BILE PHYSIOLOGY

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BILE

- COMPLEX LIPID-RICH MICELLAR SOLUTION
- ISO-OSMOTIC WITH PLASMA
- VOLUME OF HEPATIC BILE = 500 – 600 CC/DAY

COMPOSITION

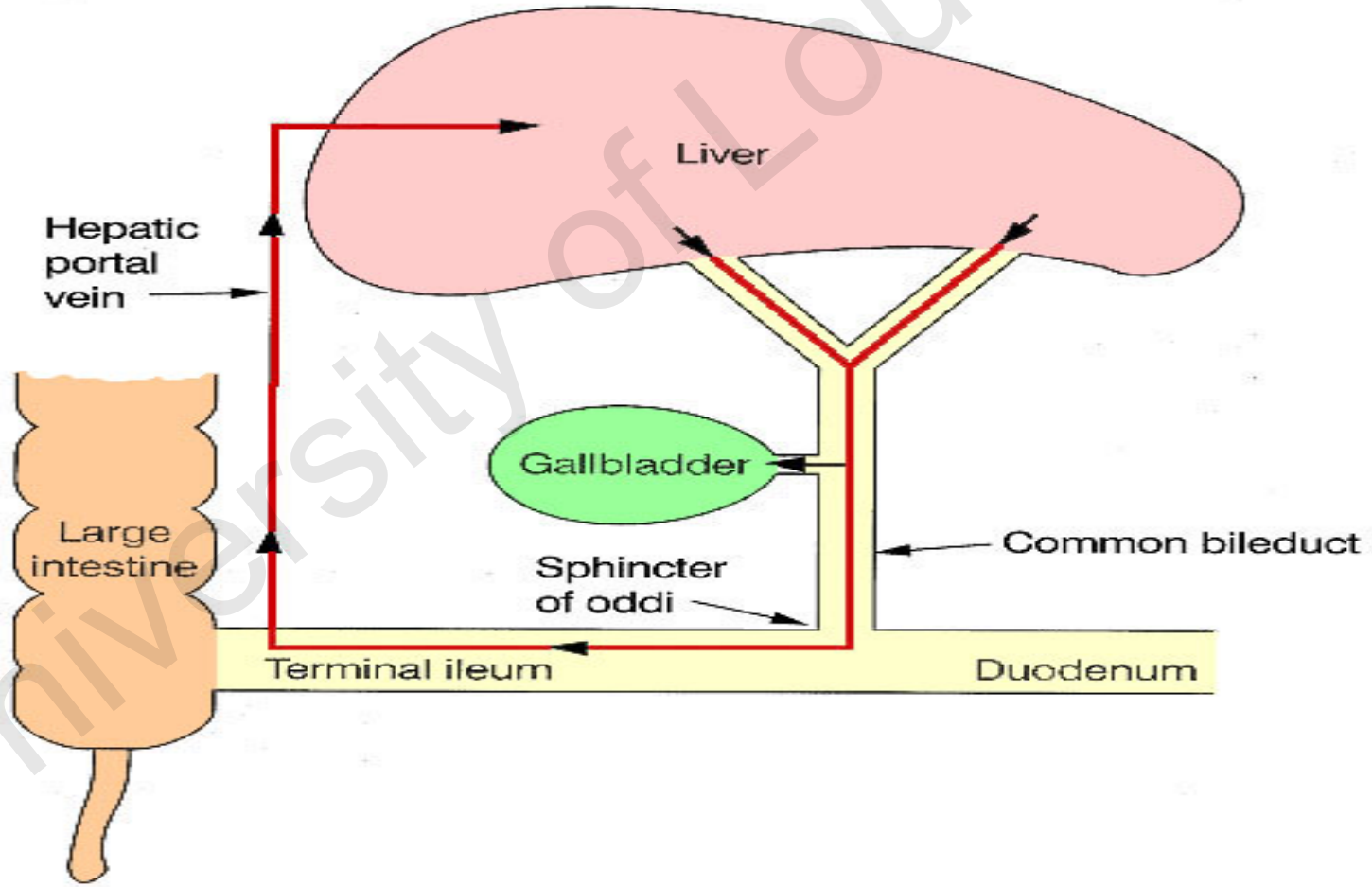
COMPOSITION OF BILE

	Liver Bile (mM)	*Gallbladder Bile* (mM)
Bile salts	35	310
Bile Pigments	0.8	3.2
Cholesterol	3.0	25
Lecithin	1.0	8.0
Na^+	165	280
K^+	5	10
Ca^+	2.5	12
Cl^-	90	15
HCO_3^-	45	8

FUNCTION OF BILE

- INDUCE BILE FLOW AND PHOSPHOLIPID AND CHOLESTEROL SECRETION
- ESSENTIAL FOR INTESTINAL ABSORPTION OF DIETARY CHOLESTEROL , FATS AND VITAMINS
- BIND CALCIUM AND HELP TO PREVENT Ca GALLSTONES AND OXALATE KIDNEY STONE FORMATION
- EXCRETION OF LIPID SOLUBLE XENOBIOTICS, DRUGS AND HEAVY METALS

