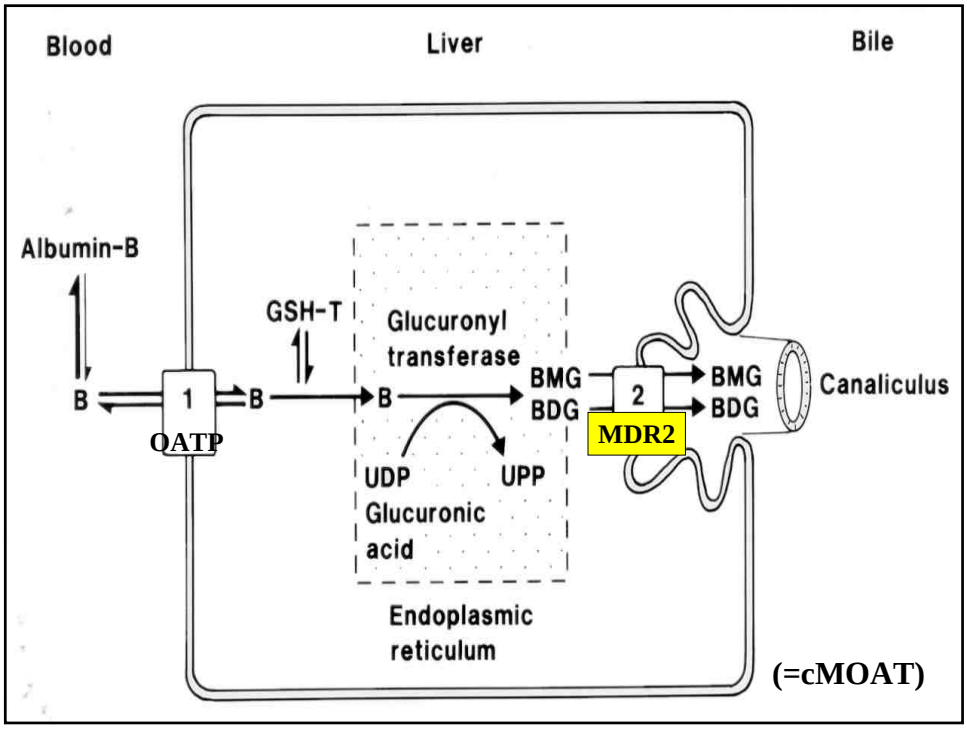
UDPGA

UDP

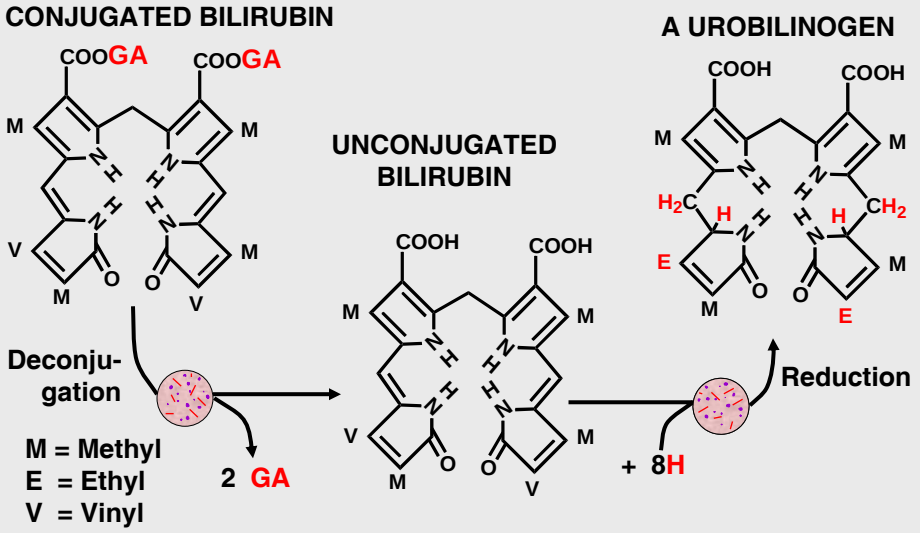
UDPGA

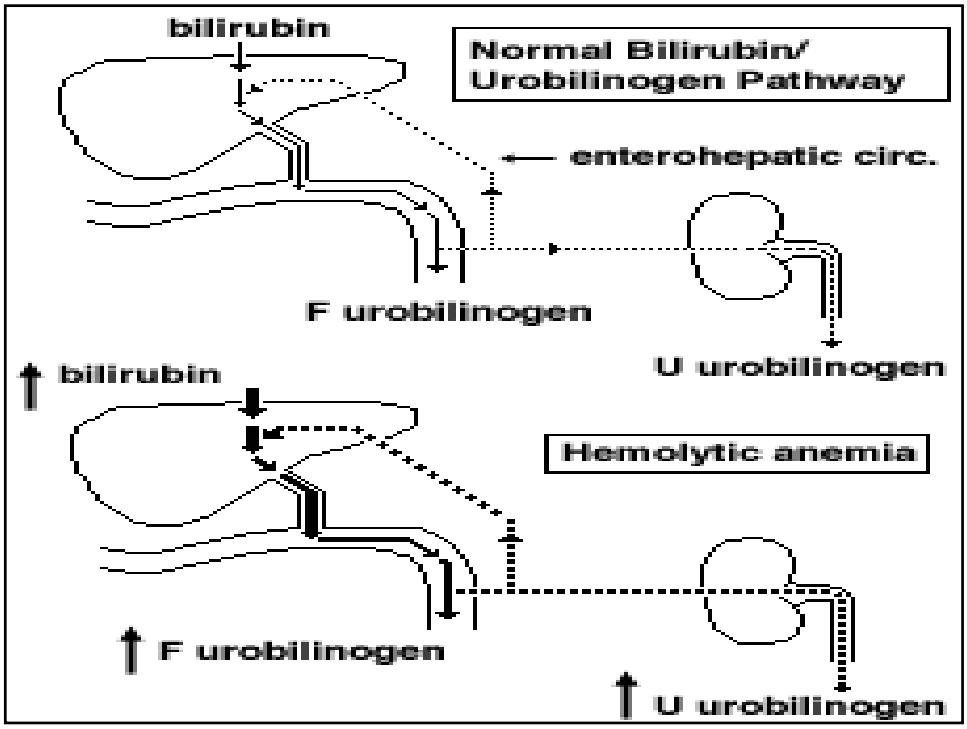
UDP

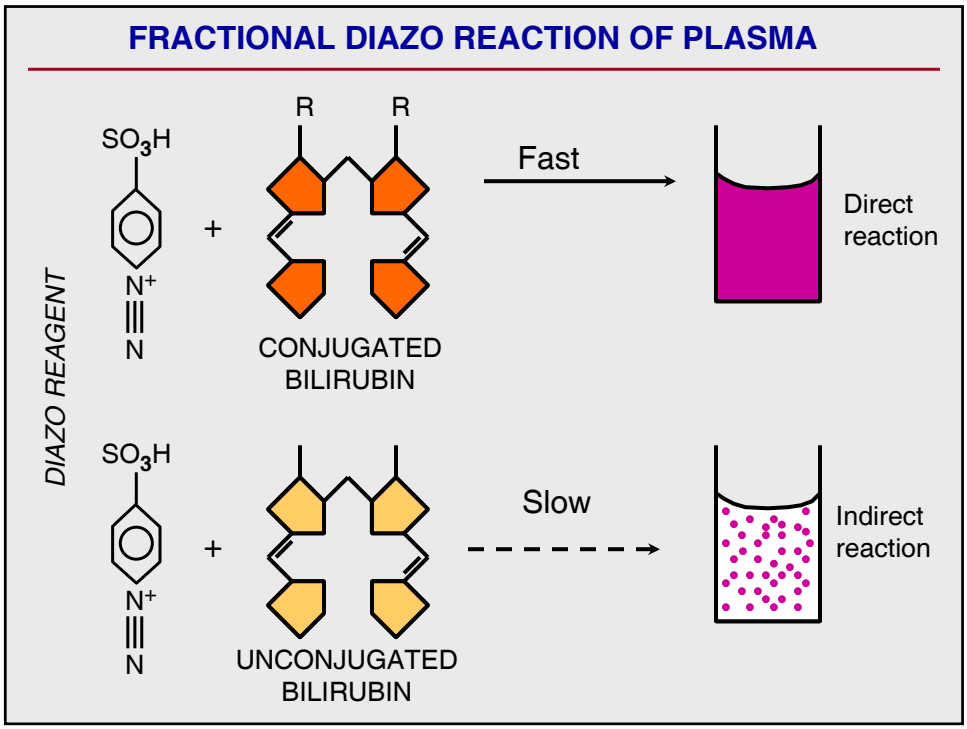
Conjugation prevents internal H-bonding by the -COOH groups of Bilirubin



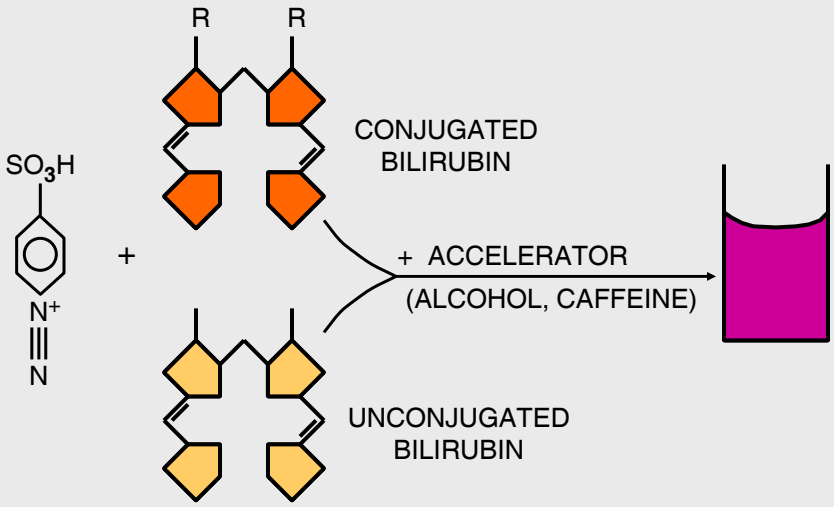
UROBILINOGENS ARE FORMED BY DECONJUGATION AND REDUCTION OF BILIRUBINS BY INTESTINAL BACTERIA




