

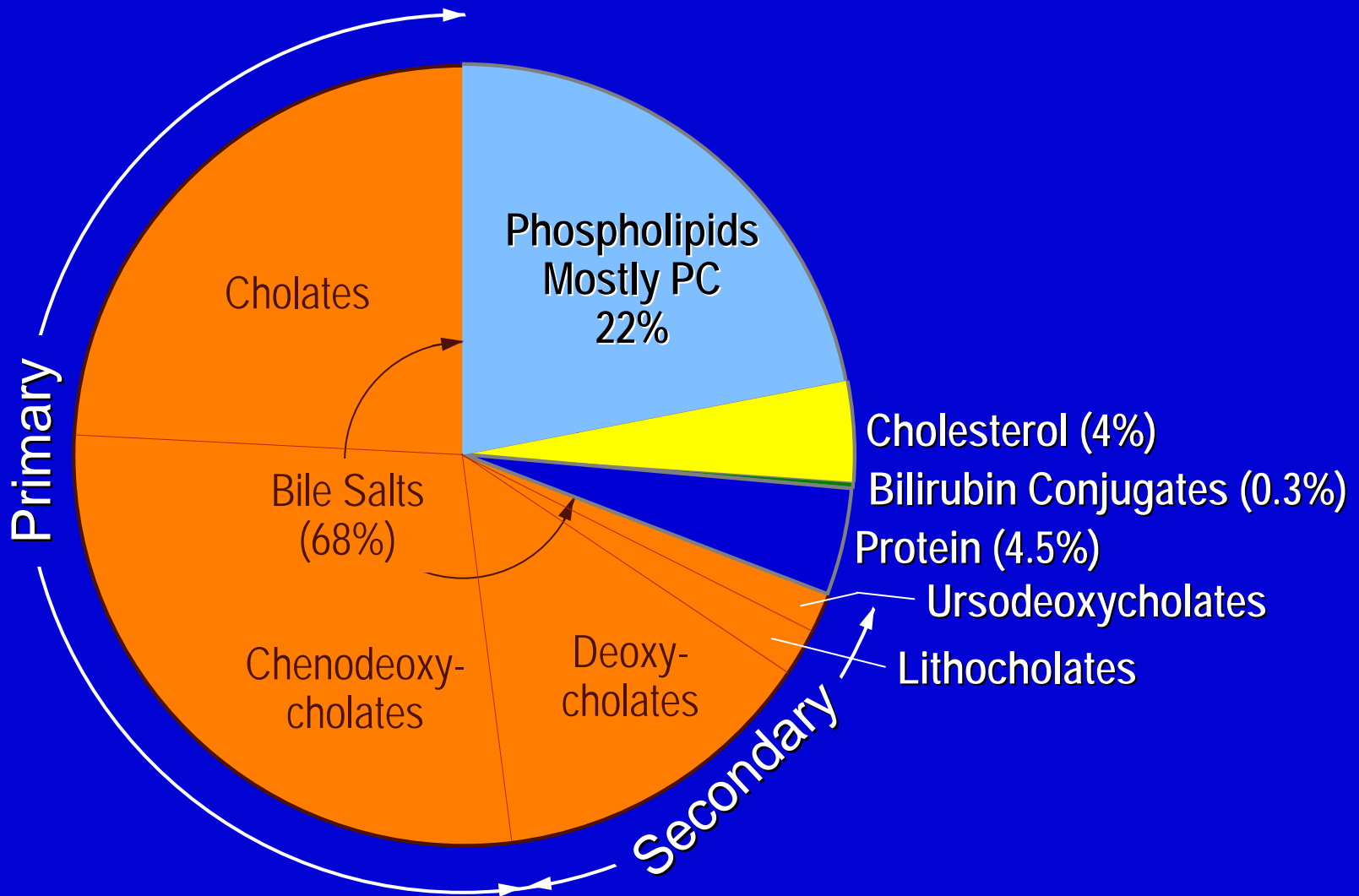
Pathophysiology of Bile Secretion

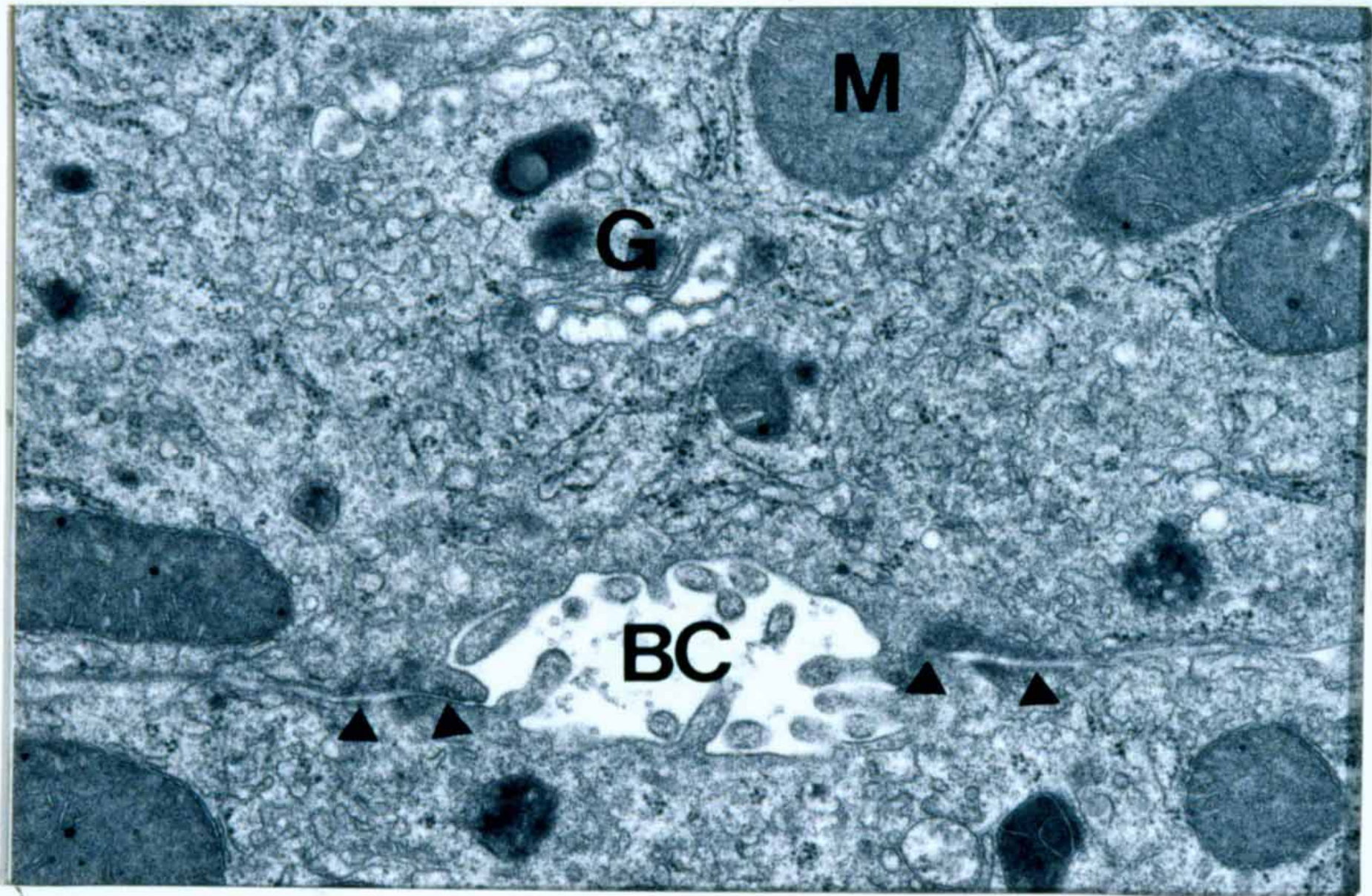
Martin C. Carey, D.Sc., M.D.
Division of Gastroenterology,
Brigham and Women's Hospital and
Department of Medicine, Harvard Medical School
Boston, MA, U.S.A.

Functions of Bile

- Promotes “exocrine” lipid secretion, especially cholesterol elimination
- Facilitates dietary lipid absorption, obligatory for sterol and fat-soluble vitamin absorption
- Enhancement of dietary protein and carbohydrate digestion
- Conduit for endobiotic and xenobiotic excretion
- Distributes immunoglobins and antioxidants throughout the gut