BILE FORMATION AND CIRCULATION



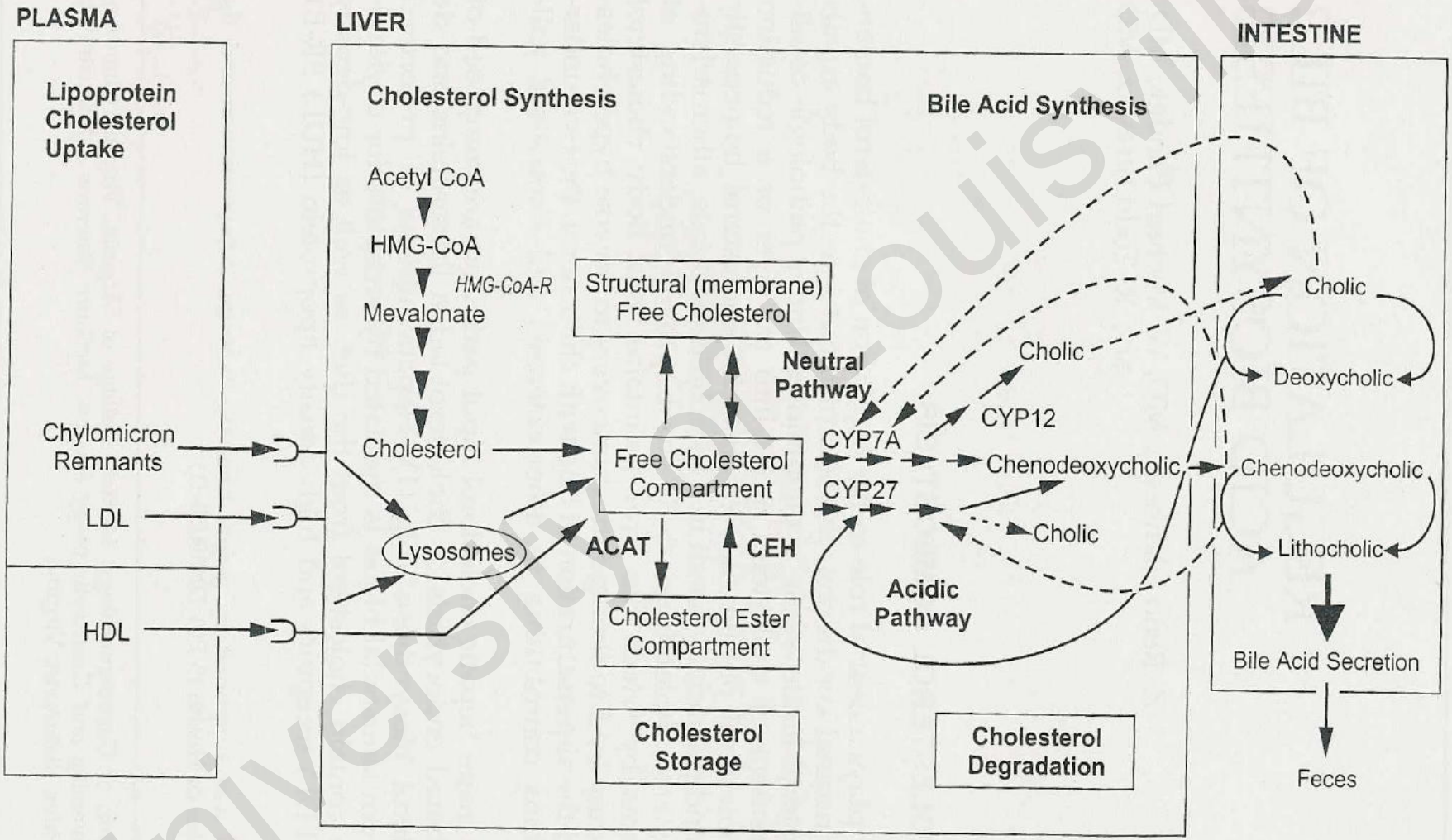


Figure 1. Cholesterol homeostasis. Input and output pathways of cholesterol in the liver are shown. The input pathways consist of de novo biosynthesis of cholesterol from acetate and the uptake of preformed cholesterol by way of several receptor-mediated mechanisms. The output pathways consist of the conversion of cholesterol to bile acids (neutral and acidic pathways) and biliary cholesterol secretion. Primary and secondary bile acids feedback inhibit cholesterol 7α-hydroxylase (CYP7A) and sterol 27-hydroxylase (CYP27), the two enzymes that initiate bile acid biosynthesis from cholesterol. LDL = low density lipoprotein; HDL = high density lipoprotein.