bilirubin
Normal Bilirubin/
Urobilinogen Pathway
enterohepatic circ.
F urobilinogen
U urobilinogen
bilirubin
Hemolytic anemia
F urobilinogen
U urobilinogen

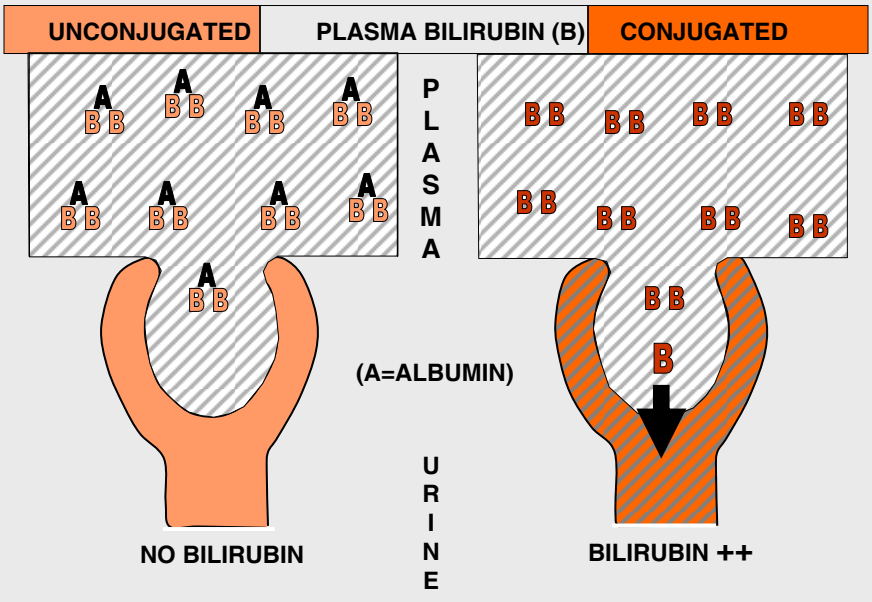

FRACTIONAL DIAZO REACTION OF PLASMA
DIAZO REAGENT
SO3H
N+
N
R
R
CONJUGATED
BILIRUBIN
Fast
Direct
reaction
SO3H
N+
N
UNCONJUGATED
BILIRUBIN
Slow
Indirect
reaction

