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Author: John Williams, M.D., Ph.D., 2009

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M1 - GI Sequence

Liver

John Williams, M.D., Ph.D.

Winter, 2009

University of Michigan
Medical School

FUNCTIONS OF LIVER

- Storage, metabolism and release of nutrients and some vitamins.
- Detoxification and elimination of toxins, drugs and metabolites.
- Synthesis of biologically important protein such as albumin, clotting factors, apolipoproteins.
- Synthesis and secretion of bile important for lipid digestion and absorption.
- Role in immune function and clearance of intestinally absorbed bacteria.

Cellular Components of the Liver

Hepatocytes

Stellate or Ito Cells

Kupfer Cells (macrophages)

Sinusoidal Endothelial Cells

Bile Ductular Epithelial Cells
(Cholangiocytes)

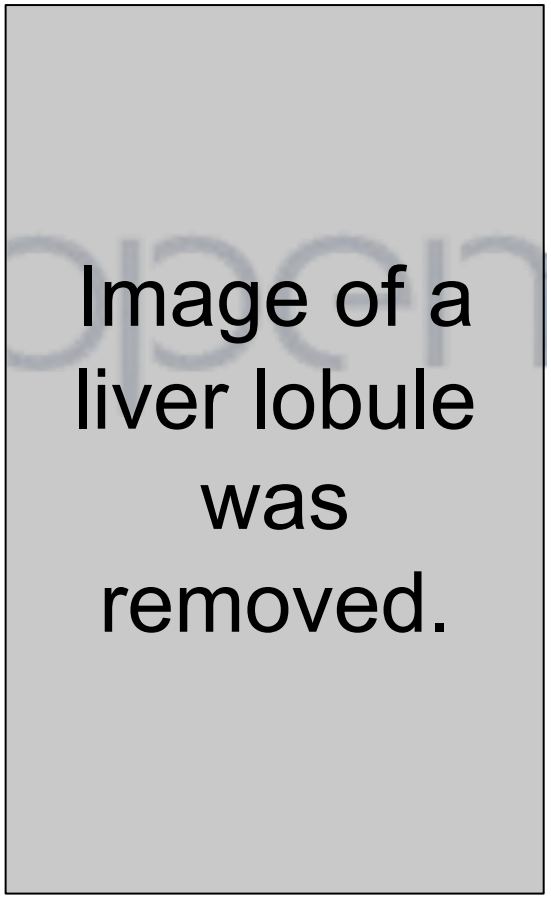
Image of a
liver lobule
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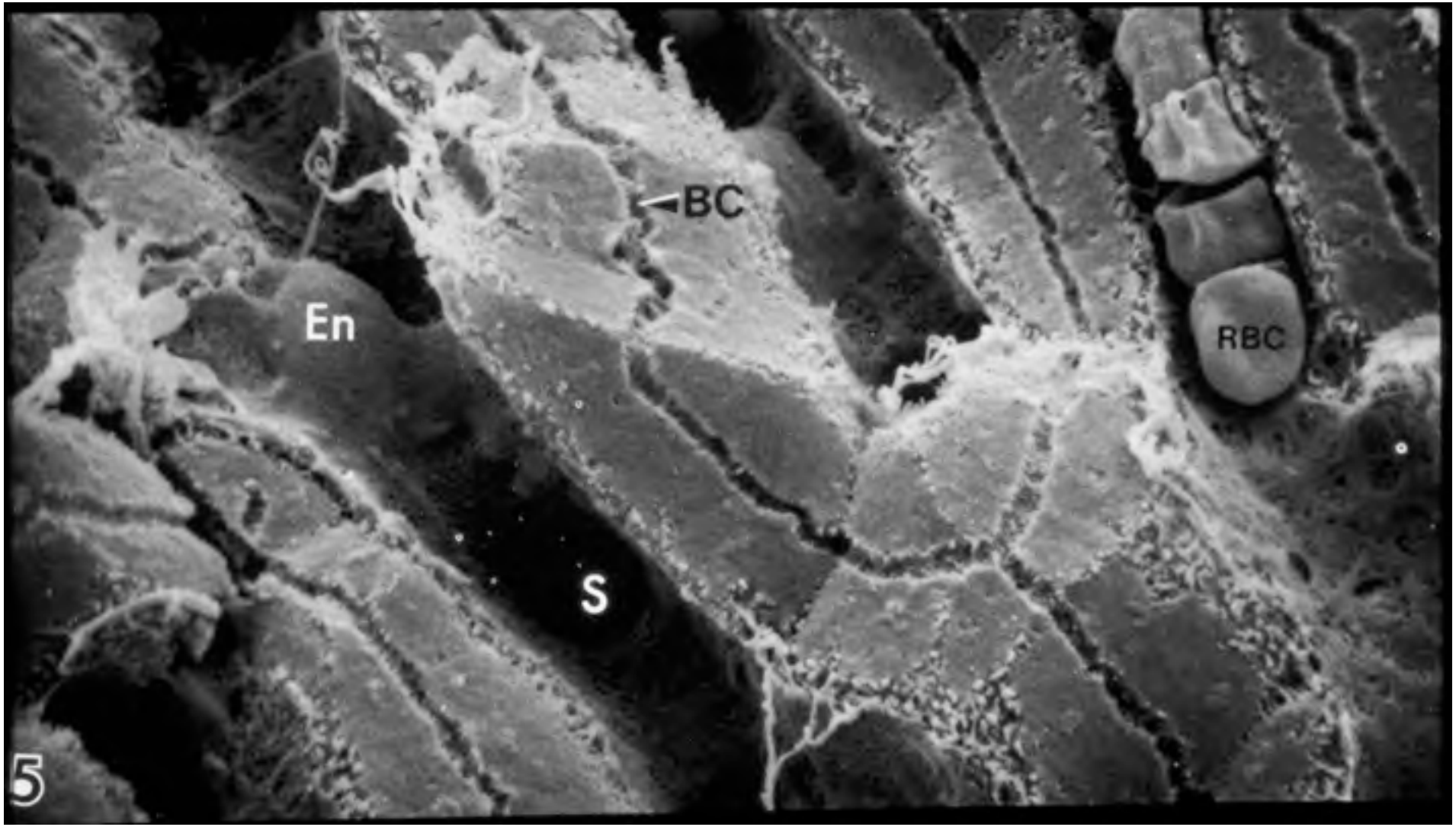
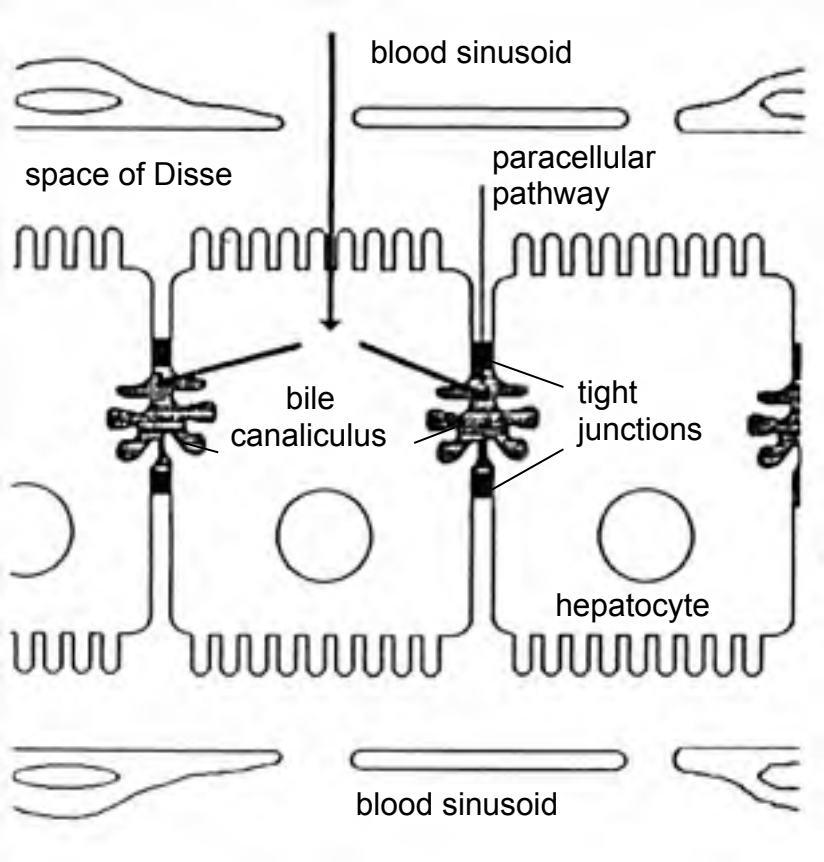