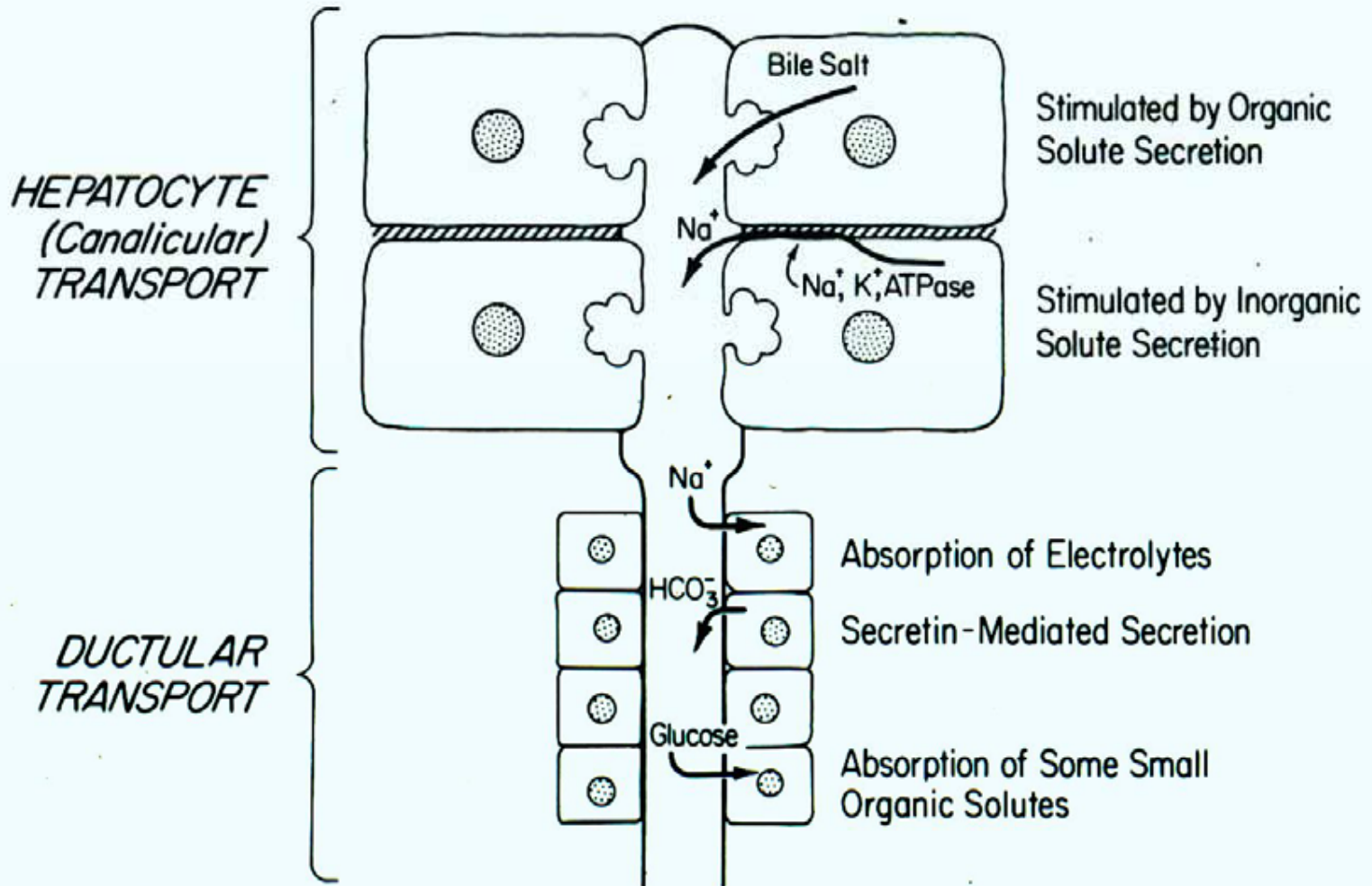
Solute Composition of Human Bile



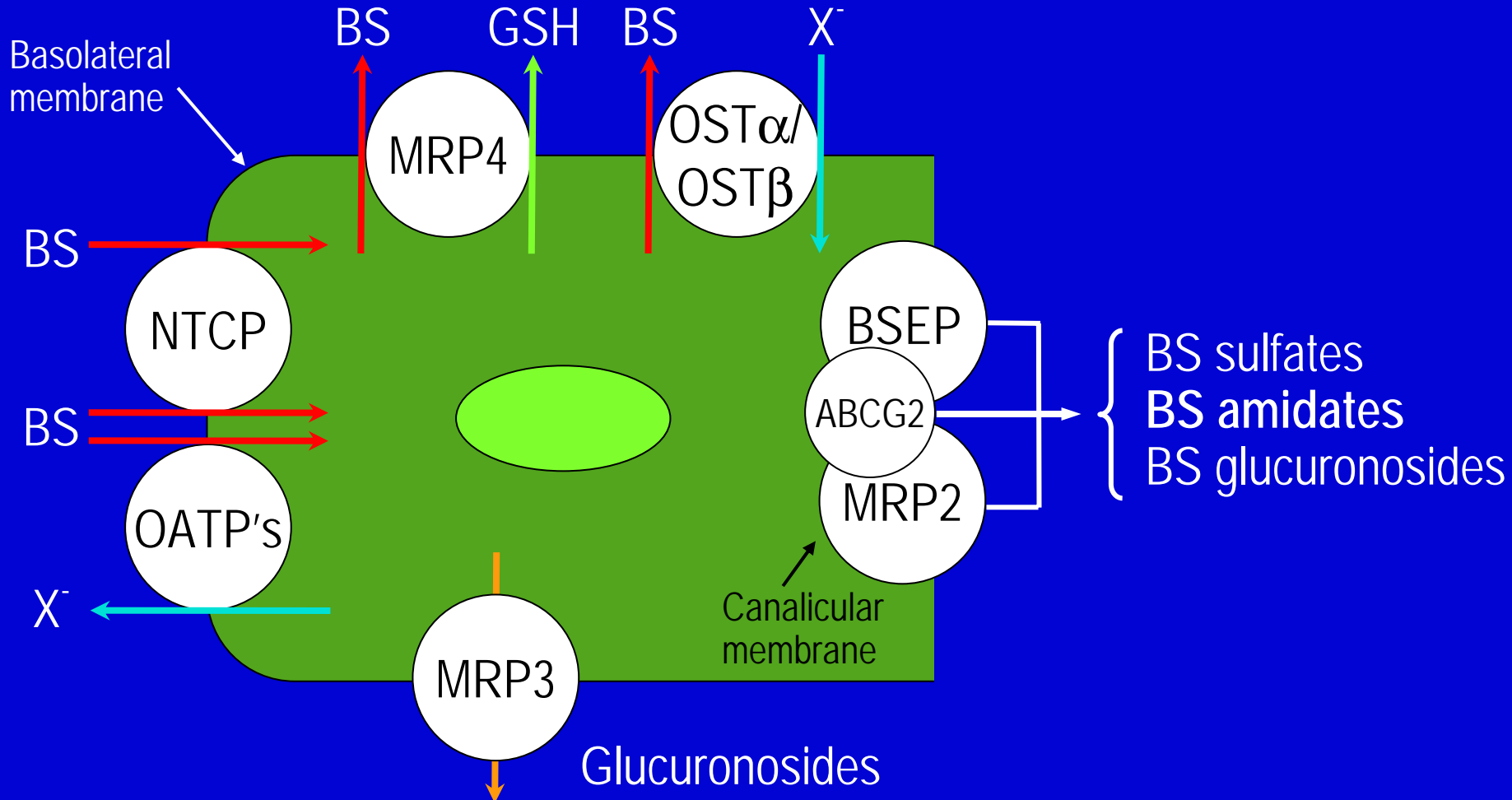


BILE WATER PRODUCTION

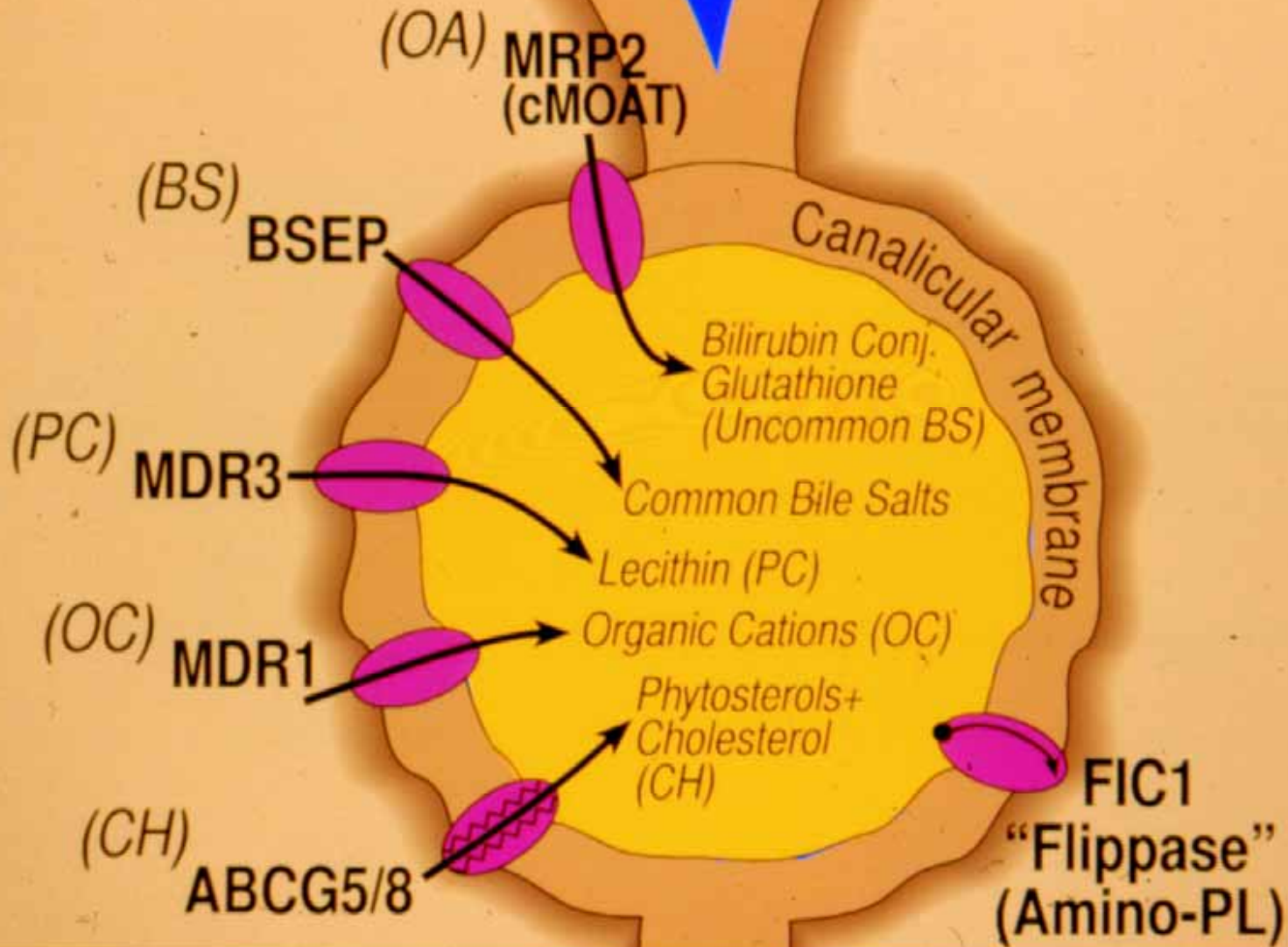
Via Aquaporins and Intercellular Spaces



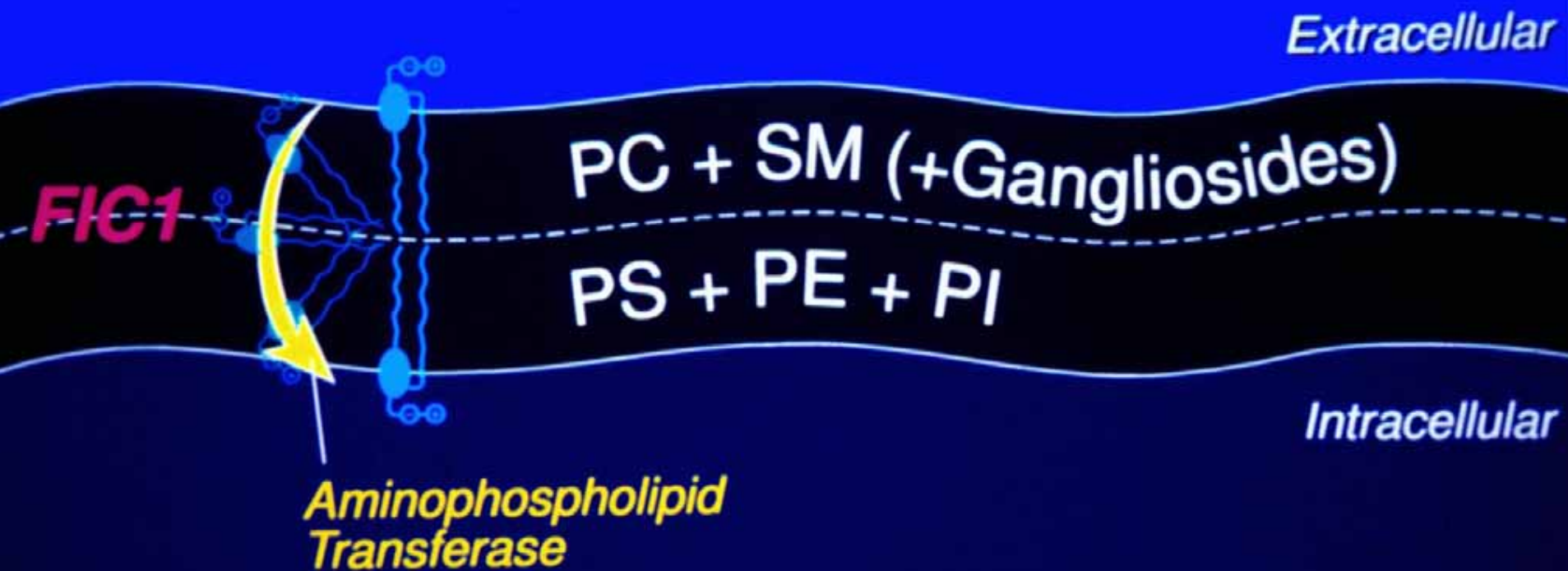
Vectorial Bile Salt Transport by the Hepatocyte