TOTAL DIAZO REACTION OF PLASMA



TOTAL – DIRECT = INDIRECT

Bilirubinuria in Jaundice

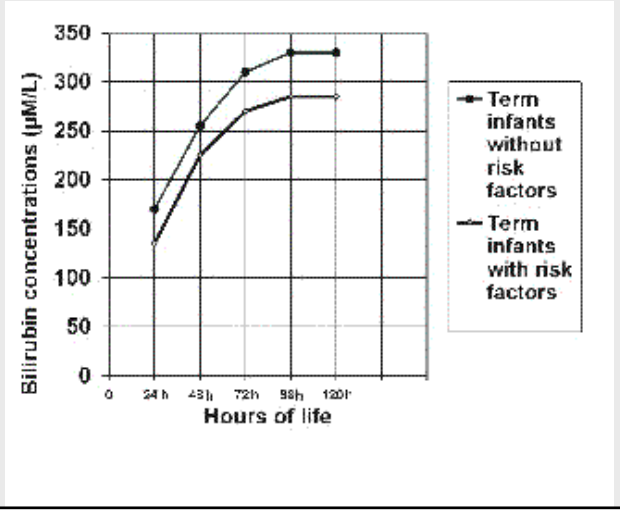


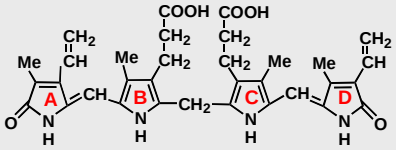

URI-3 Test

Phototherapy for neonatal jaundice

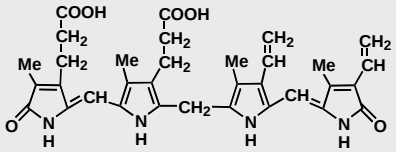
Treatment for Neonatal Jaundice

Prevention of kernicterus



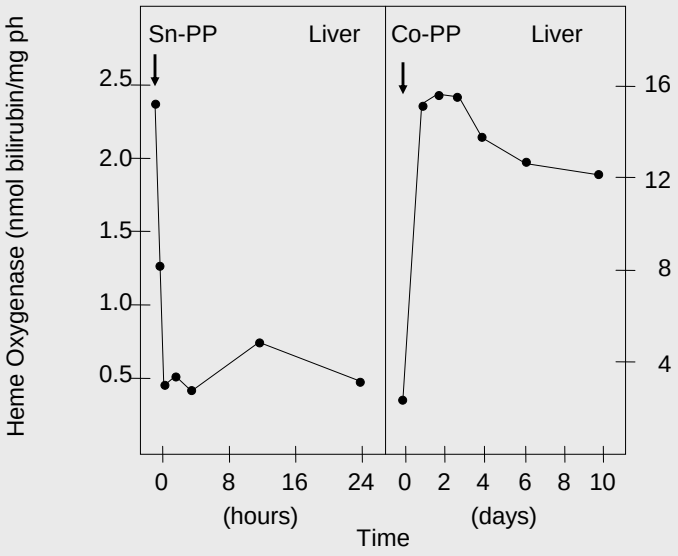


Bilirubin IX α

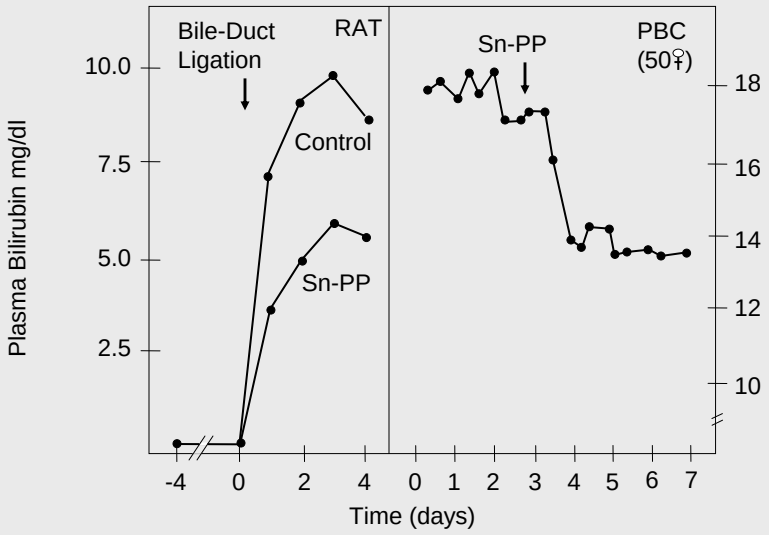


Bilirubin IX β

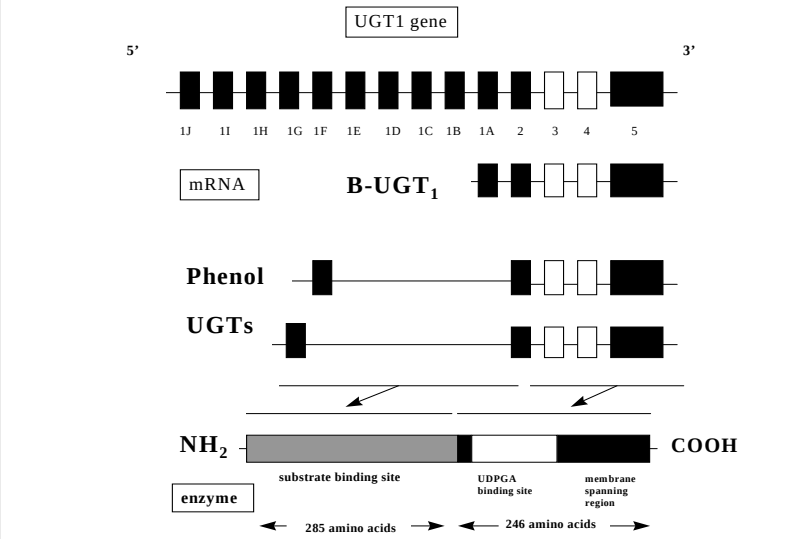
Structure of the α and β isomers of bilirubin IX. In the IXβ isomer (and in the γ and δ isomers, not shown) the propionic acid groups are moved to positions other than those indicated on the central pyrrole rings *B* and *C* of bilirubin IXα.