Anatomical Relationships in Liver



Components of Bile

Water ~ 1 liter/day

Bile Acids - major organic constituents

Phospholipids

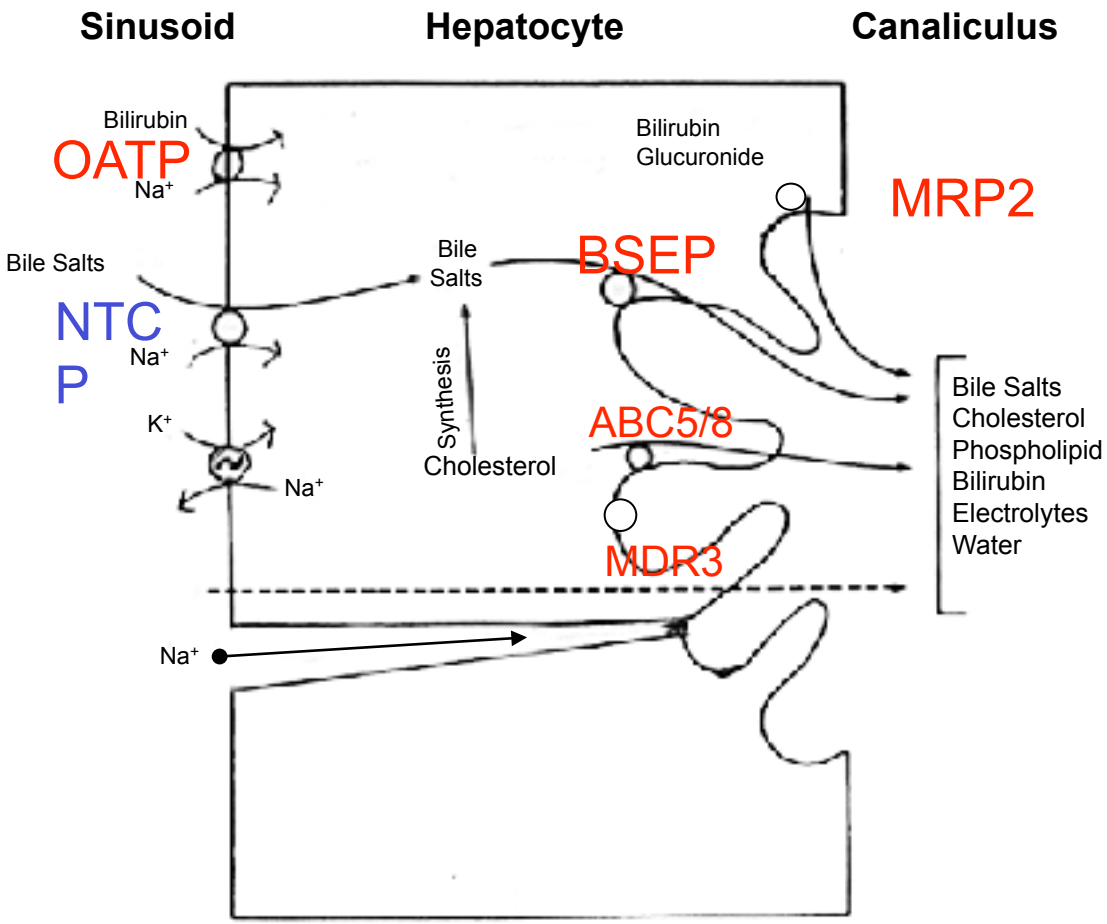
Cholesterol

Bile pigments - bilirubin

Metabolites of Hormones, Drugs

Inorganic ions - HCO_3 from duct cells

Transport of Biliary Components by Hepatocytes



PD-INEL John Williams modified from Fig. 6-6 Granger, D, *et al. Clinical Gastrointestinal Physiology*. W.B. Saunders, Philadelphia, PA; 1985: 125.

MOLECULAR COMPONENTS OF BILE SECRETION

1. Uptake of bile salts by Na^+ coupled co-transporter (NTCP)

2. Basolateral membrane also contains several organic anion transport proteins (OATP)

3. Bile salts excreted into bile by the Bile Salt Export Protein (BSEP) an ATP binding cassette protein which belongs to multidrug resistance (MDR) gene family

4. Other apical proteins are MRP2 which transport a number of drugs, ABC 5/8 involved in cholesterol transport and MDR3 a phospholipid transporter (flipase)

5. Gene expression of many of above transporters is regulated by bile salts through the Bile Acid Receptor/ Farnesoid X Receptor (FXR)

Function of Bile Ducts

1. Bile ducts are lined by cholangiocytes, columnar epithelial cells specialized to modify bile.

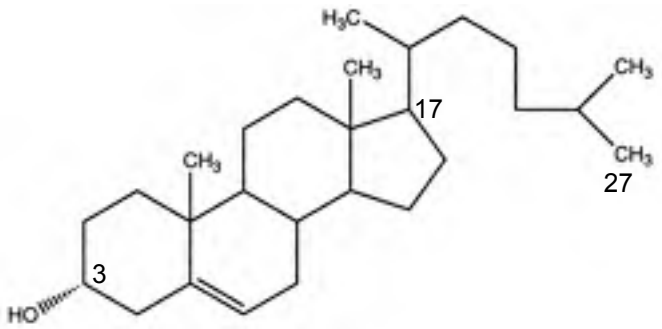
2. Ductules are freely permeable to water so bile rapidly becomes isotonic.