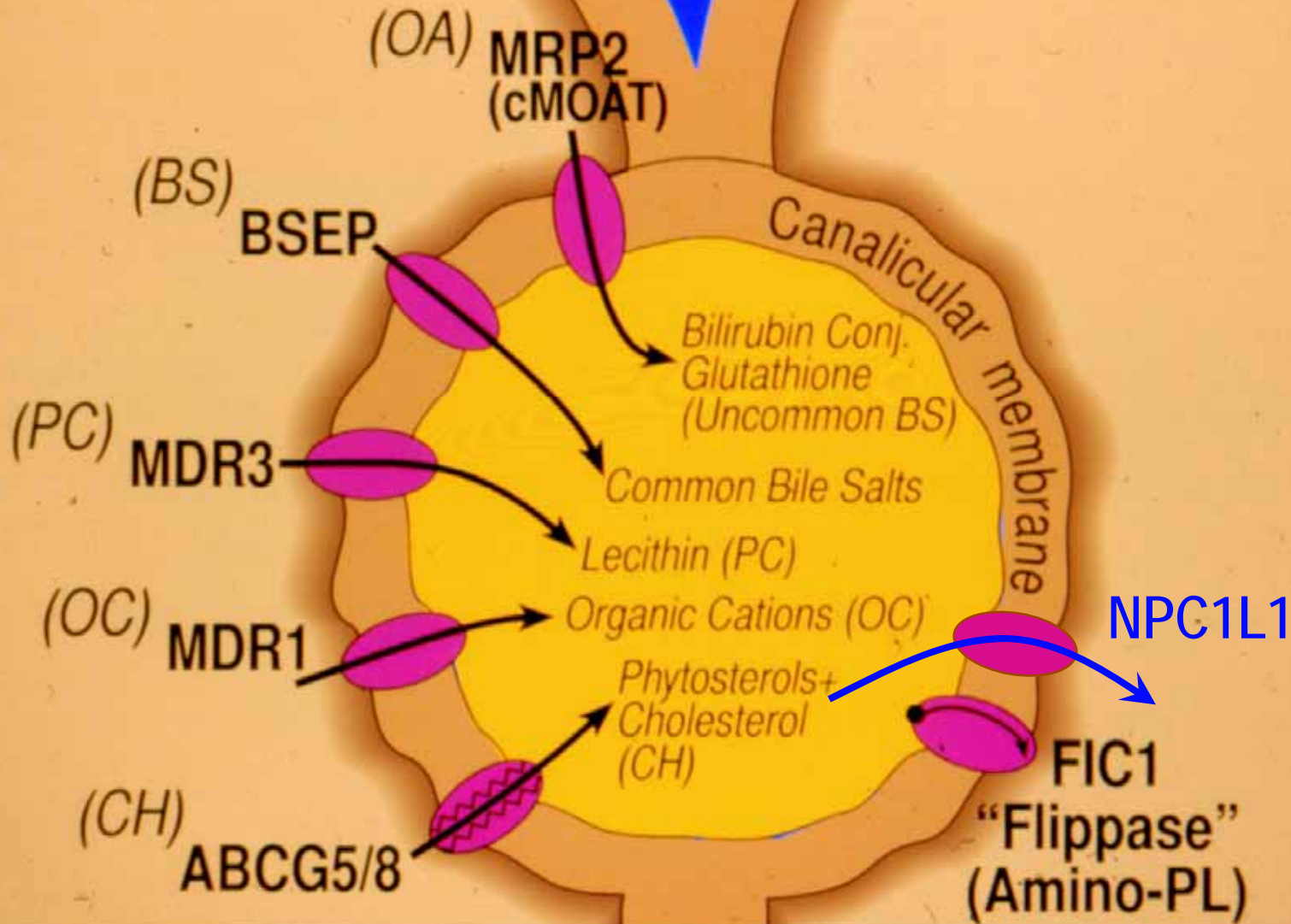
CANALICULAR LIPID TRANSPORTERS



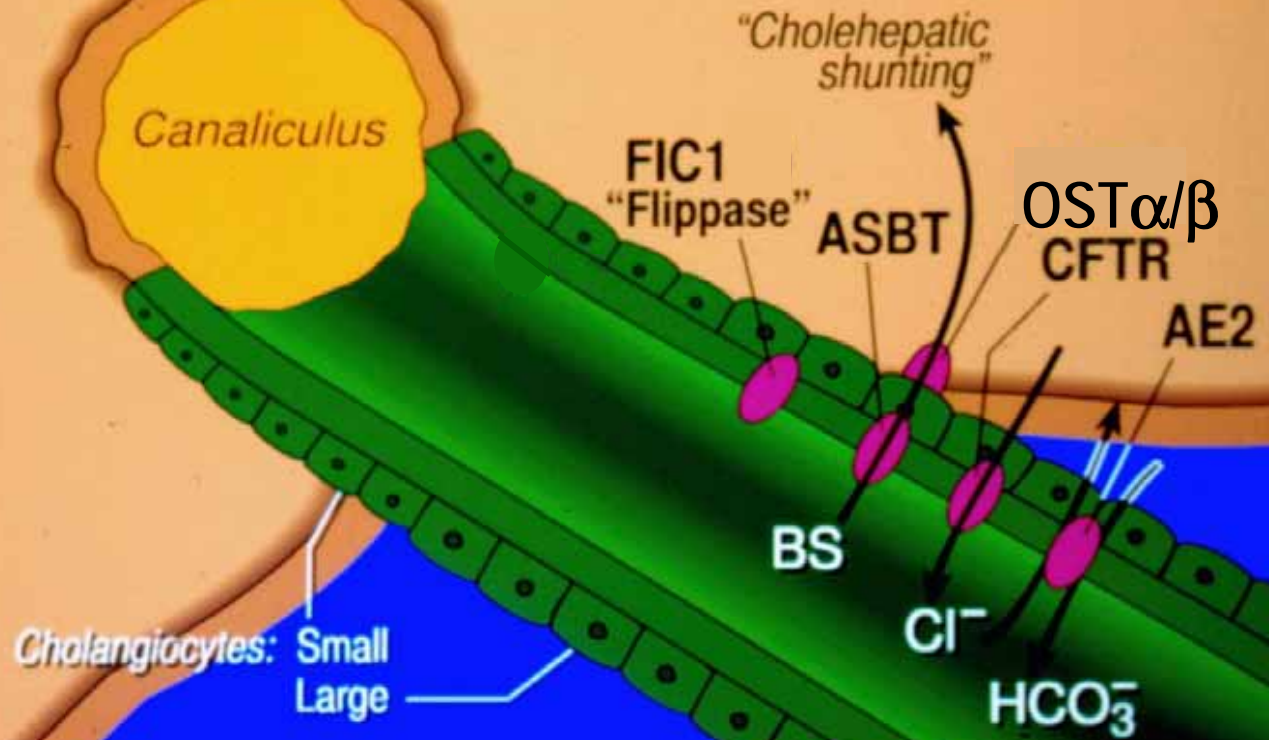
LIPID ASYMMETRY OF PLASMA MEMBRANES: Role of FIC1, a P-type ATPase