Effect of Sn-protoporphyrin (Sn-PP) and CO-protoporphyrin (Co-PP) when administered once at a dose of 50 μmol/kg body wt on hepatic heme oxygenase activity in the rat.



Effect of Sn-protoporphyrin (Sn-PP) (100 μmol/kg body wt) administered at 4d before and on the day of surgery on hyperbilirubinemia in the bile-duct-ligated rat. Effect of Sn-PP (2 x 0.25 μmol/kg body wt) on the levels of serum bilirubin in a patient with primary biliary cirrhosis (PBC).

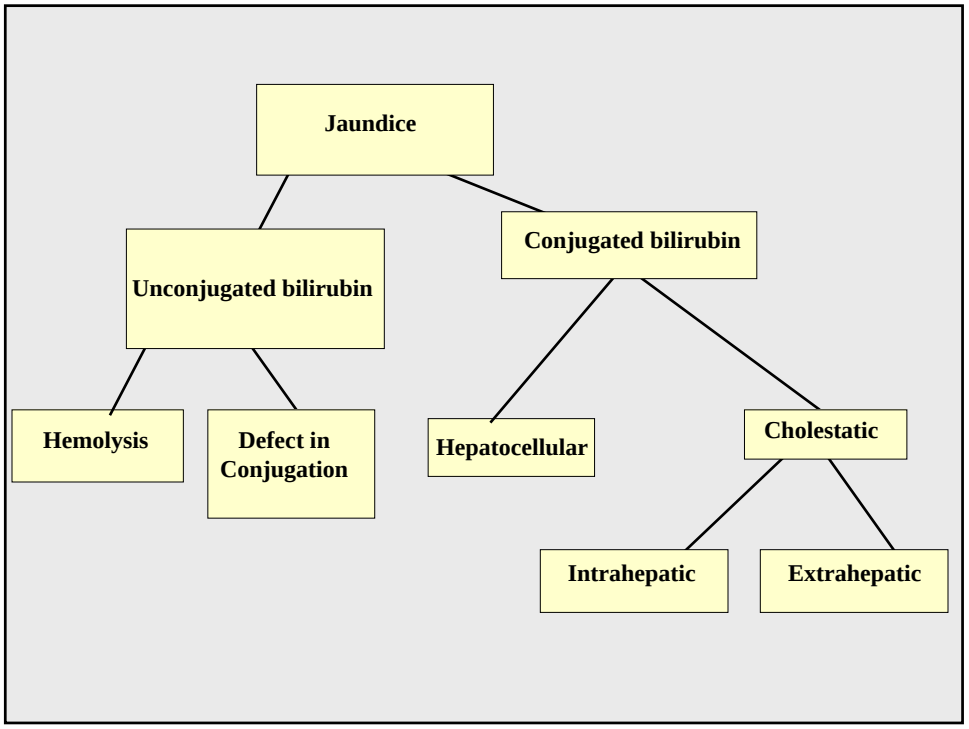


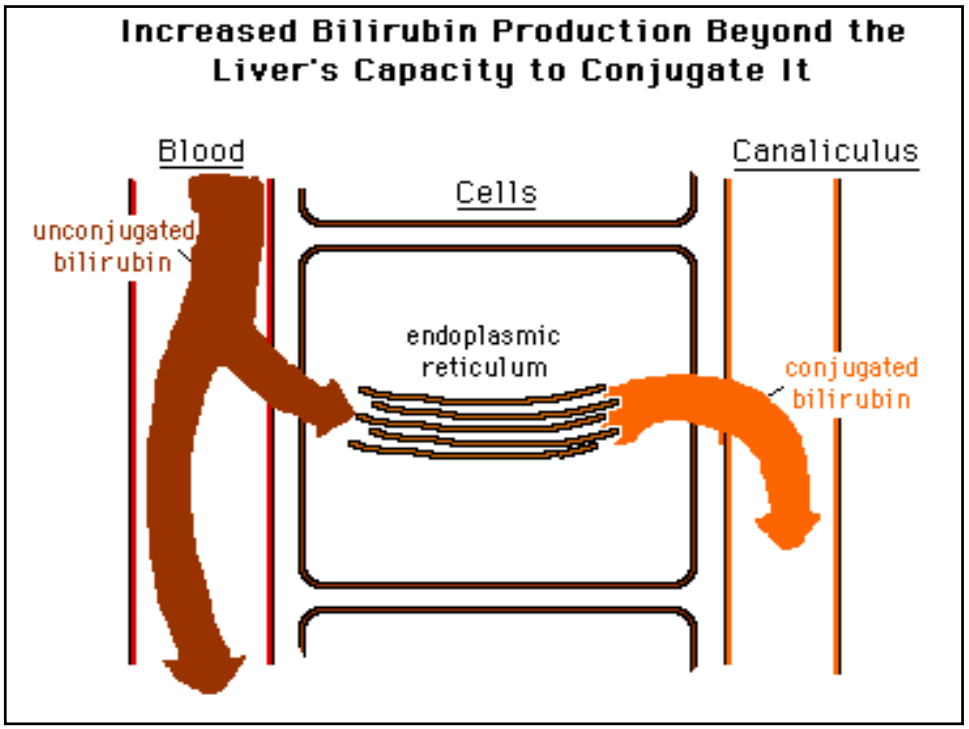
Unconjugated Hyperbilirubinemia

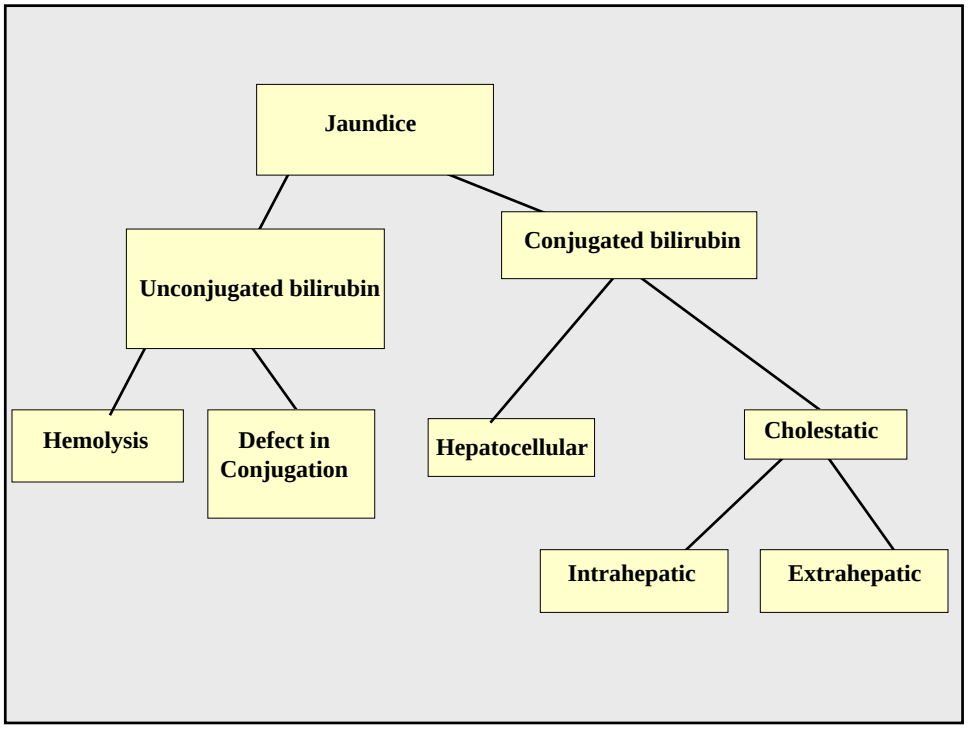
Characteristics	Crigler-Najjar Type I	Gilbert Syndrome
Plasma bilirubin	340-860 μM	50-85 μM (fluctuates)
Plasma BSP retention at 45 min	Normal	Usually normal; elevated in a minority of cases
Hepatic bilirubin-UDPGT activity	Undetectable	30-50% of normal
Effect of Phenobarbital on plasma bilirubin	No effect	Reduction
Pigments in bile	Small amounts of unconjugated bilirubin	Increased proportion of monoglucuronide
Prevalence	Rare	2-7% of population
Prognosis	Kernicterus	Benign
Animal Model	Gunn rat	Bolivian Squirrel Monkey
Mutation	UDPGT null	UDPGT promoter $A(TA)_6TAA$

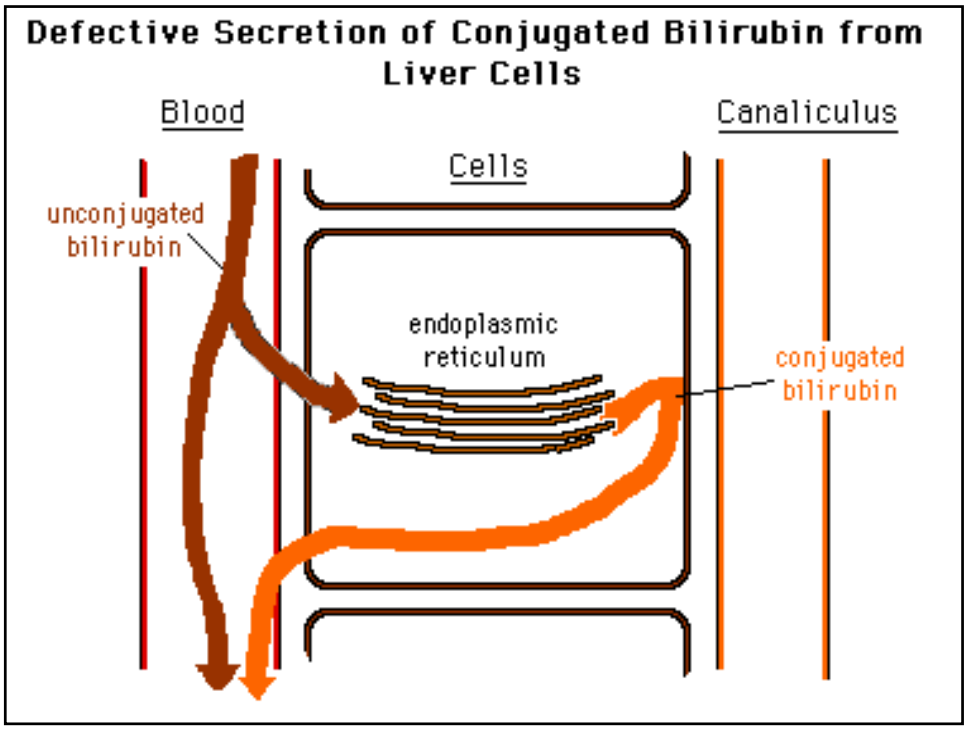
Chronic conjugated hyperbilirubinemias