3. Ductules scavenge solutes such as glucose and amino acids that entered leaky canaliculus.

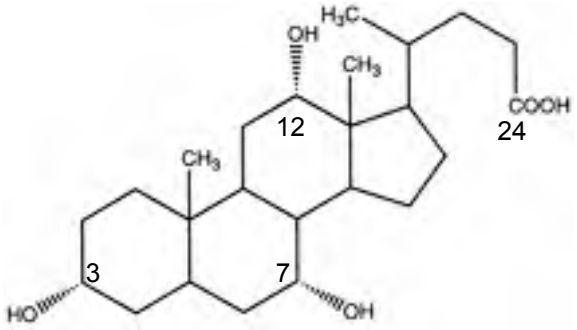
4. Cholangiocytes secrete HCO_3^- in response to secretin (bile slightly alkaline)

5. Ductules secrete IgA molecules into bile

Chemistry of Bile Acids



Cholesterol

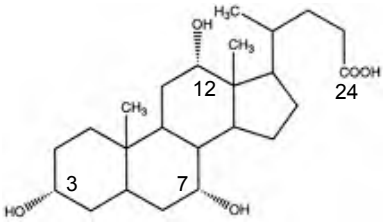


Bile acid
(Cholic acid)

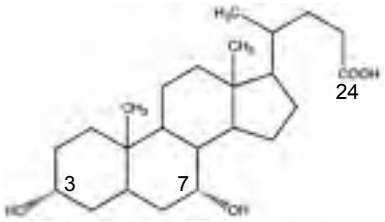
BILE SALT SYNTHESIS

- Bile acids synthesized in the liver from cholesterol
- In the “classical pathway” the first and most important regulated step is 7α hydroxylation by 7α hydroxylase (CYP7A1)
- Next 12α hydroxylation is followed by several steps leading to cholic acid
- The “alternative pathway” starts with initial formation of oxysterols and leads to chenodeoxycholic acid

Primary Bile Acids



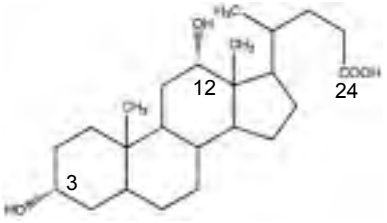
Cholic acid
(3 OH groups)



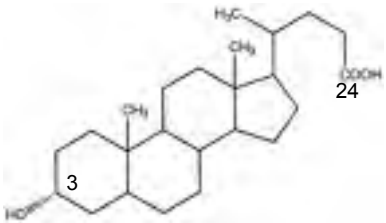
Chenodeoxycholic acid
(2 OH groups)

7-dehydroxylation
by gut bacteria

Secondary Bile Acids

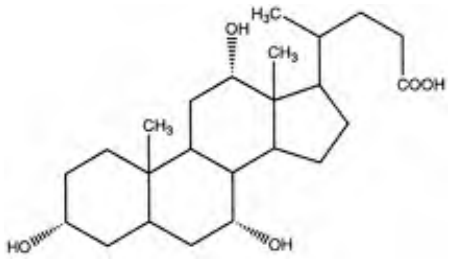


Deoxycholic acid
(2 OH groups)



Lithocholic acid
(1 OH group)

Bile Acid Conjugation

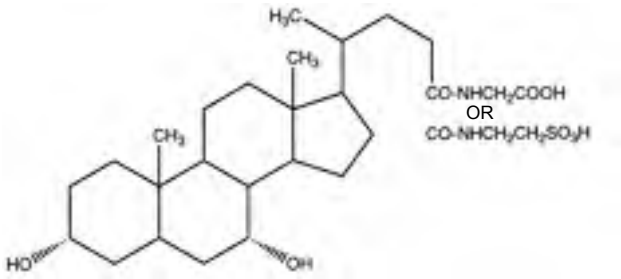


Cholic acid

Bile Acids

+

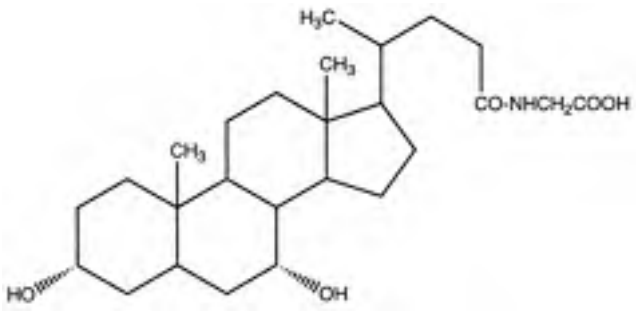
H_2NCH_2COOH
Glycine
OR
$H_2NCH_2CH_2SO_3H$
Taurine