CANALICULAR LIPID TRANSPORTERS

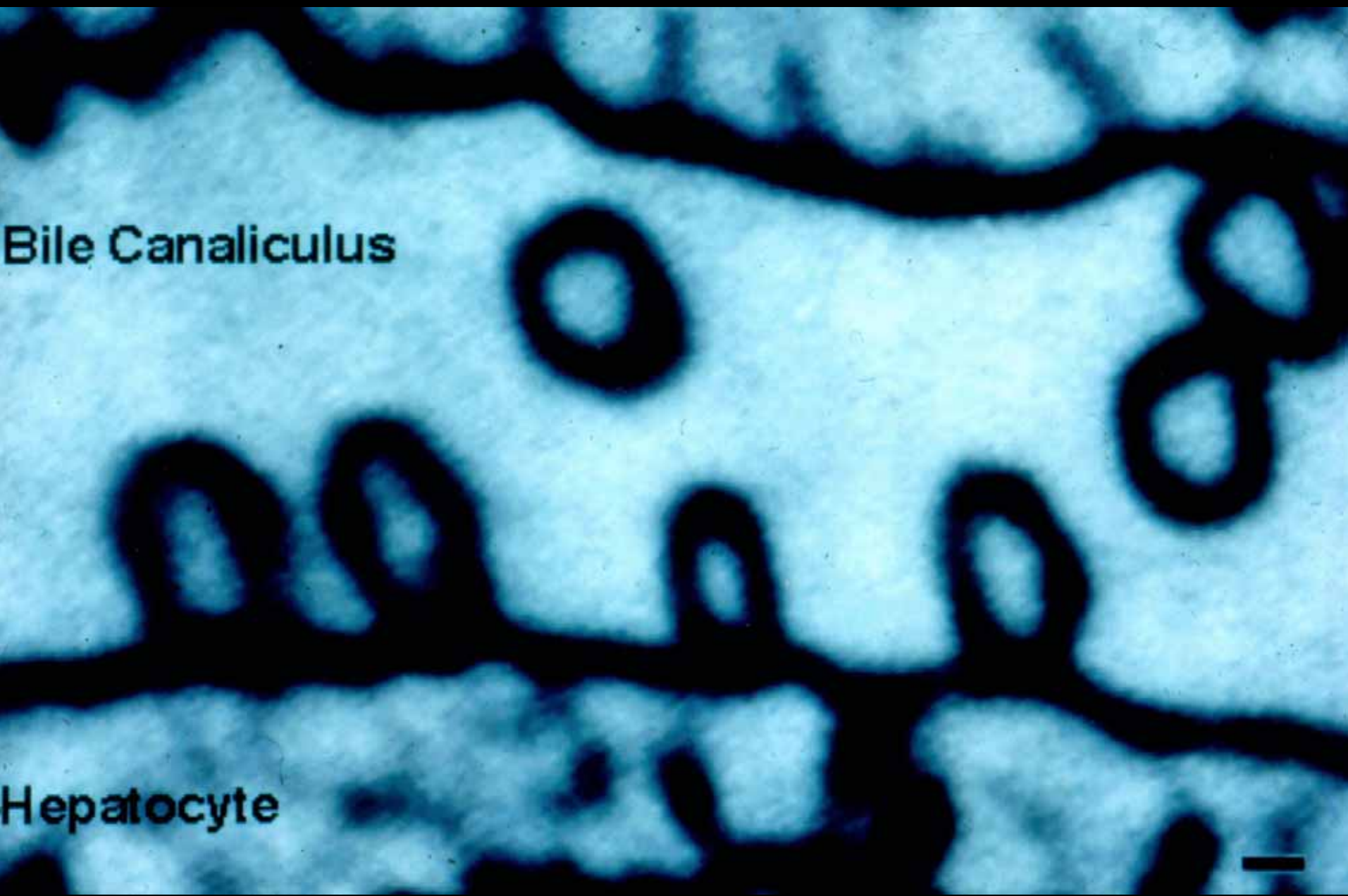


HEPATOBIILIARY DUCTULAR FUNCTION

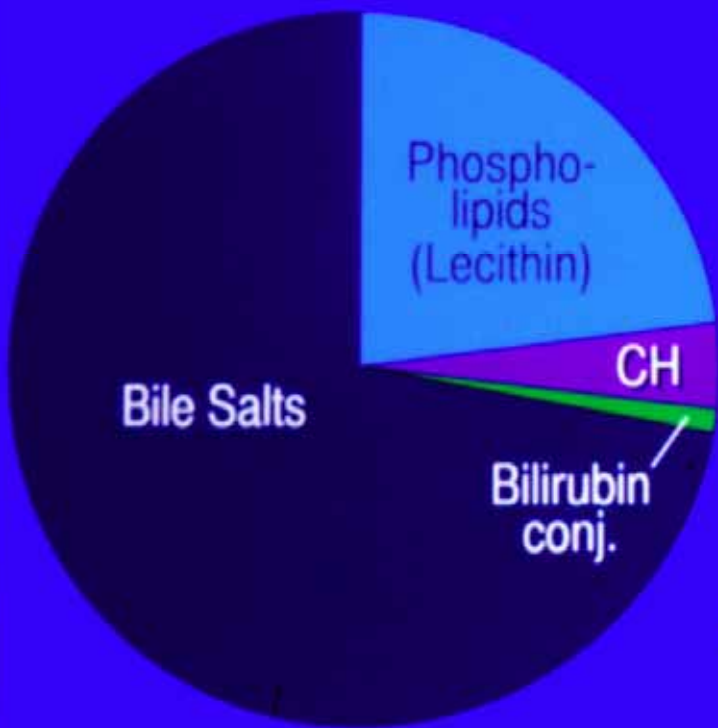


Bile Canaliculus

Hepatocyte



BILE: LIPID COMPOSITION, MOLECULAR MODELS & PHYSICAL STATE



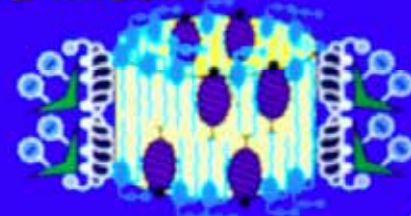
Models



Simple Micelle



Mixed Micelle



Unilamellar Vesicle

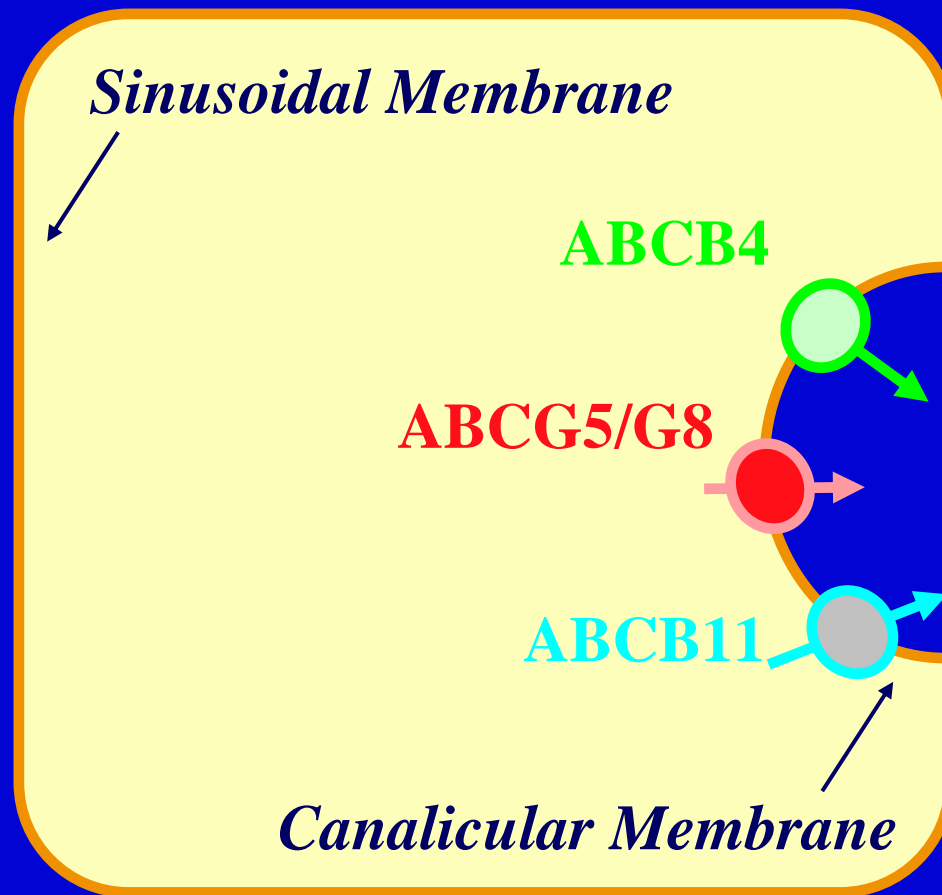


Hepatocellular Trafficking

