FUNCTIONS OF BILE

- Promotes “exocrine” lipid secretion, especially cholesterol elimination
- Facilitates dietary lipid absorption, obligatory for fat-soluble vitamin absorption
- Conduit for endobiotic and xenobiotic excretion
- Distributes immunoglobins and antioxidants throughout the gut
BILE WATER PRODUCTION

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THE "SECRETORY" MIXED MICELLE

Phospholipid  Bile salt  Cholesterol
Water  NaCl

Courtesy of Dr. Siewert-Jan Marrink. Used with permission.
THE "SECRETORY" MIXED MICELLE

- Phospholipid
- Bile salt
- Cholesterol
- Water
- NaCl

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LIPID PARTICLES IN HUMAN BILES

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Coordinate Regulation of Cholesterol Homeostasis (Nuclear Receptors)

Cholesterol \rightarrow \text{Cholesterol 7α-Hydroxylase (CYP 7a)} \rightarrow \text{Bile Acids}

\rightarrow \text{Oxysterols} \leftrightarrow \text{LXRα} \leftrightarrow \text{FXR (BAR)}

Wang et al., 1999
Membrane Transporter Defects in Hereditary Cholestatic Disorders

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Content removed due to copyright reasons.
Pathophysiology of Bile Secretory Failure (Cholestasis)

Biliary Lipids in the Systemic Circulation:

- Bilirubin Conjugates (MRP1) $\rightarrow$ Icterus (Jaundice), Bilirubininuria
- Biliary Phospholipids (MDR3) $\rightarrow$ Lipoprotein X (LpX) – a vesicular LDL
- Biliary Cholesterol $\rightarrow$ LpX – Hypercholesteroleemia
- Bile Salts (MRP3) $\rightarrow$ Cholemia, Choluria, Pruritus, Bradycardia
Pathophysiology of Bile Secretory Failure (Cholestasis)

Deficit of Biliary Lipids in the Alimentary Tract

- Fat Malabsorption, principally Lipovitamins, Cholesterol, Monoglycerides but not Fatty Acids

- Delayed Chylomicron Formation and Large Particles

- Acholic Stools – Delayed Peristalsis – Constipation

- Changed Ecology of Gut Flora
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AUTOPSY PREVALENCE RATES OF GALLSTONES IN WOMEN (1951-1981)
PREVALENCE OF GALLSTONES

Germany

PERCENT WITH GALLSTONES

AGE (years)

Berndt et al. (1989)
FORMATION OF CHOLESTEROL GALLSTONES: KEY ELEMENTS

Mucin Gel

Cholesterol Supersaturation

Gallbladder Hypomotility

Crystals

Nucleation and Phase Transitions
Image removed due to copyright reasons. Please see:


Principles of Cholesterol Solubilization and Supersaturation in Bile

Stability

\[ \text{CH} \]

\[ \text{[BS + PL]} \]

Lithogenicity

\[ \text{CH} \]

\[ \text{[BS + PL]} \]
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Etiology of Cholesterol Cholelithiasis

• Genetic predisposition
  - Monogenic
  - Polygenic

• “Cholelithogenic” environment
  - Diet/Drugs
  - Adiposity/Weight Loss
  - Gestation/Estrogens/Progestogens
The Genetic Factor in Human Cholesterol Gallstone Disease

• Apparently due to “thrifty” genes (like obesity, Type 2 diabetes)
• Possible genetic drift during last glaciation: “The Stone That Came in from the Cold”
• American Indian and Viking migrations
• Strong family clustering: Pedigrees, twin studies, etc.
• Essentially absent in sub-Saharan populations
GALLSTONES IN FIRST-DEGREE RELATIVES OF GALLSTONE PATIENTS

van der Linden & Simonson (1973)

Gilat et al (1983)


PERCENT WITH STONES

Sex

F

M

F

M

F

M

F + M

Family

Controls

25

20

15

10

5

0

van der Linden & Simonson

Gilat et al

Sarin et al
Genetic and Environmental Influences on Symptomatic Gallstone Disease

- Genetic: 25%
- Environmental (unique): 13%
- Environmental (shared): 62%

Emergence of *Helicobacter* Taxa Causing Disease (to 2001*)

- Gastric *Helicobacter* species $\approx 10$ (Humans and other animals)
- Enterohepatic *Helicobacter* species $\approx 18$ (Humans, rodents, other mammals, and birds)

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C57L Murine Cholesterol Gallstone Model: Lithogenic Diet Feeding

- **With Helicobacter spp. infection**
  - Supersaturated Bile
  - Liquid Crystals
  - Solid Crystals
  - Sandy Stones
  - Cholesterol Gallstones

- **Without Helicobacter spp. infection**
  - Supersaturated Bile
  - Liquid Crystals
  - Solid Crystals (crossed out)
Proposed New Paradigm for Cholesterol Gallstone Formation and Perhaps Biliary Cancer

Complex Genetics (LithGenes)  

*Helicobacter* spp. Infection

Environment: Diet, Medication, Hormones, etc.

Cholesterol Gallstones

Chronic Cholecystitis

Gallbladder Cancer
Frequency Distribution of Cholesterol in Gallstones

N = 53

- Pigment Stones (26%)
- Cholesterol Stones (74%)

% of Patients

% Cholesterol in Stones
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FORMA\n\nFORMATION OF BILIRUBIN

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BROWN PIGMENT STONE FORMATION

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Evolution of Cholesterol Gallstones
(As Currently Conceived)

I
Metabolic stage
Defective metabolism of biliary lipids

II
Chemical stage
Bile contains EXCESS cholesterol

III
Physical stage
Cholesterol crystals form

IV
Growth stage
Macrosopic stones GROW

V
Obstructive stage
Blockage of cystic or common duct

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GALLSTONES

Asymptomatic

Symptomatic

Complicated

1-2%/yr

<1%/yr

3-5%/yr
BILE ACID THERAPY

% Primary Effectiveness

% Symptomatic Gallstone Patients

Superoptimal
Optimal
Acceptable

Strasberg and Clavien (1992)

(Courtesy of Dr. Steven M Strasberg. Used with permission.)
TO AVOID GALLSTONES, A WOMAN SHOULD

Image removed due to copyright reasons. please see:

PREVENTION

(Courtesy of Dr. Steven M Strasberg. Used with permission.)