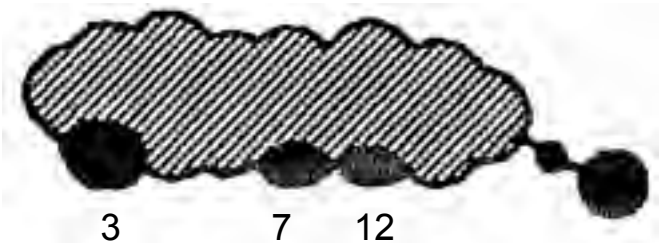
Glycocholic acid
OR
Taurocholic acid

Conjugation lowers the pKa so bile acids exist in the more soluble dissociated form

Amphipathic Nature of Bile Acids

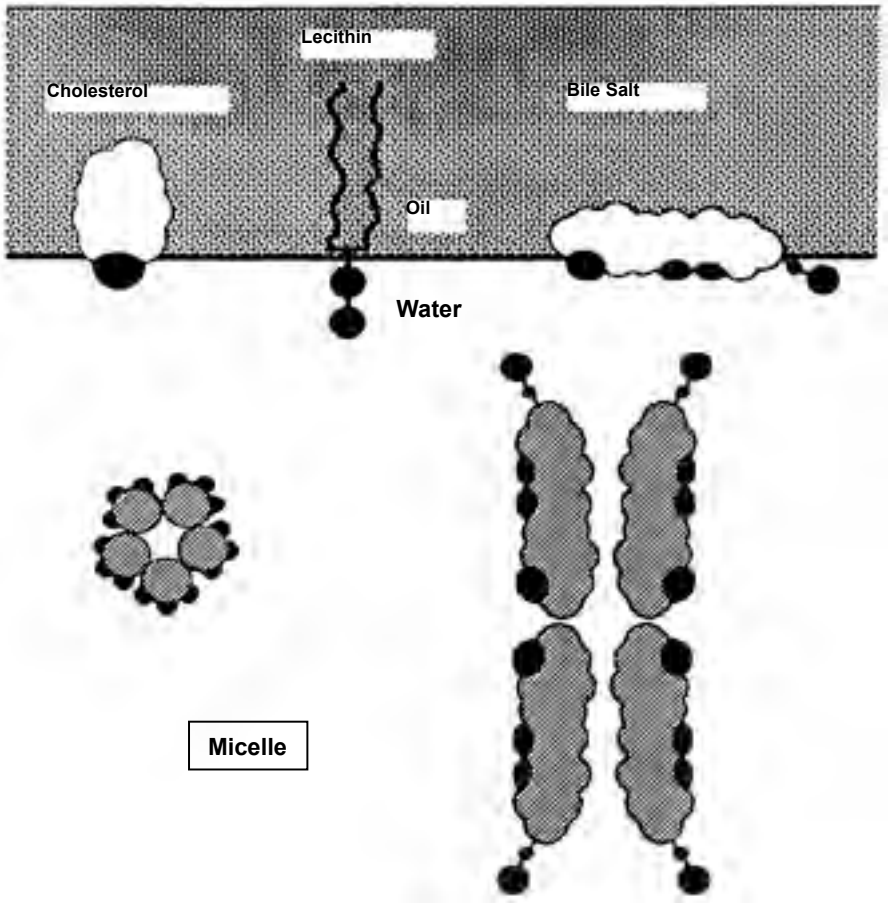


Glycocholic acid



Polar groups

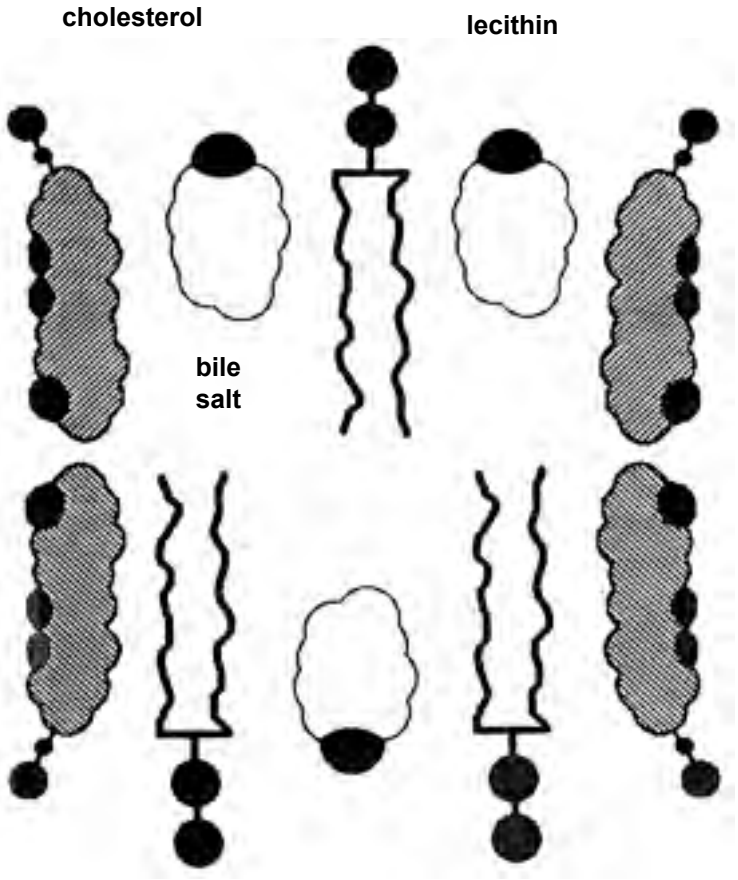
Amphipathic Molecules



Exist in micelles when concentration is greater than the CMC (Critical Micellar Concentration)