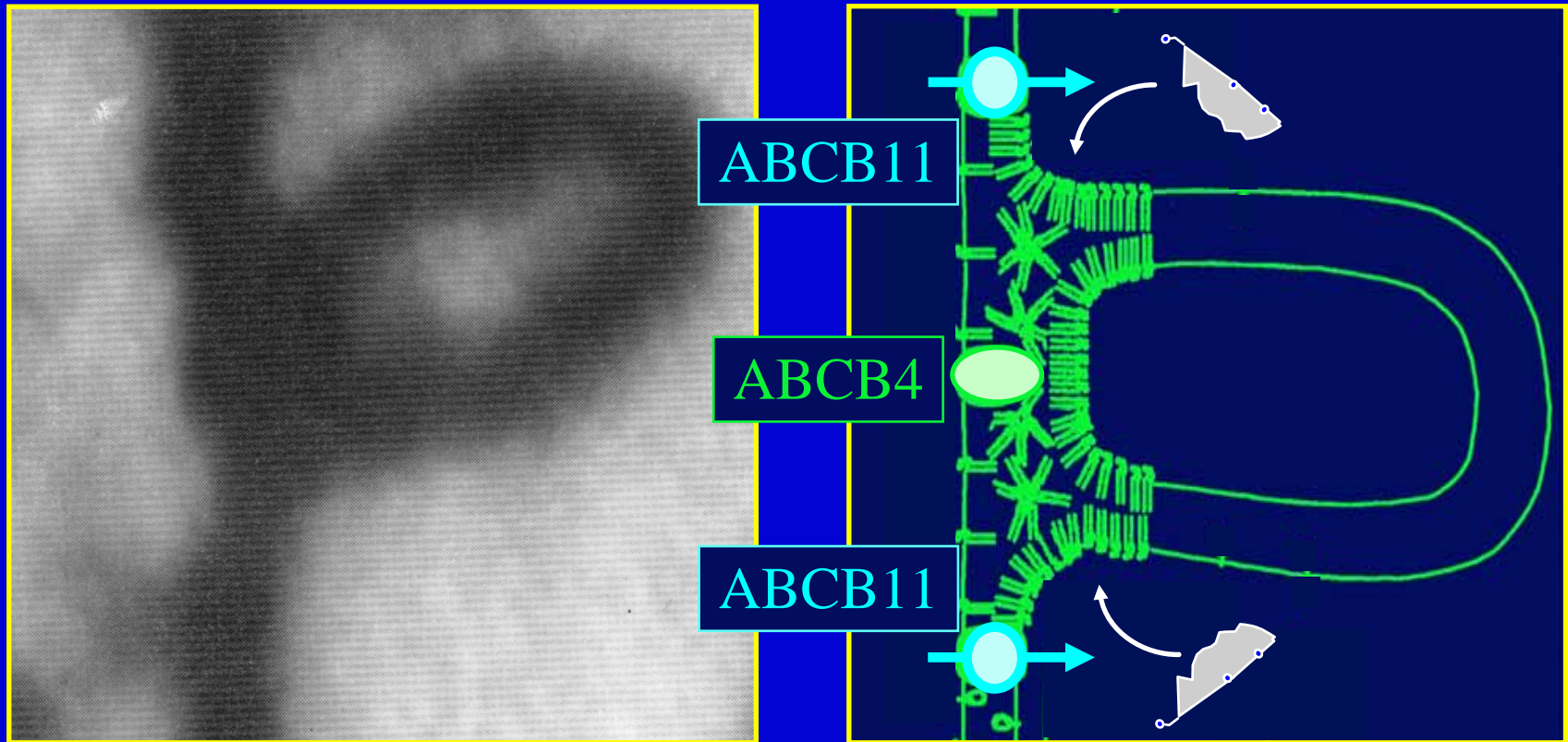
BLOOD

HEPATOCYTE

BILE



Bile Salt-Canalicular Membrane Interactions Promote Biliary Vesicle Formation



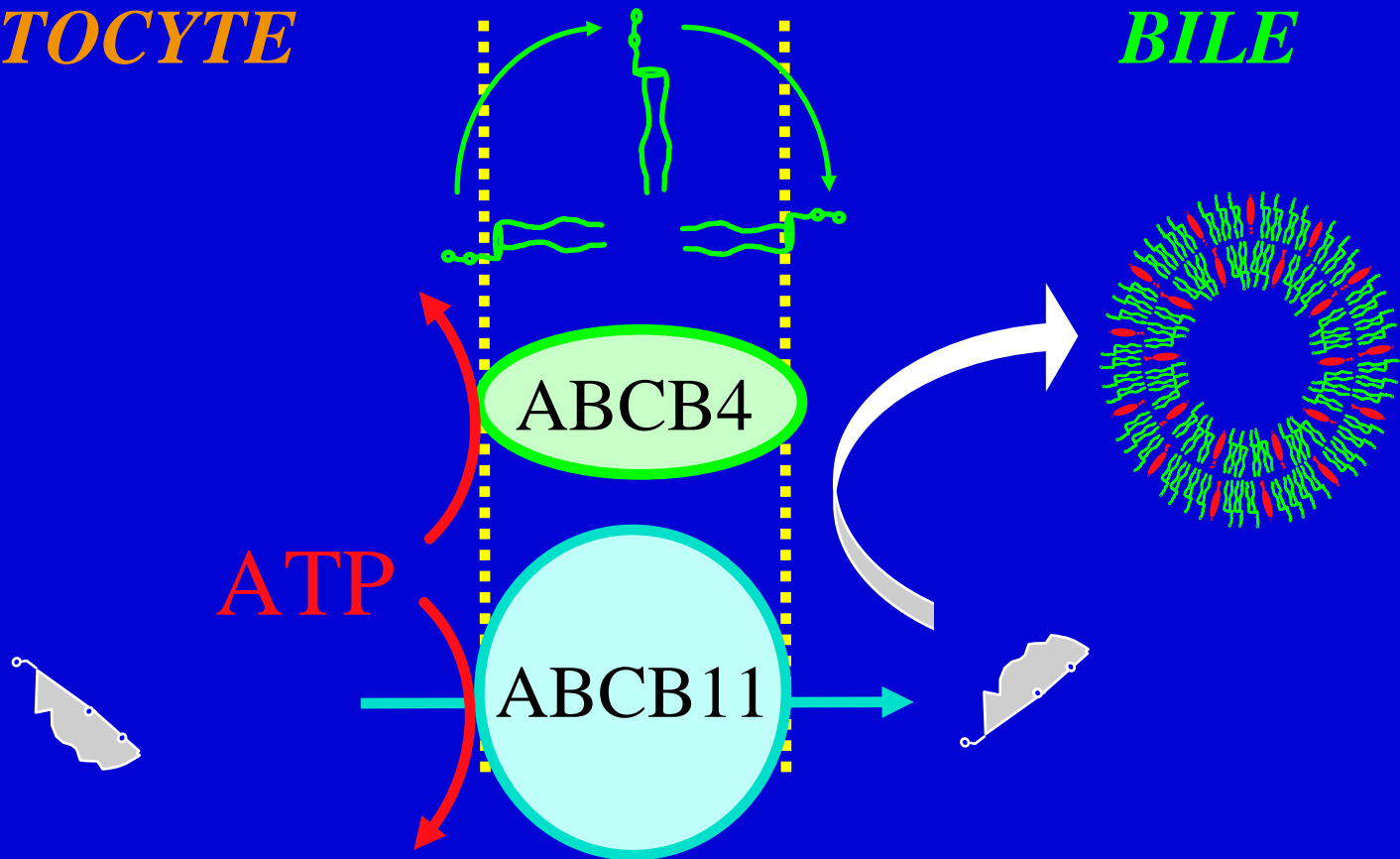
Crawford et al, *J Lipid Res*, 1995

Crawford et al, *J Clin Invest*, 1997

Transport of Bile Salts and Phospholipids Across the Canalicular Membrane

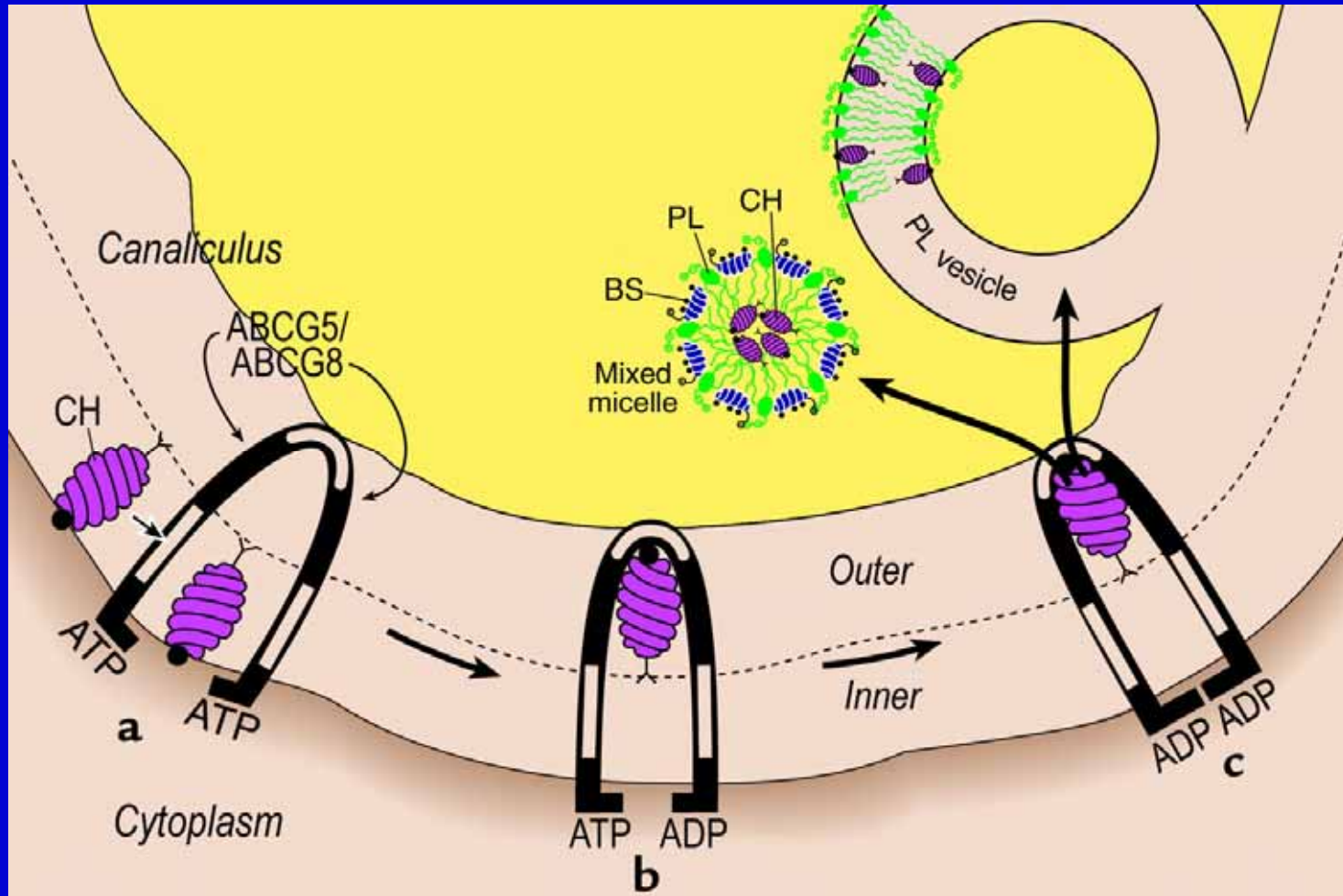
HEPATOCYTE

BILE



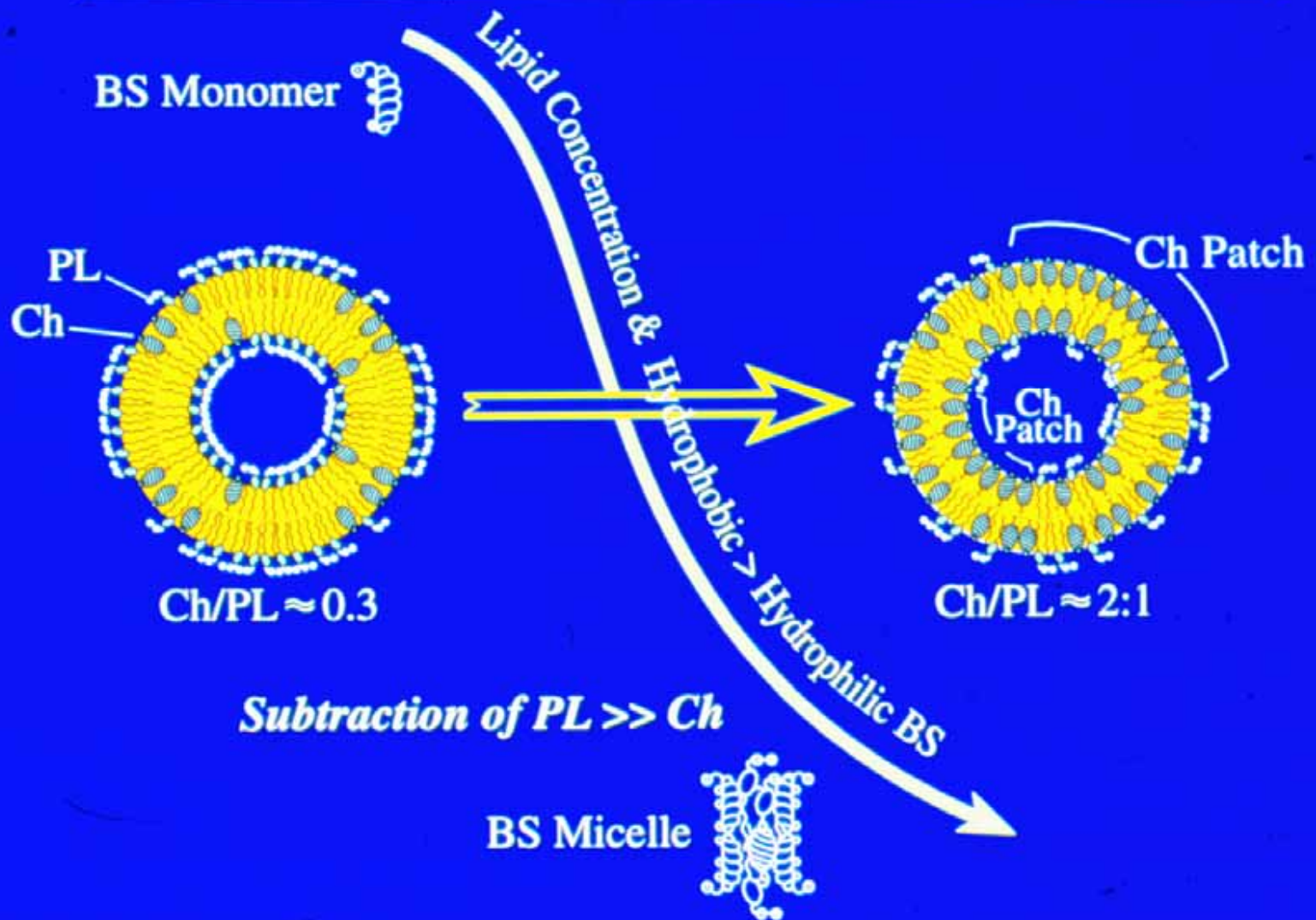