Characteristic	Dubin-Johnson Syndrome	Rotor Syndrome
Appearance of liver	Grossly black	Normal
Histology of liver	Dark pigment; predominantly in centrilobular areas; otherwise normal	Normal
Serum bilirubin	Elevated, usually between 2 and 5 mg%, occasionally as high as 20 mg%; predominantly direct-reacting	Elevated, usually between 2 and 5 mg%, occasionally as high as 20 mg%; predominantly direct-reacting
Routine liver function tests	Normal except for bilirubin	Normal except for bilirubin
45-min plasma BSP retention	Normal or elevated; secondary rise at 90 min	Elevated; no secondary rise at 90 min
Urinary coproporphyrin	Normal total >80% as coproporphyrin I	Elevated total; elevated proportion of coproporphyrin I but <80%
Mode of inheritance	Autosomal recessive	Autosomal recessive
Prevalence	Uncommon (1:1300 in Persian Jews)	Rare
Prognosis	Benign	Benign
Mutation	MRP2	


Jaundice
Unconjugated bilirubin
Conjugated bilirubin
Hemolysis
Defect in Conjugation
Hepatocellular
Cholestatic
Intrahepatic
Extrahepatic


Increased Bilirubin Production Beyond the Liver's Capacity to Conjugate It
Blood
Cells
Canaliculus
unconjugated bilirubin
endoplasmic reticulum
conjugated bilirubin


Jaundice
Unconjugated bilirubin
Conjugated bilirubin
Hemolysis
Defect in Conjugation
Hepatocellular
Cholestatic
Intrahepatic
Extrahepatic