BILE ACID SYNTHESIS

TWO PATHWAYS

1) CLASSICAL / NEUTRAL

- RESULTS IN THE SYNTHESIS OF APPROXIMATELY 1:1 RATIO OF CHOLIC AND CHENODEOXYCHOLIC ACIDS

2)ALTERNATE / ACIDIC

- YIELDS PREDOMINANTLY CHENODEOXYCHOLIC ACID

BILE ACID SYNTHESIS

CLASSICAL / NEUTRAL PATHWAY

- PREDOMINANT PATHWAY IN HEALTH
- POSTCHOLECYSTECTOMY PATIENTS WITH BILE FISTULA
- INFUSED WITH RADIOLABELLED PRECURSORS
    * [3H]7αOH CHOLESTEROL
    * [3H]27-OH CHOLESTEROL

[3H]7αOH CHOLESTEROL

70-95% CONVERTED TO BILE ACIDS

[3H]27-OH CHOLESTEROL

<20% CONVERTED TO BIL ACIDS

BILE ACID SYNTHESIS

ALTERNATE / ACIDIC PATHWAY

- MORE IMPORTANT IN CHRONIC LIVER DISEASE

-CIRRHOTICS

- LOW RATE OF BILE ACID SYNTHESIS
- ALMOST EXCLUSIVELY CHENODEOXYCHOLIC

BILE ACID SYNTHESIS

FINAL STEP =

- CONJUGATION OF CHOLIC AND CHENODEOXYCHOLIC ACIDS WITH GLYCINE AND TAURINE
- CONJUGATION ENHANCES THE HYDROPHILICITY, THUS DECREASE THE PASSIVE DIFFUSION OF BILE AS IT MOVES THROUGH THE BILIARY TREE AND SMALL INTESTINE

BILE ACID

SYNTHESIS

REGULATION

RATE LIMITING ENZYMES

1) CLASSICAL PATHWAY=

CHOLESTEROL 7α HYDROXYLASE

2) ALTERNATE PATHWAY=

STEROL 27 HYDROXYLASE

BILE ACID

SYNTHESIS

REGULATION

CHOLESTEROL 7Aα HYDROXYLASE

1) BILE ACIDS

2) CHOLESTEROL

3) HORMONES

4) INTESTINAL FACTORS

5) CYTOKINES

BILE ACID SYNTHESIS

REGULATION

CHOLESTEROL 7α HYDROXYLASE

- BILE ACIDS

-Interruption of enterohepatic circulation-increases bile acid synthesis

-Intraduodenal reperfusion-reduces bile acid synthesis

- Bile acids are not equal in their ability to feedback inhibit CYP7αOH activity

- hydrophobic bile acids – repressed
- hydrophilic bile acids – no effect

URSO = HYDROPHILIC

CLINICAL CORRELATION

1)Resection of Terminal Ileum

Increased bile acid secretion

2)Infants with inborn errors of bile acid biosynthesis

-Accumulation of toxic intermediates in the hepatocytes causing cholestasis and chronic liver damage

-Oral bile acids supplements containing hydrophobic bile acids –decreased accumulation of toxic intermediates