Canalicular Membrane

Model for “Flipping” of Cholesterol into Bile

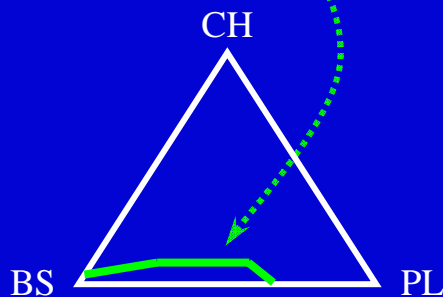
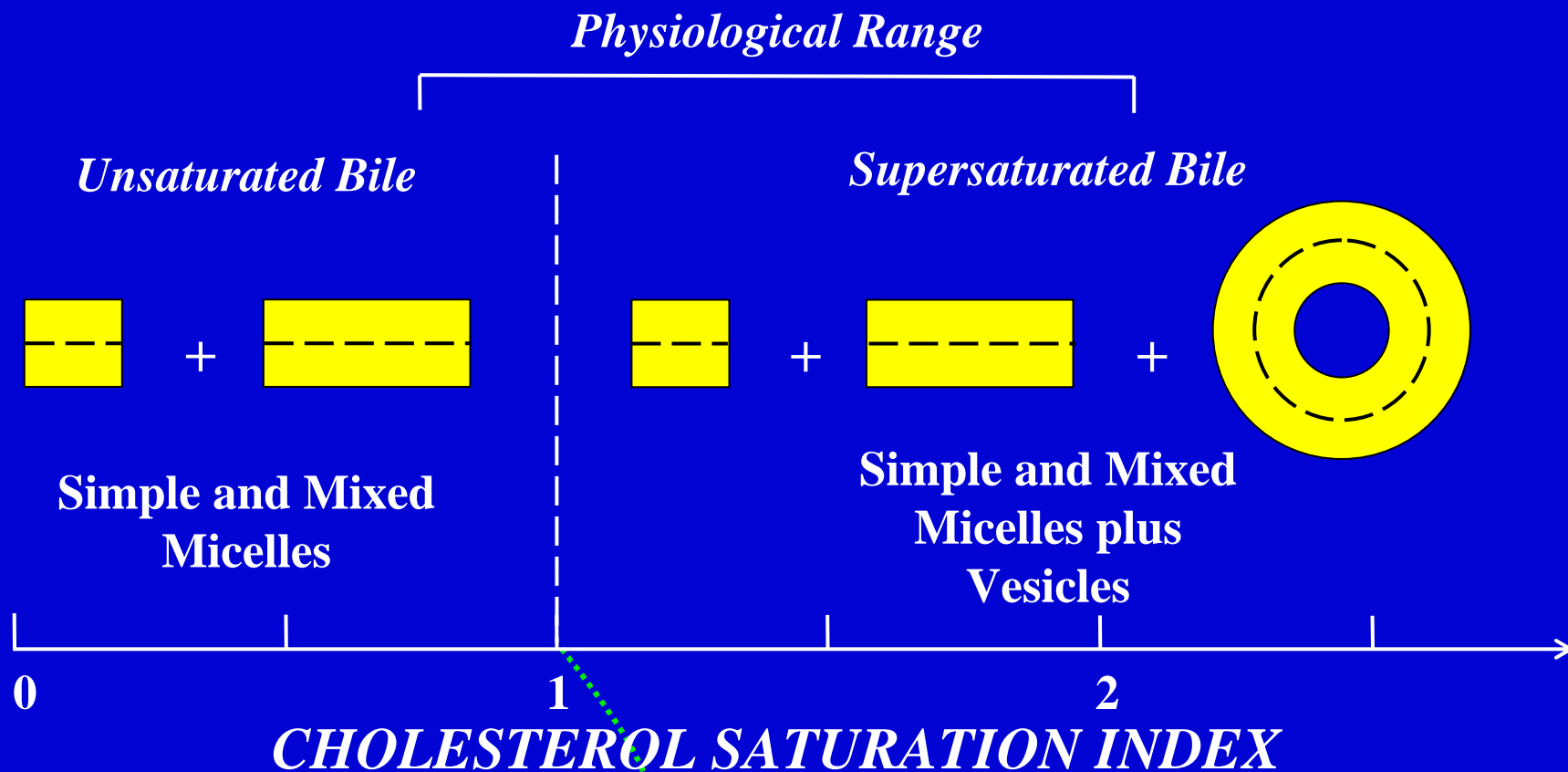


Wittenburg and Carey, *J Clin Invest*, 2002

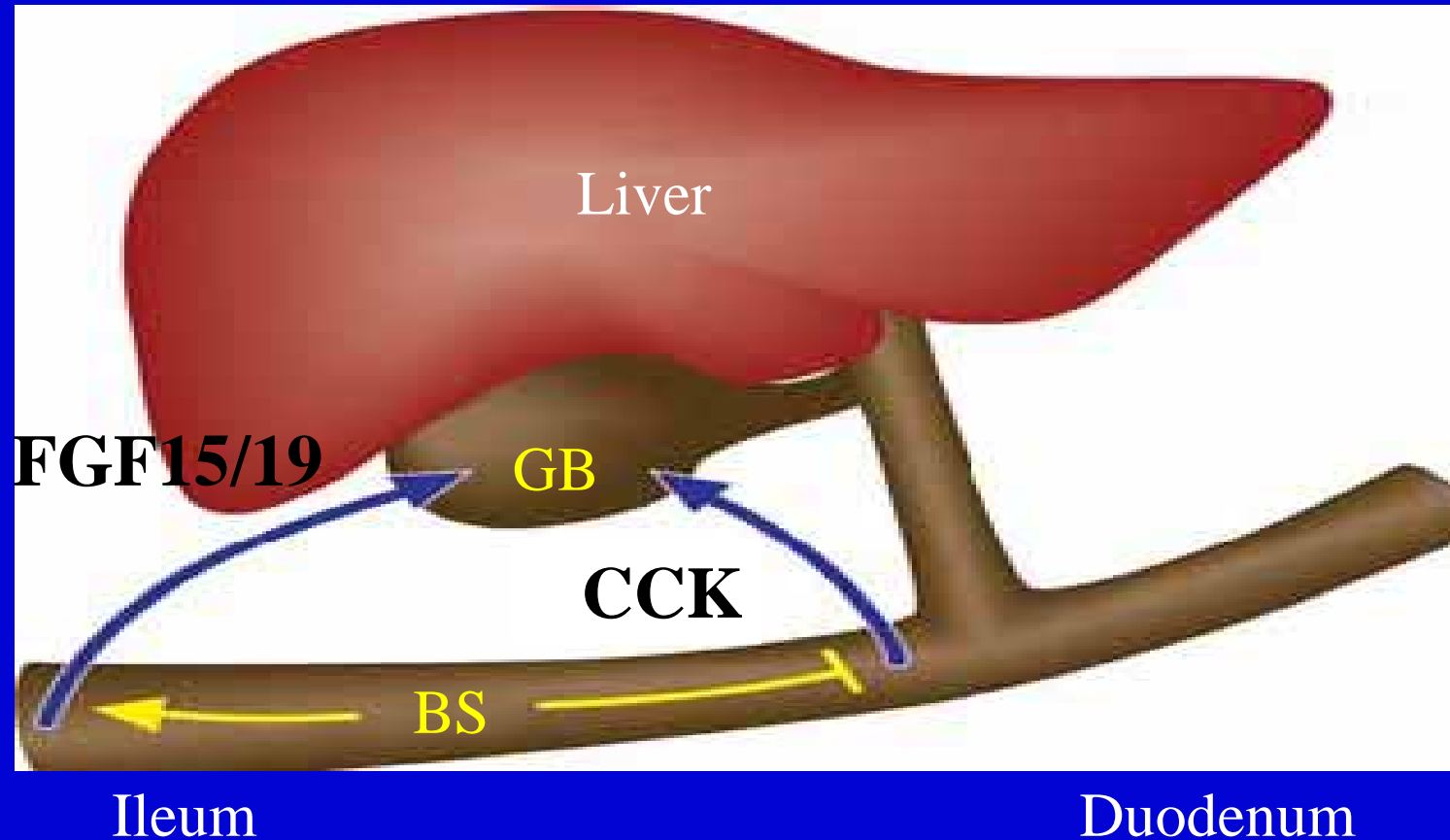
CHOLESTEROL ENRICHMENT OF BILIARY VESICLES BY BILE SALTS



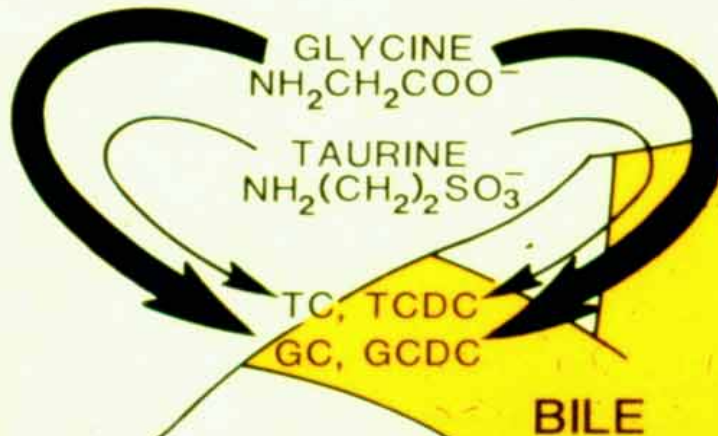
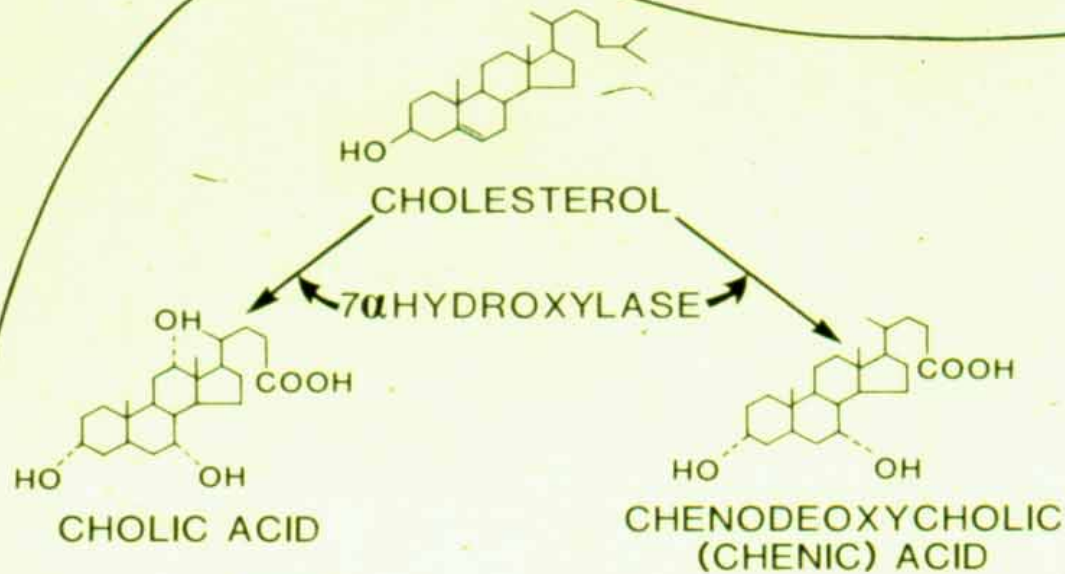
Lipid Particles in Human Biles