PD-INEL Source Undetermined

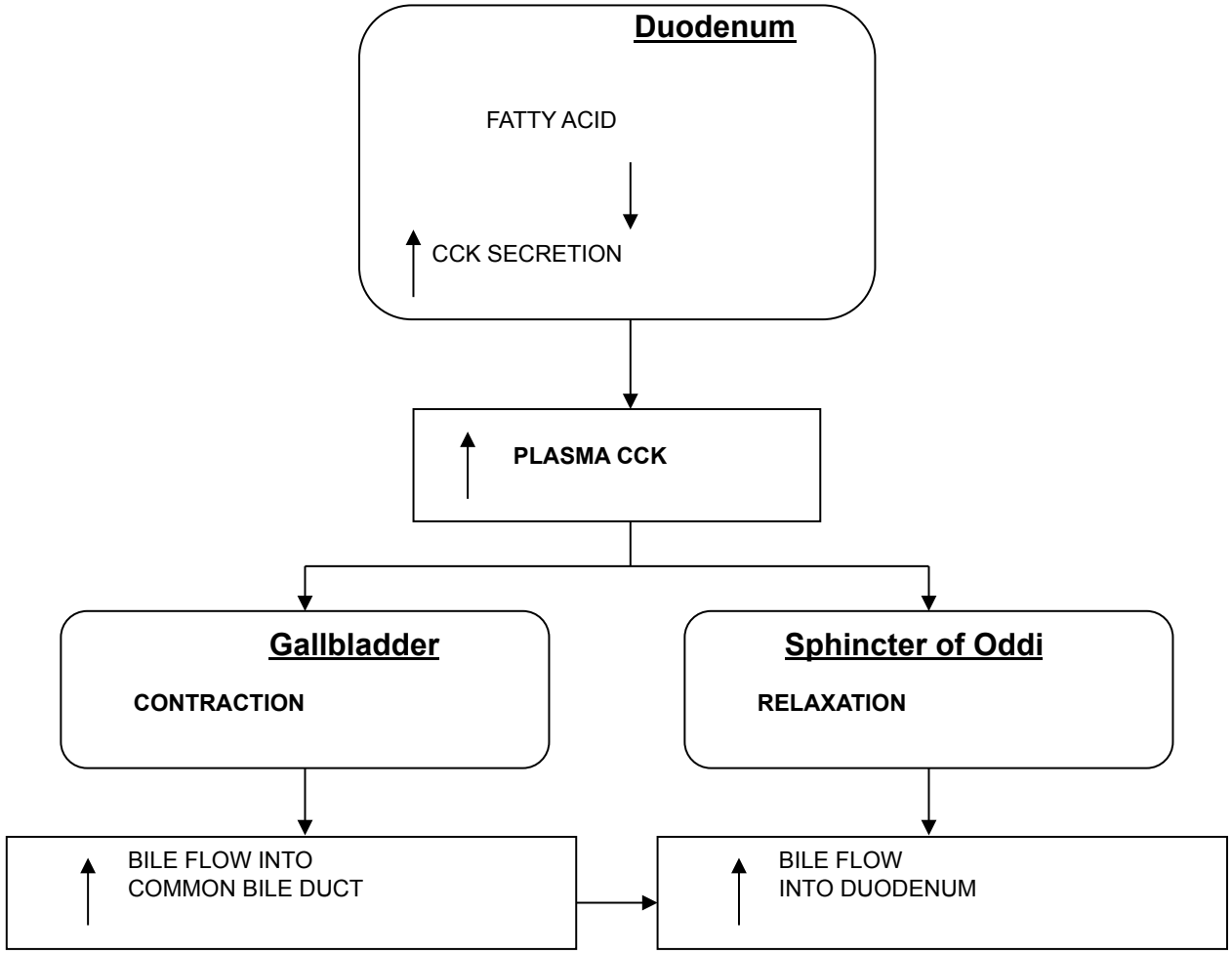
Mixed Micelle



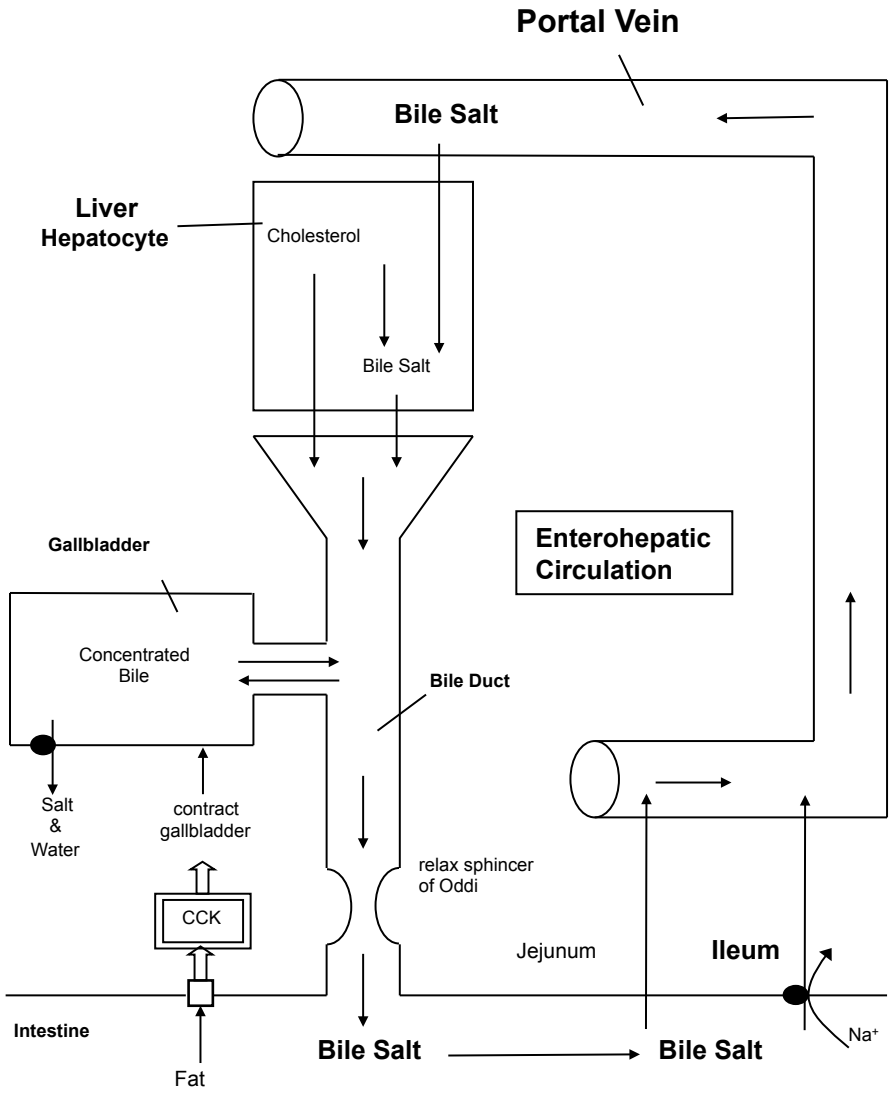
GALLBLADDER FUNCTION

- The gallbladder concentrates bile and stores much of the bodies bile salt pool during fasting
- Epithelia absorbs Na^+, Cl^- and H_2O
- Isotonicity maintained as a result of micelles having minimal osmotic activity
- Postprandially the gallbladder contracts in response to CCK (cholecystokinin)