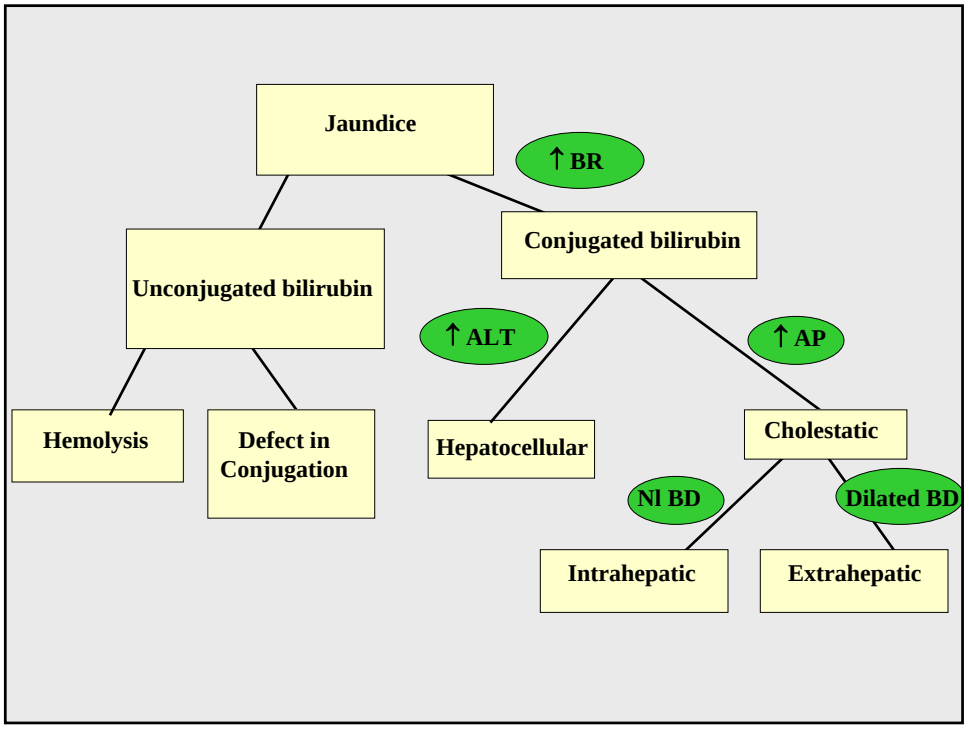

Defective Secretion of Conjugated Bilirubin from Liver Cells
Blood
Canaliculus
Cells
unconjugated bilirubin
endoplasmic reticulum
conjugated bilirubin

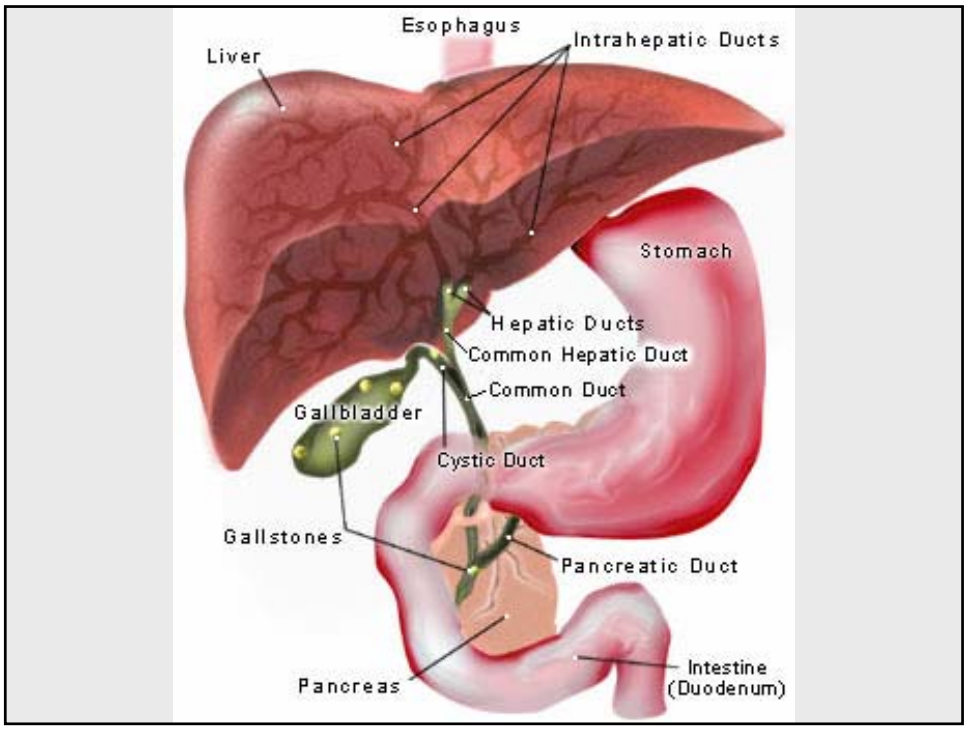
Liver Function Tests

- Bilirubin
- PT (Prothrombin time)
- Glucose
- Cholesterol
- ALT (alanine aminotransferase)
- AST (aspartate aminotransferase)
- Alkaline phosphatase
- GGT (γ-glutamyltranspeptidase)

Imaging

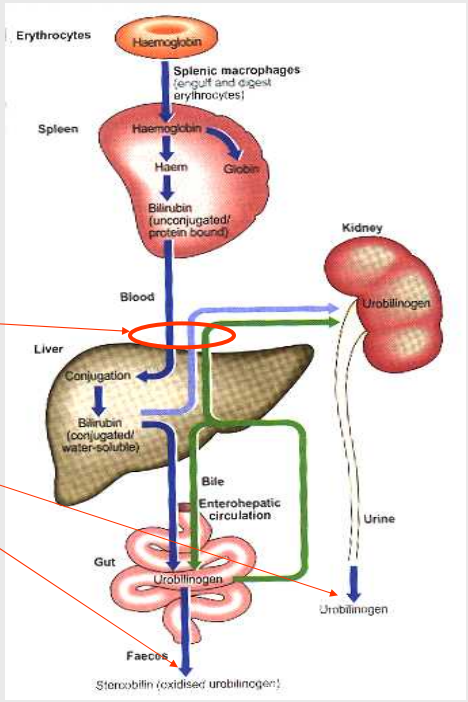
- Ultrasound
- CT scan
- Liver-spleen scan
- Radionuclide biliary scan
- ERCP (endoscopic retrograde cholangiopancreatography)
- Transhepatic cholangiography