2) CHOLESTEROL

-Increased dietary cholesterol

Rats-Increased CYP7αOH Activity

? Humans -Decreased CYP7αOH Activity

3) HORMONES

-Glucocorticoids

-Thyroid hormones

-Insulin

-Glucagon

CLINICAL CORRELATION

-Hamsters-CYP 7A

-Led to lowered LDL

-May find a role in treating hyperlidiemia

BILE ACID TRANSPORT

-Bile acid pool is recirculated 10-20 times a day

-Bile acid pool is 1.5 to 4 gm

-Circulating bile acid pool is 17 to 40 g

0.2 to 0.5 gm of bile is lost in feces =replaced by de novo synthesis

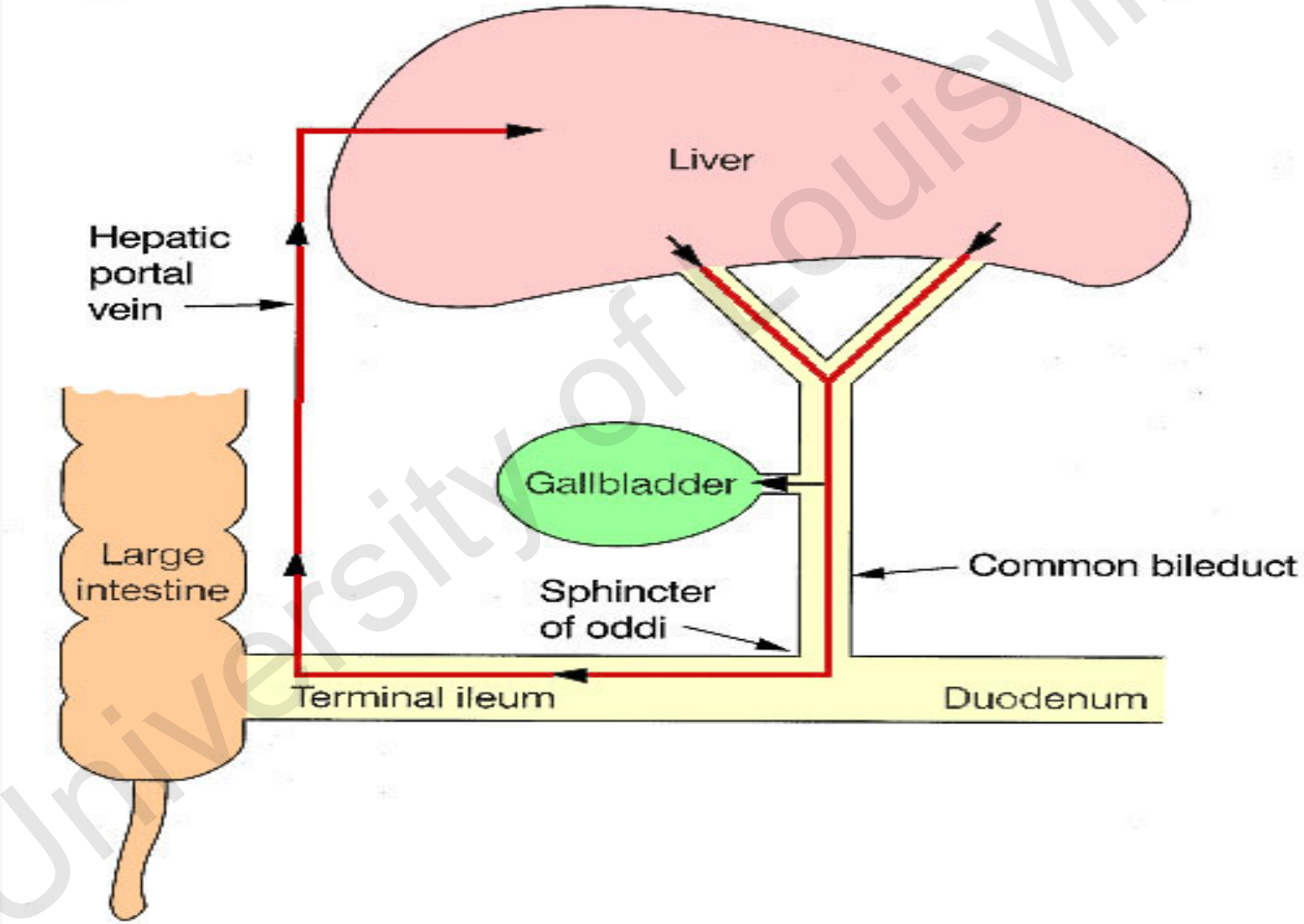
ENTEROHEPATIC CIRCULATION

1) TWO PUMPS - LIVER

- INTESTINE

2)TWO RESERVOIRS

- INTESTINAL LUMEN
- BLOOD



ENTEROHEPATIC CIRCULATION PUMPS

- LIVER

1) Synthesizes new bile acids - <2% of bile acid pool

2) Extracts bile acids from portal blood

3) Secretes bile acids into the canaliculi

ENTEROHEPATIC CIRCULATION PUMPS

- INTESTINE

1) Resorbs bile acids from intestinal lumen

2) Secretes bile acids into the portal blood

TRANSPORT IN THE LIVER

HEPATOCYTE

- APICAL
- BASOLATERAL
  - SINUSOIDAL
  - LATERAL

TRANSPORT IN THE LIVER

HEPATOCYTE

- BASOLATERAL

- SINUSOIDAL

TWO MAJOR MECHANISMS

1) CARRIER MEDIATED

2) SIMPLE DIFFUSION

TRANSPORT IN THE LIVER

- SINUSOIDAL

1) CARRIER MEDIATED

   a- Na Dependent

   b- Facilitative

TRANSPORT IN THE LIVER

- SINUSOIDAL

1) CARRIER MEDIATED

   a- Na Dependent

-Utilizes the low intracellular [Na+] created by Na-K ATPase

-Used to transport hydrophilic glycine or taurine conjugated bile acids

TRANSPORT IN THE LIVER

- SINUSOIDAL

1) CARRIER MEDIATED

   a- Na Dependent

-Two Na Dependent Bile Acid transporters

1) NTCP
2) Rats-mEH

TRANSPORT IN THE LIVER

- SINUSOIDAL

1) CARRIER MEDIATED

   b- Facilitative

ANTIPORTER = Exchange uptake of bile acid with the efflux of an intracellular compound

-Nonconjugated secondary bile acids are the preferred substrate

-OAT1=Organic Anion Transporter

TRANSPORT IN THE LIVER

- SINUSOIDAL

1) SIMPLE DIFFUSION

- Noncharged Hydrophobic bile acids
- Unconjugated bile acids are uncharged at physiologic pH
- Primary bile acids can undergo 7 α dehydroxylation by intestinal bacteria generating the secondary hydrophobic bile acids=lithocholic and dexycholic acids