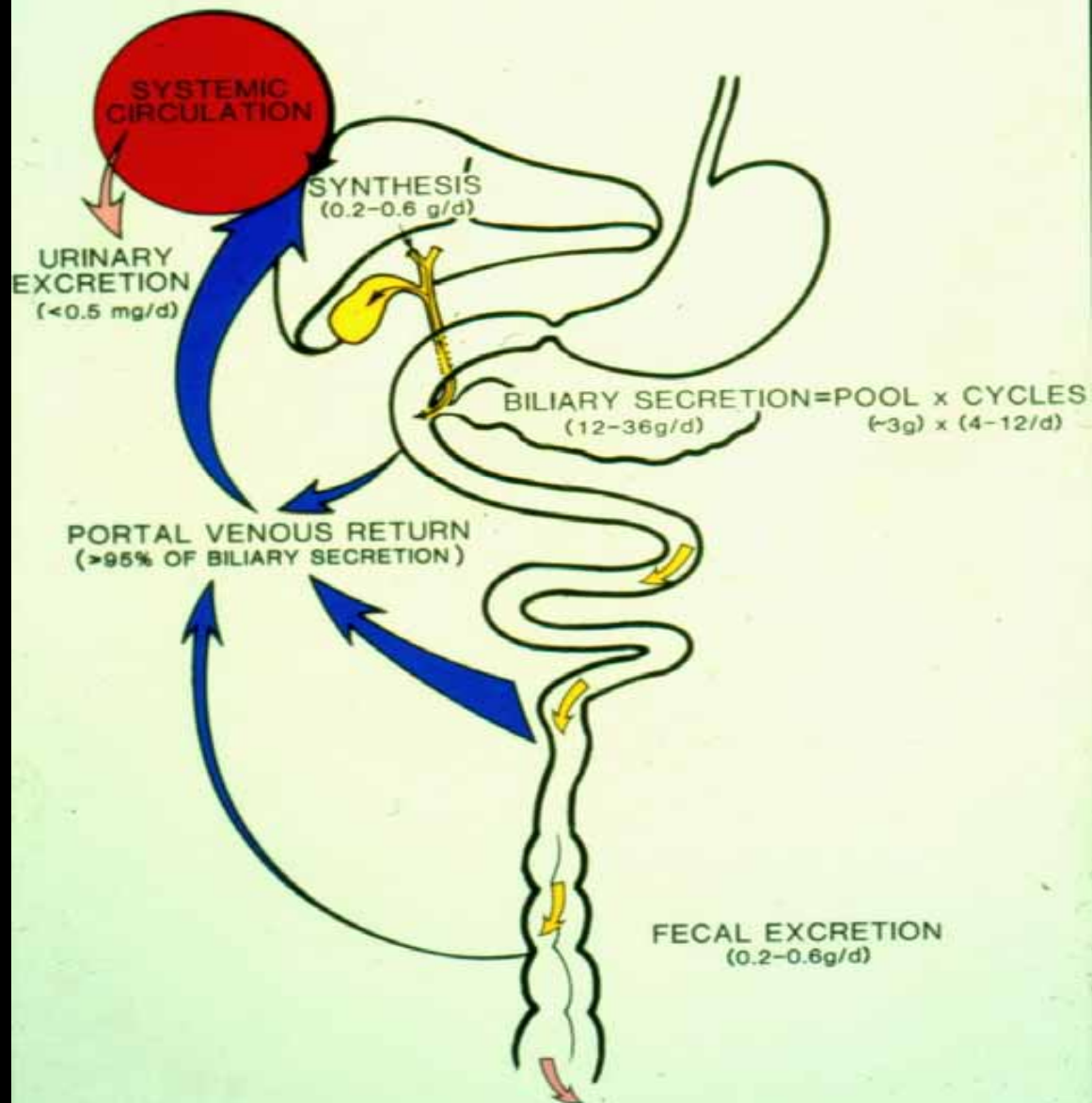
The “Ying-Yang” of Gallbladder Filling and Relaxation



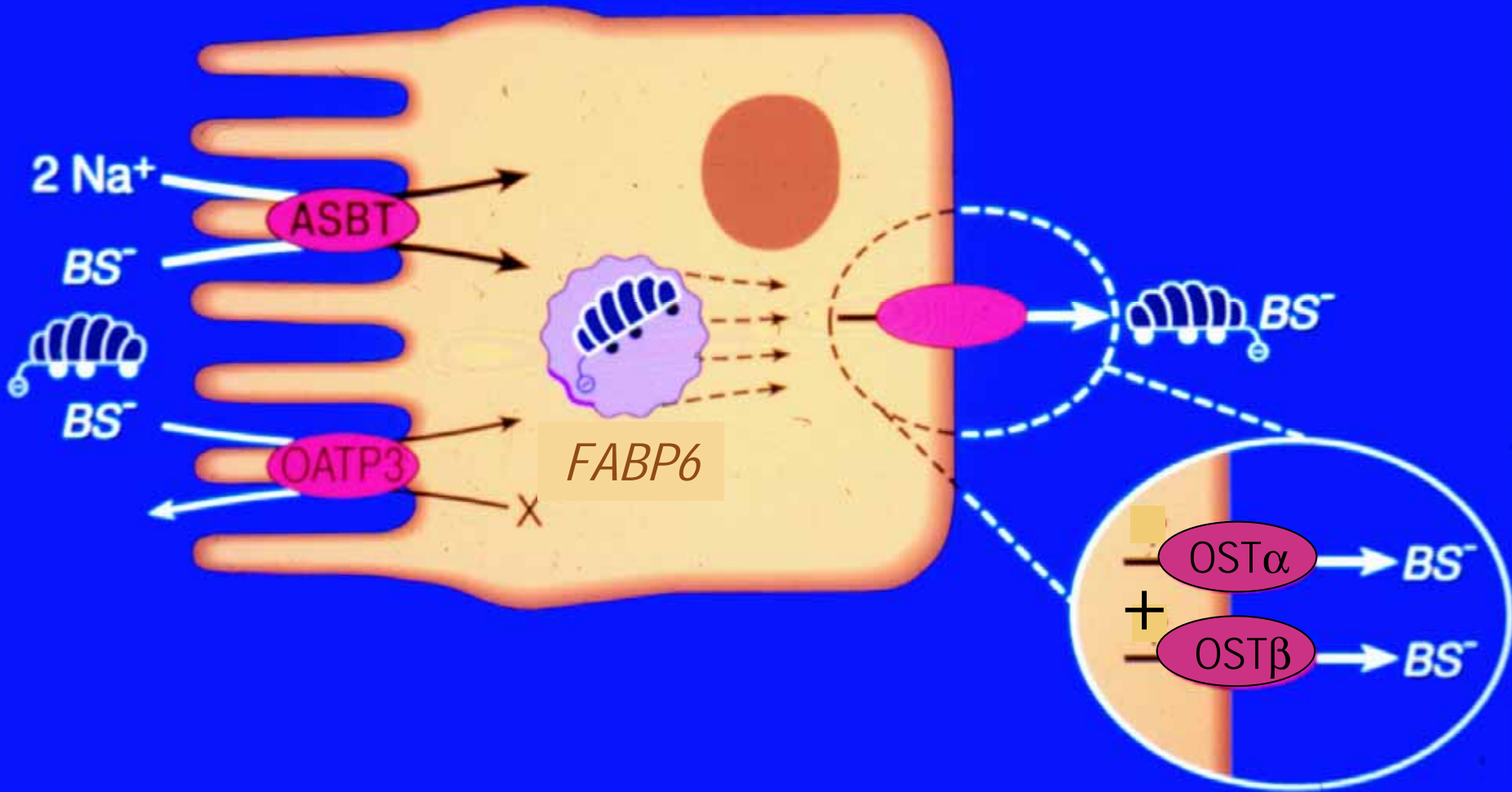
BIOCHEMICAL ORIGIN OF PRIMARY BILE SALTS