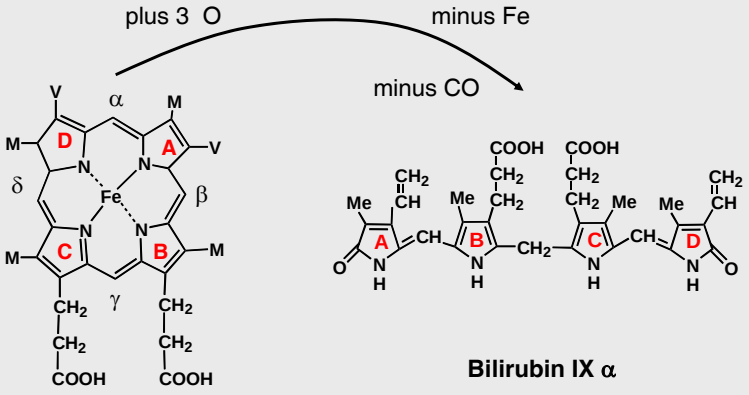

Jaundice
↑BR
Unconjugated bilirubin
Conjugated bilirubin
↑ALT
↑AP
Hemolysis
Defect in Conjugation
Hepatocellular
Cholestatic
Nl BD
Dilated BD
Intrahepatic
Extrahepatic


Esophagus
Intrahepatic Ducts
Liver
Stomach
Hepatic Ducts
Common Hepatic Duct
Common Duct
Gallbladder
Cystic Duct
Gallstones
Pancreatic Duct
Pancreas
Intestine
(Duodenum)

Bilirubin Metabolism

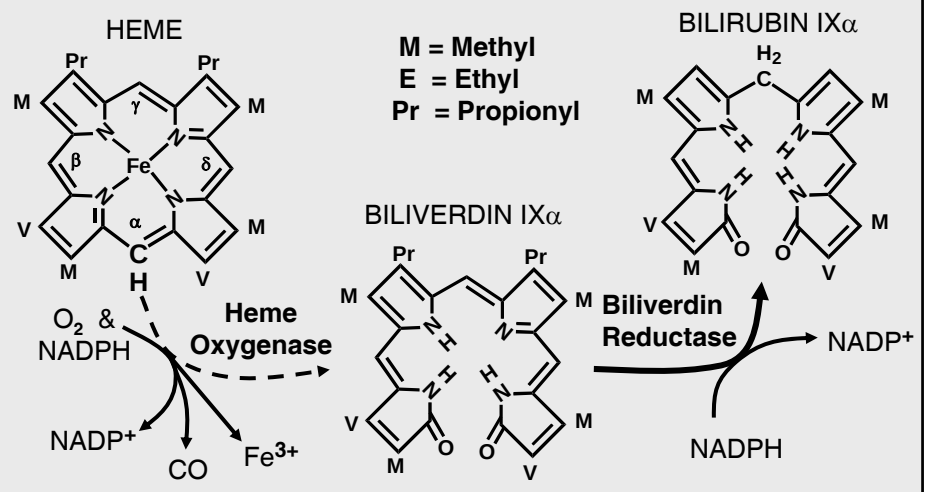
- Blood
  - Conjugated & Conjugated
- Urine – Urobilinogen
- Stool – Stercobilin