Role of CCK in Bile Secretion



ENTEROHEPATIC CIRCULATION OF BILE SALTS



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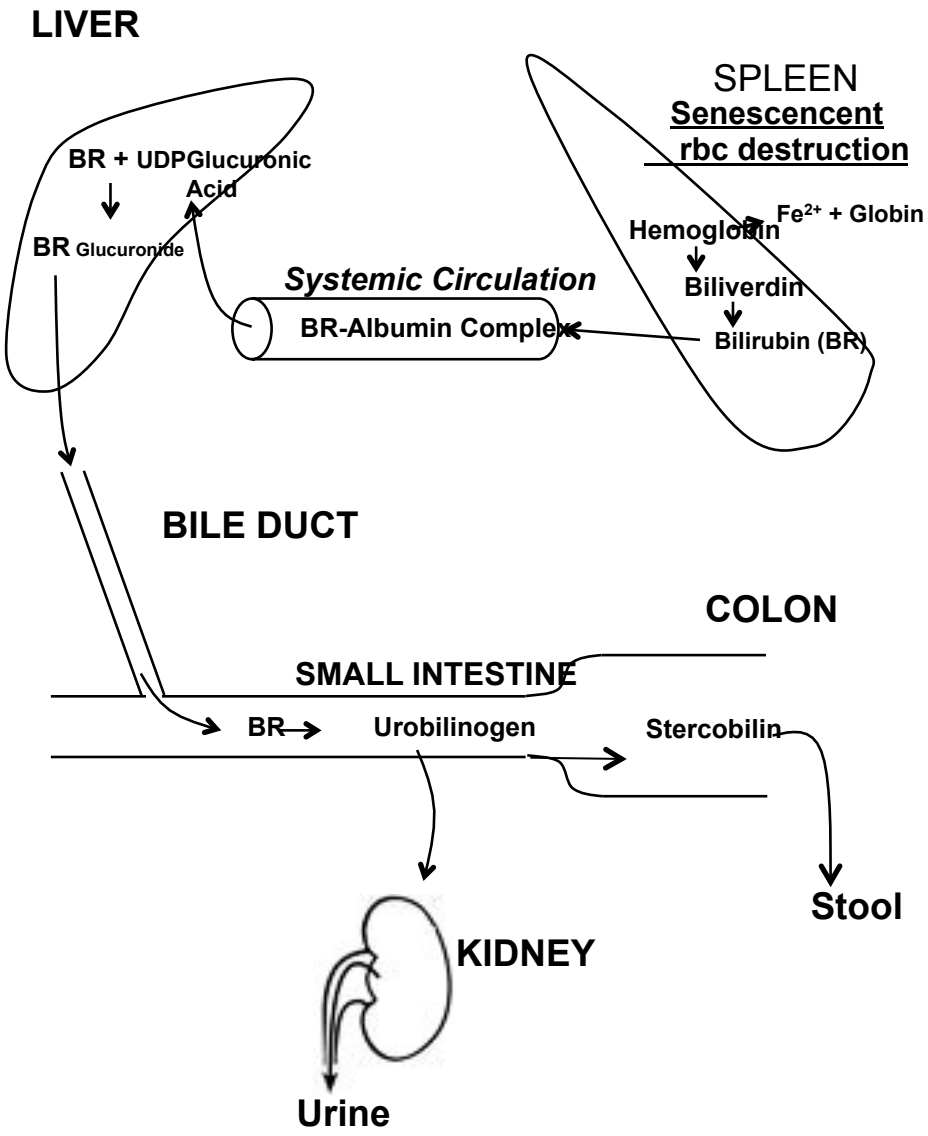
Metabolism of Bile Pigment (Bilirubin)



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The Liver Synthesizes a Variety of Plasma Proteins

Major Plasma Proteins	Albumin, α fetoprotein, α_2-Microglobulin
Hemostasis Proteins	Fibrinogen, clotting factors and inhibitors Plasmin (fibrinolysis) Complement C3
Binding Proteins	Ceruloplasmin (copper) Steroid binding proteins Thyroid hormone binding globulin (TBG) Transferrin
Prohormones	Angiotensinogen
Apolipoproteins	Apo A-I, -II, and IV Apo B-100 Apo D, Apo E

THE LIVER METABOLIZES AND EXCRETES FOREIGN MOLECULES (Drugs, Xenobiotics)

1. Most often involves oxidation (hydroxylation) and/or conjugation

2. Most hydroxylation is by family of enzymes termed cytochromes P450

   a. Now usually referred to as CYPs. Three main gene families CYP1, CYP2, and CYP3

   b. Genetic and nongenetic factors influence P450 activity

3. Conjugation is by UDP glucuronyltransferases (glucuronic acid), glutathione S-Transferase (glutathione) and sulfotransferases (sulfate)

4. Metabolites which are more water soluble are secreted into bile or plasma where can be excreted by kidney.

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