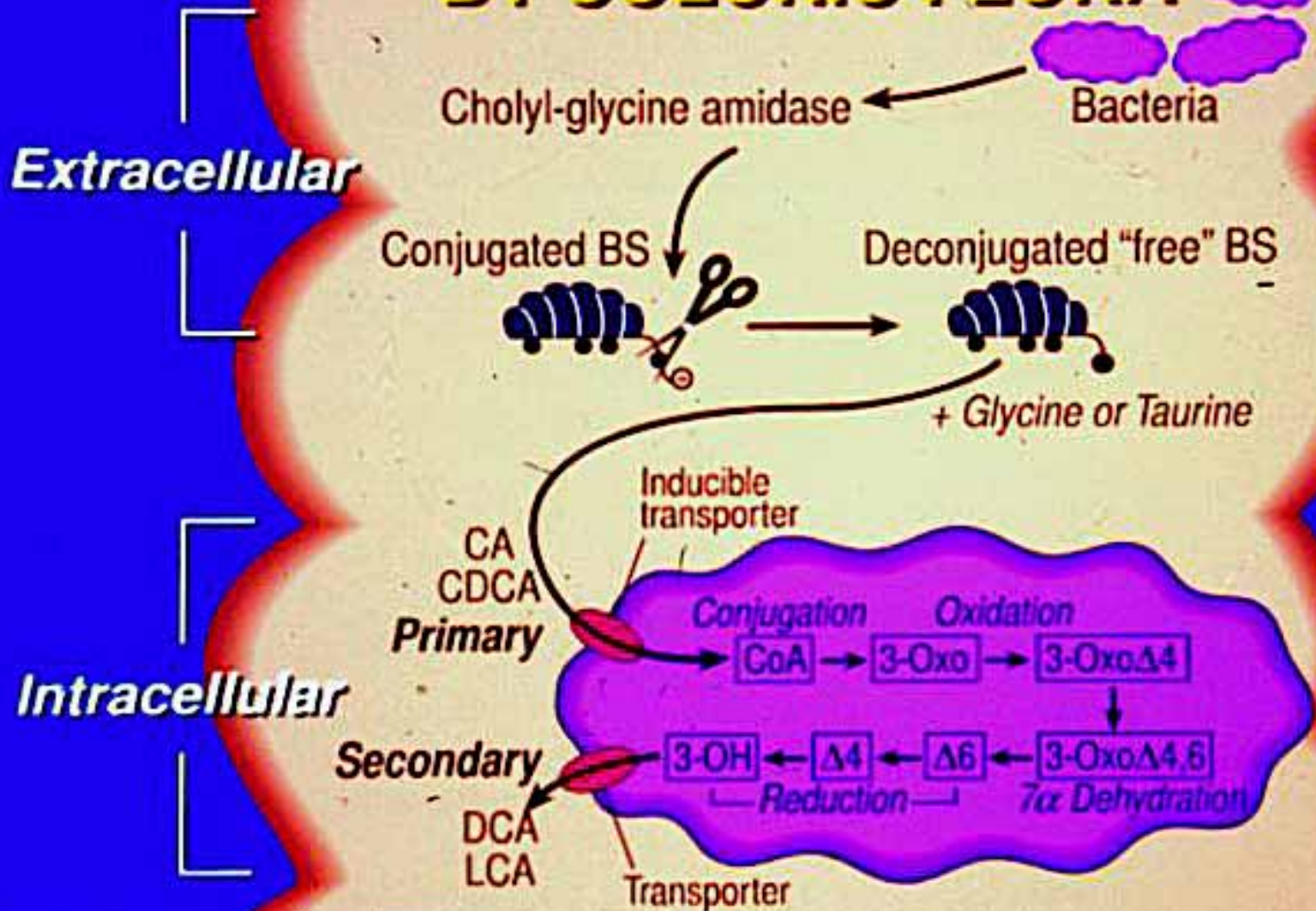
ENTEROHEPATIC CIRCULATION OF BILE SALTS



ABSORPTION OF BILE SALTS BY ILEOCYTES

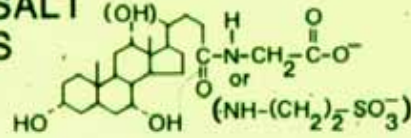


CONJUGATED BILE SALT CATABOLISM BY COLONIC FLORA

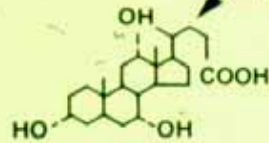


BIOCHEMICAL ORIGIN OF SECONDARY BILE SALTS

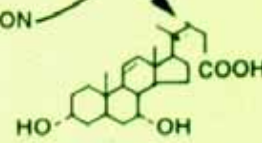
PRIMARY BILE SALT CONJUGATES



DECONJUGATION

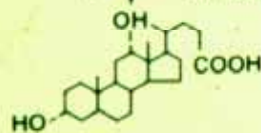


CHOLIC ACID



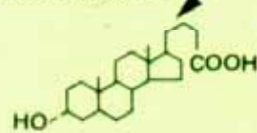
CHENODEOXYCHOLIC (CHENIC ACID)

7 α DEHYDROXYLATION



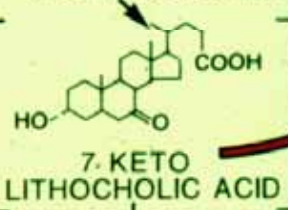
DEOXYCHOLIC ACID

7 α DEHYDROGENATION



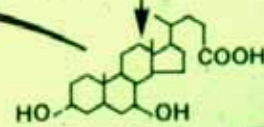
LITHOCHOLIC ACID

7 α DEHYDROGENATION



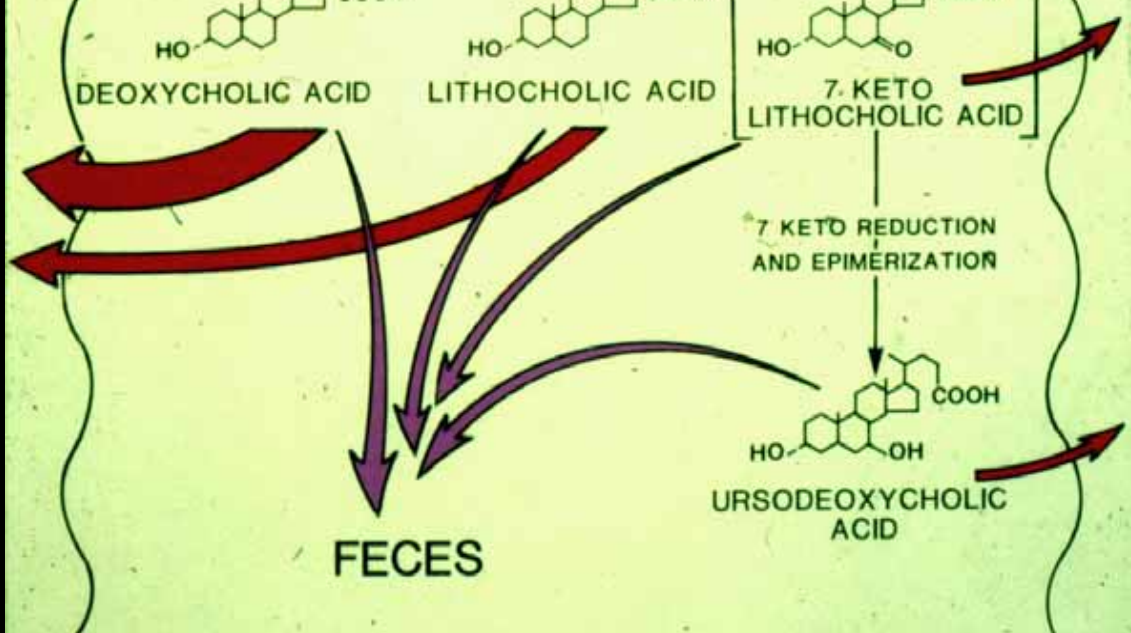
7-KETO LITHOCHOLIC ACID

7 KETO REDUCTION AND EPIMERIZATION



URSODEOXYCHOLIC ACID

FECES



Functions of the Nuclear Bile Salt Receptor FXR

Nuclear Receptor	Ligand	Effect of activation
FXR (bile salt-activated receptor; previously called farnesoid X receptor)	Primary bile salts (but not UDCA) GW 4064 6-ethyl CDCA	P1: H: ↓ BS biosynthesis (via SHP) P2: H: ↑ BS N-acylamidation (conjugation) P2: IE: ↑ BS binding in ileocytes by FABP6 P3: H: ↓ BS uptake by basolateral NTCP P3: H: ↑ BS secretion by canalicular BSEP P3: IE: ↓ BS uptake by apical ASBT P3: H, IE, C: ↑ BS efflux by basolateral OST α/β

Abbreviations:

H, hepatocyte; IE, ileal enterocyte; C, cholangiocyte. P1, phase 1 biotransformation (hydroxylation and related pathways); P2, phase 2 biotransformation (conjugation pathways); P3, phase 3 – transporter activity.

Membrane Transporter Defects in Hereditary Cholestatic Disorders

	<u>Disease</u>	<u>Molecular Change</u>
Progressive Familial Intrahepatic Cholestasis (PFIC)	<i>PFIC1 (low γGT)</i>	Mutation of <i>FIC1</i> gene (Chr 18q21-22)
	<i>PFIC2 (low γGT)</i>	Mutation of <i>BSEP</i> gene (Chr 2q24); canalicular BSEP protein absent
	<i>PFIC3 (high γGT)</i>	Mutation of <i>MDR3</i> gene (Chr 7q21); canalicular MDR3 protein absent
	<i>Benign Recurrent Intrahepatic Cholestasis (BRIC)</i>	Mutation of <i>FIC1</i> gene (Chr 18q21-22)
	<i>Dubin-Johnson syndrome</i>	Mutation of <i>MRP2</i> gene (Chr 10q23-24); canalicular MRP2 protein absent

Pathophysiology of Bile Secretory Failure (Cholestasis)

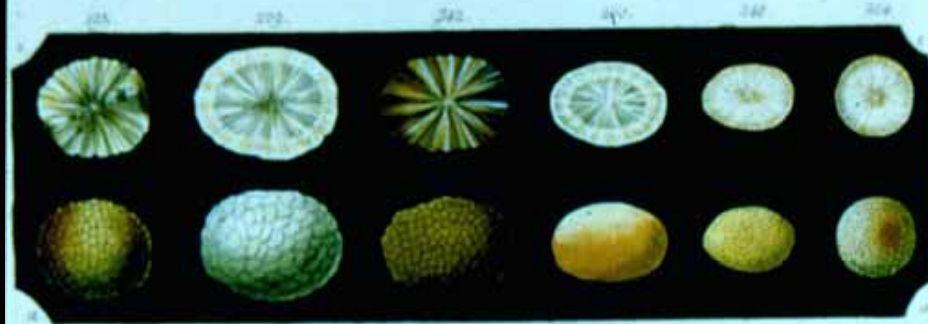
Biliary Lipids in the Systemic Circulation:

- Bilirubin conjugates (MRP3) → Icterus (jaundice), bilirubinuria
- Biliary phospholipids (MDR3) → Lipoprotein X (LpX) – a vesicular LDL
- Biliary cholesterol (ABCG5/8) → LpX – hypercholesterolemia
- Bile salts (MRP4) → Cholemia, choluria, pruritus, bradycardia

Pathophysiology of Bile Secretory Failure (Cholestasis)

Deficit of Biliary Lipids in the Alimentary Tract

- Fat malabsorption: Principally lipovitamins, cholesterol, monoacylglycerides, but not long-chain fatty acids
- Delayed formation of chylomicrons and large particles
- Acholic stools – Delayed peristalsis – Constipation
- Changed ecology of gut flora – defective small intestinal antimicrobiosis, including FXR-mediated secretion of antimicrobial factors
- Dysregulation of gene expression via nuclear receptors



Il. Magna ad nat. par.

Il. Magna ad nat. par.

J. A. Walter del.

Etiology of Cholesterol Cholelithiasis

- Genetic predisposition
 - Monogenic
 - Polygenic
- “Cholelithogenic” environment
 - Diet / Drugs
 - Adiposity / Weight loss
 - Gestation / Estrogens / Progestogens
 - ? Enteric microflora, enterohepatic *Helicobacter* spp. infection
 - ? Acquired immune response



PREVENTION

1990

2000

2010

Lithotripsy

OC

LC

Dissolution

OTHER

That's all from me, folks!