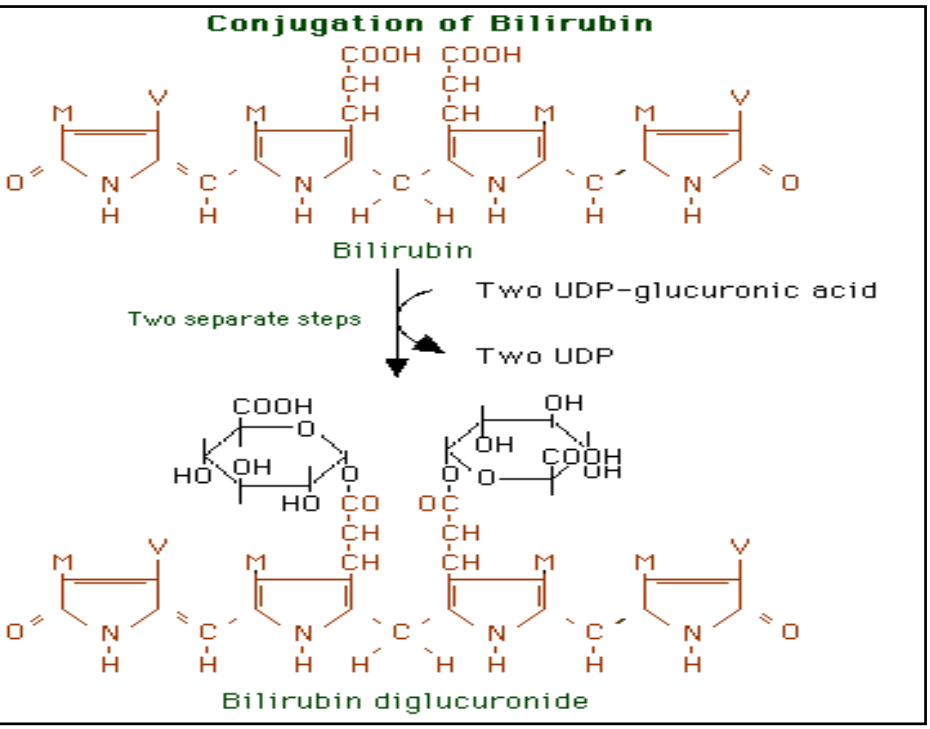


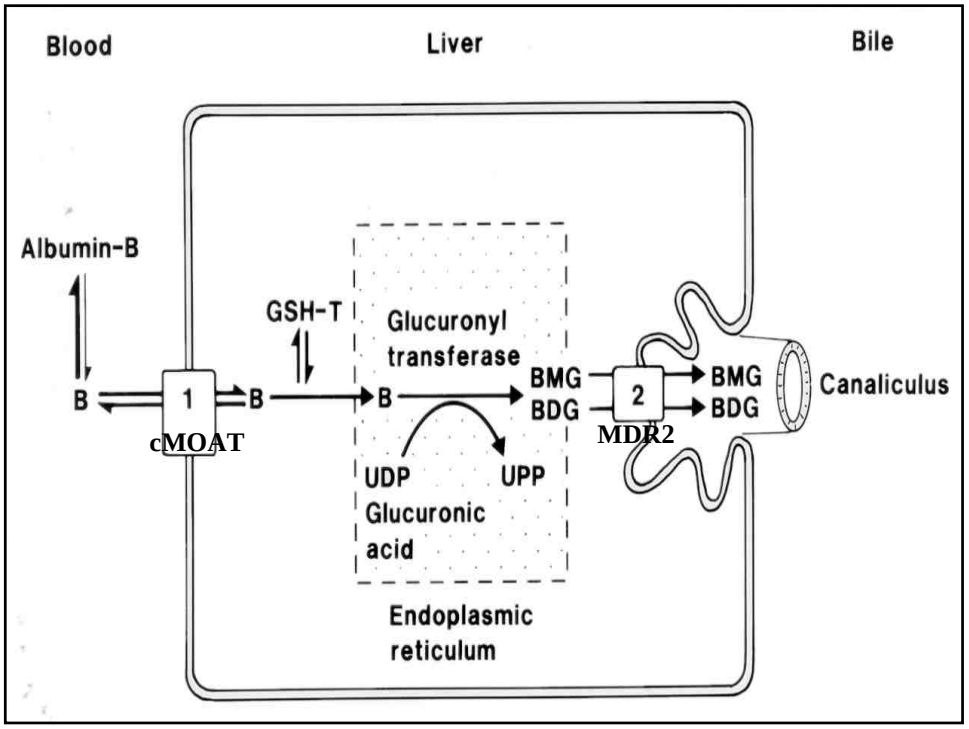


Conversion of protoheme (ferroprotoporphyrin IX) to bilirubin IXα. Cleavage of the protoporphyrin ring occurs selectively at the α-methene bridge. The bridge carbon atom is oxidized to carbon monoxide.

BILIRUBIN IS PRODUCED BY OXIDATION OF HEME AND REDUCTION OF THE RESULTANT BILIVERDIN







C.T. 5563 is a 45 y.o. Native American
etoh abuse c/o abdominal pain and fever.
05/85--psychiatric admission for etoh.
with SGOT 192, SGPT 162, BR 1.9/.5,
NI during hospitalization.
12/85--Alcoholic hepatitis, alcoholic ketoacidosis
04/86--Alcoholic hepatitis, alcoholic ketoacidosis
05/86--Diarrhea, alcohol related seizure
12/86--Alcohol hepatitis, ketoacidosis, seizure
04/87--Alcohol related seizure. No ascites, encephalopathy.
SGOT 144, SGPT 60, BR 4.3/2.3, Albumen 3.4, PT 14.3/12.5
2/8/88--Juandice with dark urine x 3
wks., fevers x 2 m with chills
and sweats. RUQ constant pain
unrelated to eating x 1 wk.
Denies diarrhea, hematemesis,
hematochezia. No travel, exposures.
PE. Juandiced, sl obese female in NAD
T-99, P96, R20, BP 130/80
HEENT-
Skin + spider angiomes
Pulm-clear to P&A
CV-VS, S2, no S3, S4, murmurs
Abd-Active BS. Liver 22cm span
moderately tender. -spleen, ascites

Rectal–Heme – stool

Neuro–tremor, – asterixis. Oriented x3

Lab Data 134 | 90 | 4 / 168 AP 198 NH345

2.6 | 3.4 | 0.1 \ SGOT 326 Etoh 0.20

SGPT 41

amylase 41 BR 31.5/22.5

Alb 2.2

11/8.5 MCV 120 Plates 76K PT 16.6/12.1

31\ 70S 5B 19L 4m 7B PIT 54.4/30.5

Initial Hospital Course

Dx severe alcoholic hepatitis. Rx vitamin K, thiamine

Temp 101 max, WBC. Diarrhea.

Tox screen –, Hep B –, Hep A –

Cultures –, LP –

Abd US–no evidence of biliary obstruction, dense liver. no lesions

Hemoccult + stools. HCT , Tx RBC

EGO–small varices, no stimata of bleeding.

Develops edema and ascites

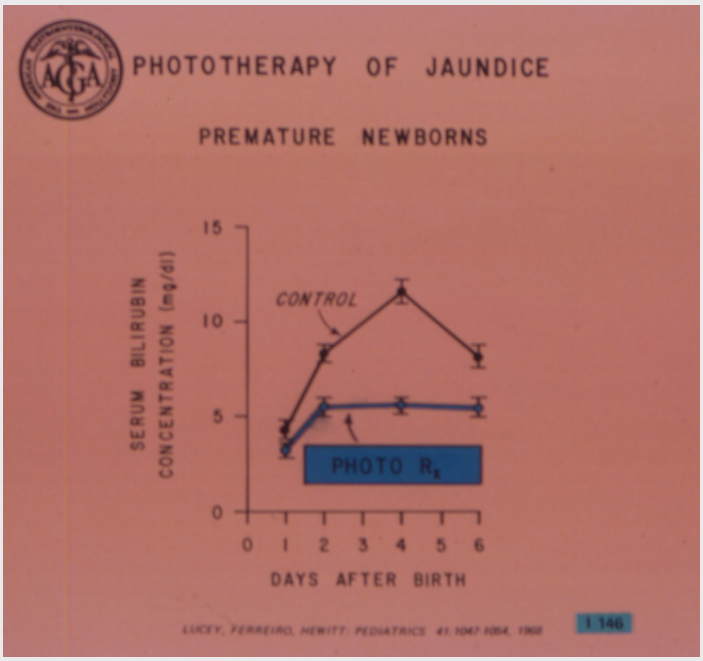
Paracentesis–80 WBC, 80% PMN. TP–50

Develops hepatic encephalopathy–asterixis, oriented x 0.

Rx–lactulose

Develops renal insufficiency BUN/creat 32/1.8

Coagulopathy worsens



Gunn Rats

*Absent bilirubin UDP-glucuronyltransferase

*Inherited as autosomal recessive trait

*Normal liver function

*Prototype of Crigler-Najjar type I

*No bilirubinuria, small amount of bilirubin in bile

*Excrete bilirubin IXß into bile

*Excrete unconjugated bilirubin into bile after phototherapy

*Defect corrected by hepatoma cells or kidney transplant