TRANSPORT IN THE LIVER

HEPATOCYTE

- APICAL = CANALICULAR MEMBRANE

-Occurs across a concentration gradient of between 100 to 1000 fold

-Mechanisms

1) Electrogenic

2) ATP Dependent-Major Mechanism

BILE FLOW

1) BILE ACID DEPENDENT

2) BILE ACID INDEPENDENT

BILE FLOW

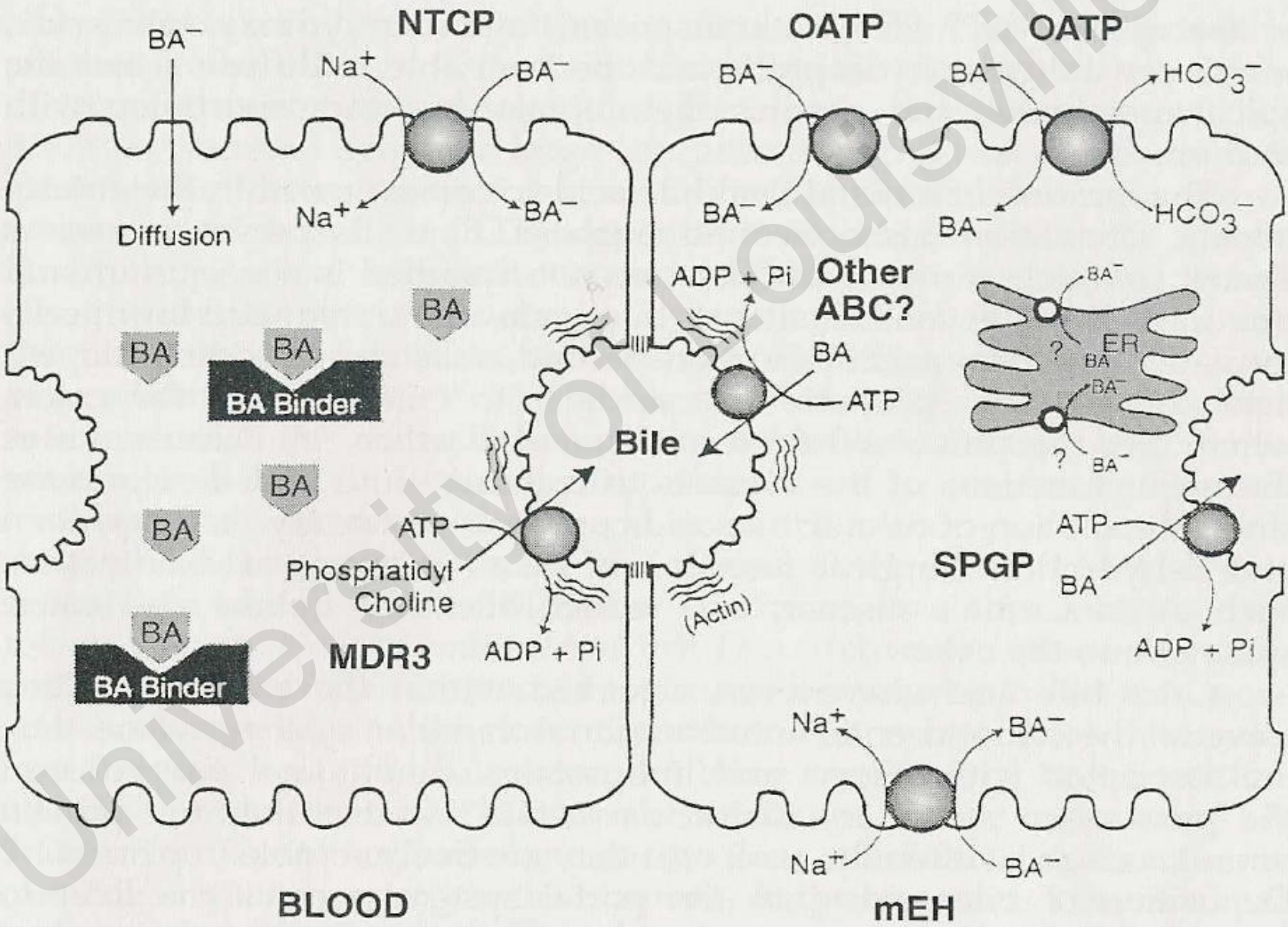
1) BILE ACID DEPENDENT

- Bile acids are Anions
- Draw Na+ to maintain electroneutrality
- Na draws water along with it

BILE FLOW

2) BILE ACID INDEPENDENT

Active secretion of organic anions esp. glutathione



TRANSPORT IN THE INTESTINE

ENTEROCYTE

- APICAL
- BASOLATERAL

TRANSPORT IN THE INTESTINE

ENTEROCYTE

- APICAL

MECHANISMS

- Diffusion
- Na Dependent

DIFFUSION

- Bile acids remain trapped in the intestinal lumen because of their net negative charge
- Intestinal bacteria

  Deconjugate a.a.- render them uncharged

  Dehydroxylate - render them more hydrophobic

GALL STONES

GALLSTONE DISEASE

-10 % overall population

-33 % women over 40

-70% adult American Indian Women

BILE

-BILIRUBIN AND CHOLESTEROL

-BOTH RELATIVELY INSOLUBLE

-SOLUBILISATION BY THE DETERGENT ACTION OF BILE SALTS

BILE

-BILE SALTS and PHOSPHOLIPIDS

- Hydrophilic and hydrophobic portions

-Self associate so that the that the exposure of their hydrophobic portion to water is minimised

-Hydrophobic domains allow the transport of

Cholesterol and Bilirubin

•BILIARY LIPID AGGREGATES

- SIMPLE BILE SALT MICELLES
- MIXED DISC MICELLES
- MIXED LIPID VESICLES

PHOSPHOLIPIDS

- Phosphatidylcholine broken down by Phospholipase A from bacteria to Lysolecithin and Fatty Acids
- FA forms soaps with Ca++ - involved in the pathogenesis of brown stones

GALLSTONES

THREE TYPES

-Cholesterol>80% gallstones in the western world

-Black pigment

-Calcium salts of unconjugated bilirubin

-Brown pigment

-Occurs only as a result of bacterial infection of the biliary tree in the presence of bacterial infection

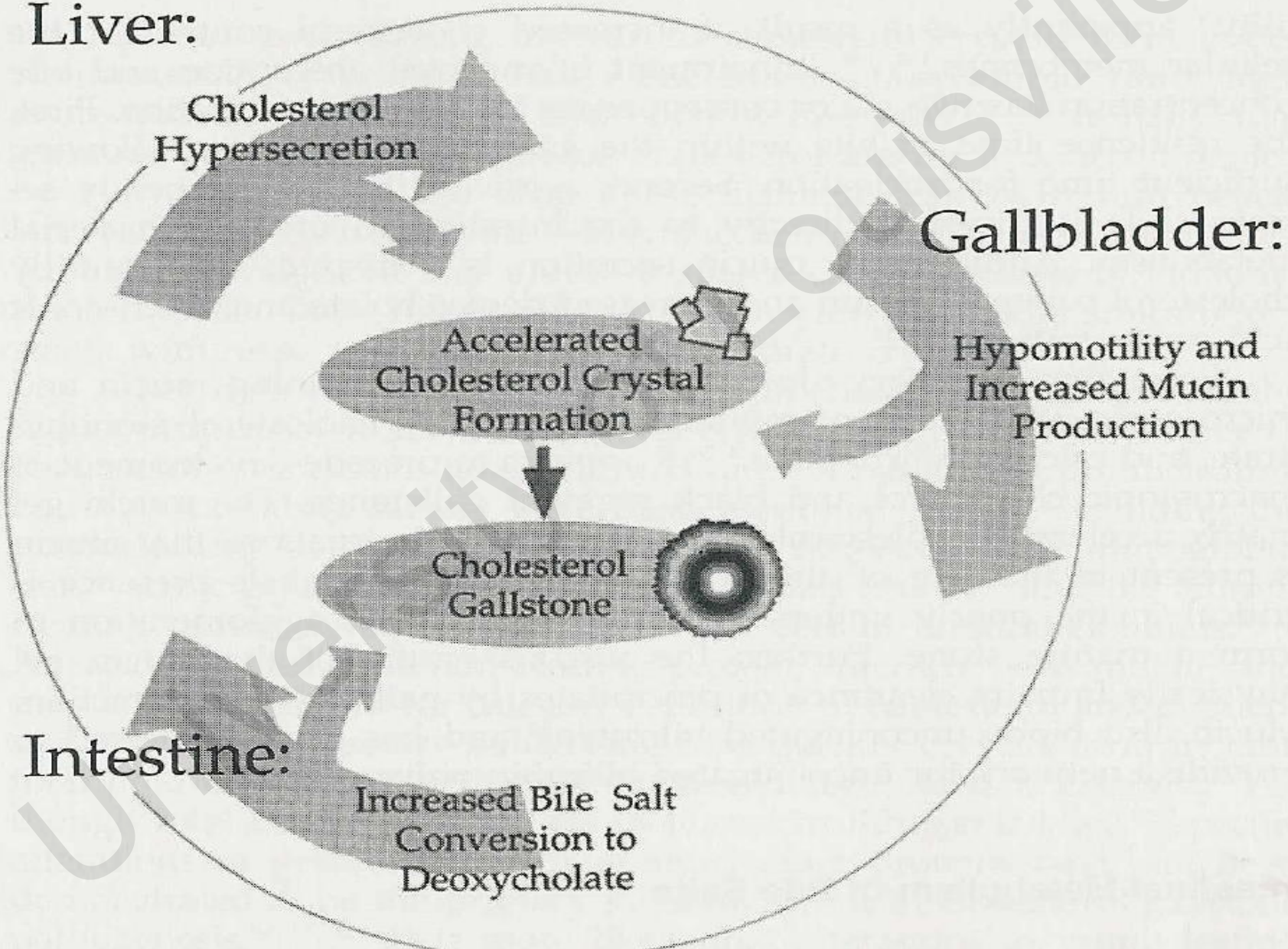
GALLSTONES

CHOLESTEROL

-PRIMARILY A METABOLIC DISORDER

-VICIOUS CYCLE

- -Cholesterol hypersecretion
- -Gall bladder factor
  - -Hypomotility
  - -Mucus hypersecretion
- -Intestinal factors


Liver:
Cholesterol Hypersecretion
Gallbladder:
Hypomotility and Increased Mucin Production
Accelerated Cholesterol Crystal Formation
Cholesterol Gallstone
Intestine:
Increased Bile Salt Conversion to Deoxycholate

GALL BLADDER HYPOMOTILITY

- Increased residence time of bile in GB leading to greater time for nucleation
- Greater fraction of bile diverted directly to the intestines-increased bacterial degradation

BILIARY SLUDGE

–Viscous gel containing mucin and microscopic precipitates of multilamellar vesicles, cholesterol and calcium bilirubinate

MUCIN

–Glycoprotein

–Major constituent of GB mucus

–Can bind bilirubin, phospholipids and cholesterol, encouraging cholesterol crystal precipitation

–Viscous nature of mucin gel physically impairs clearance of precipitates

INTESTINAL FACTORS

GB Hypomotility

- More bile directly diverted into the intestines

-Greater exposure to intestinal bacteriathat deconjugate primary bile salts to the more hydrophobic sec bile salts

-After absorption and recycling, the hydrophobic bile salts more effectively extracts cholesterol from canalicular membrane

OTHER FACTORS

- –PRONUCLEATING FACTORS
  - •N Aminopeptidase
  - •Fibronectin
  - •Immunoglobulins
  - •Haptoglobin
  - •Mucin
- –ANTINUCLEATING FACTORS
  - •Apolipoprotein
  - •immunoglobulins

- METABOLIC FACTORS
  - –ESTROGEN
  - –PREGNANCY
  - –OBESITY AND WEIGHT LOSS
  - –AGE
  - –INTESTINAL HYPOMOTILITY
  - –DIET
  - –GENETIC/ETHNIC FACTORS
  - –SPINAL CORD INJURY

GALLSTONES

BLACK PIGMENT

COMPOSITION

- Calcium bilirubinate
- Calcium PO_4
- $CaCO_3$

GALLSTONES

BLACK PIGMENT

PATHOGENESIS

1) Increased Unconjugated bilirubin

2) Decreased in solubilising micelles & vesicles

3) Increased ionised calcium

GALLSTONES

BLACK PIGMENT

PATHOGENESIS

Increased Unconjugated bilirubin

-Deconjugation

-Enzymatic-B Glucoronidase

-Bacterial infection

-Tissue

-Nonenzymatic-tissue

GALLSTONES

BLACK PIGMENT

PATHOGENESIS

Increased Unconjugated bilirubin

-Increased porduction

-Hemolysis

-Alcoholism

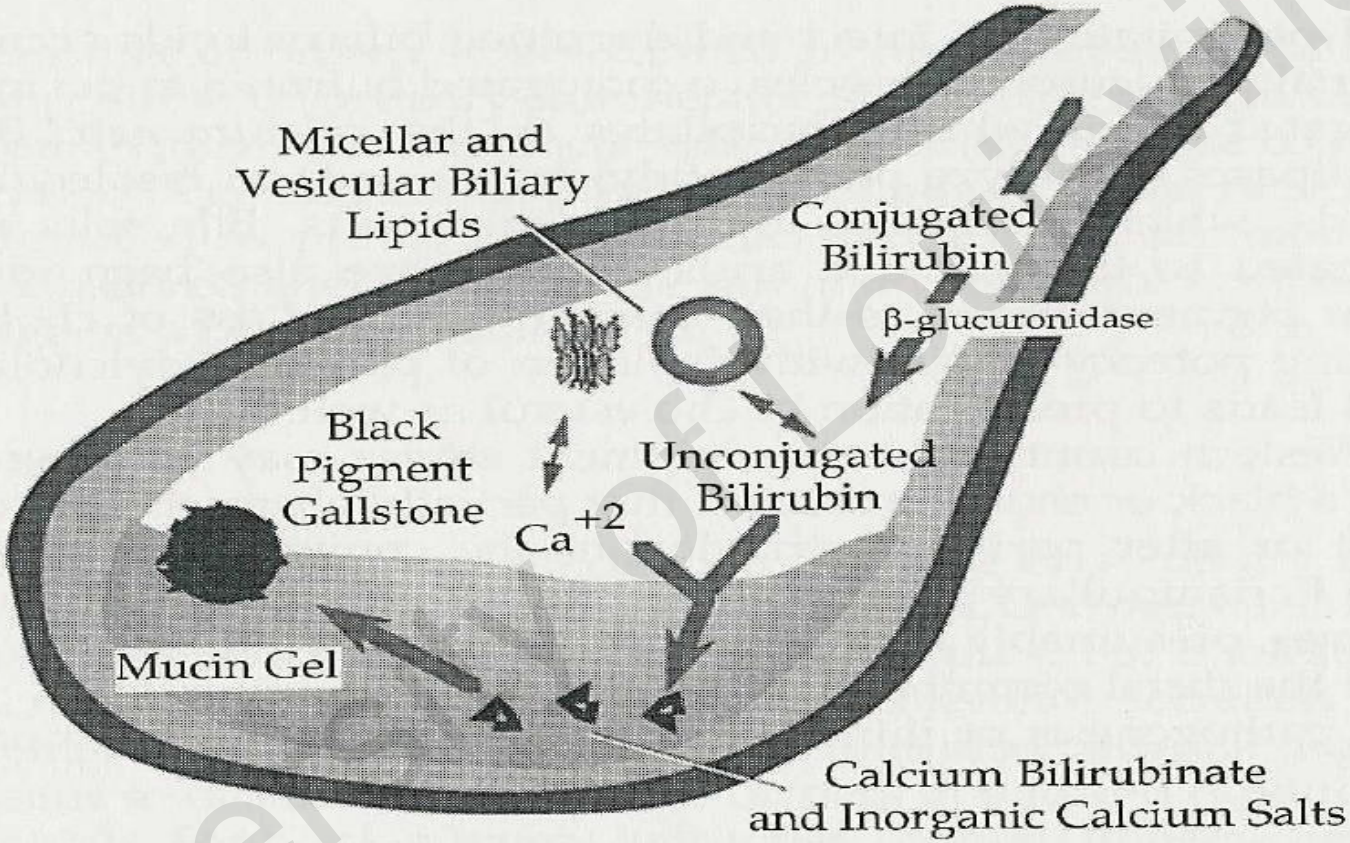


Figure 6. Pathogenesis of *black* pigment gallstones. The major initiating event is a relative increase in conjugated bilirubin secretion. Deconjugation, either by tissue β glucuronidases or non-enzymatically, produces unconjugated bilirubin. Although solubilized in part by biliary micelles and vesicles, the extreme insolubility of calcium bilirubinate enhances precipitation. Inorganic (carbonate and phosphate) calcium salts also precipitate. Mucin in conjunction with calcium-binding protein provides a scaffolding for formation of mature *black* pigment gallstones. (*From* Donovan JM, Carey MC. Physical-chemical basis of cholesterol "carriers" in bile. Hepatology 12:945–1055, 1990; with permission.)

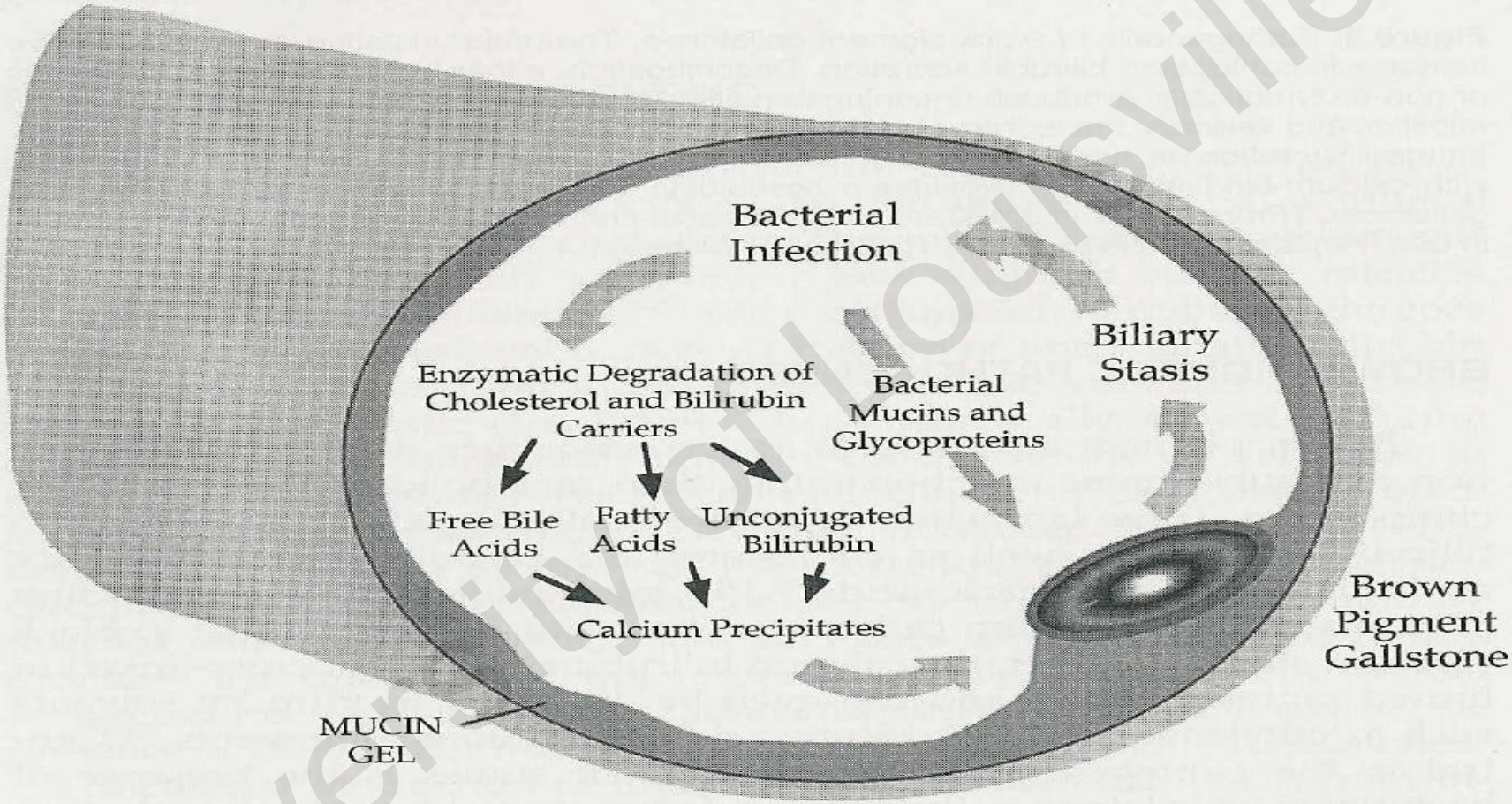


Figure 7. Pathogenesis of *brown* pigment gallstones. Bacterial enzymes degrade biliary lipids, usually in the bile ducts, producing insoluble calcium salts of fatty acids and unconjugated bilirubin. Precipitation of these compounds is exacerbated by degradation of biliary solubilizing agents, bile salts, and phosphatidylcholine. Additionally, solubility of cholesterol is impaired, with consequent precipitation. Brown pigment stones contain bacterial cytoskeletal remains as well as mucin and non-mucin glycoprotein. Obstruction caused by the stone serves as a continuing source of bacterial colonization and further obstruction with biliary stasis.