

# 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

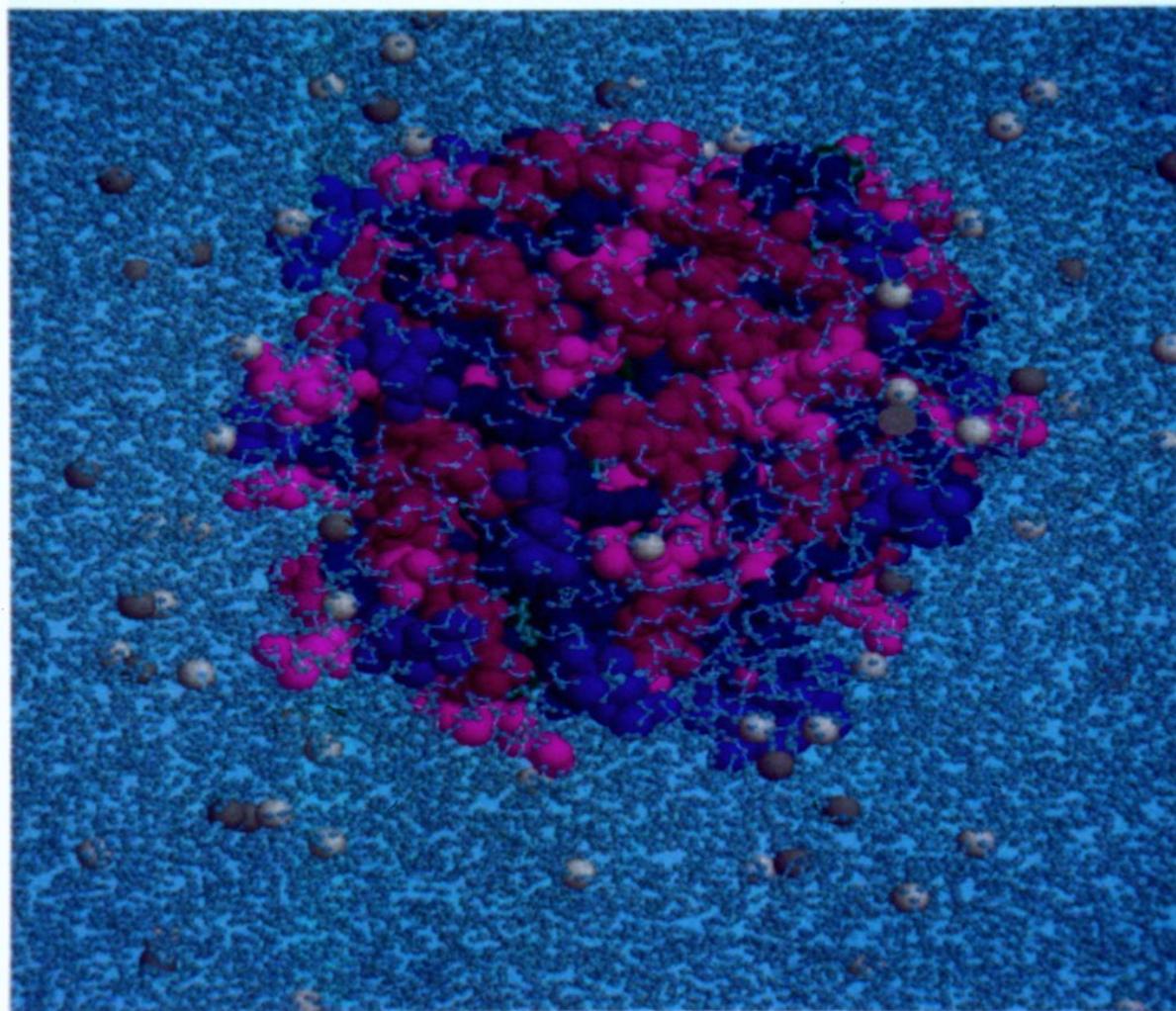
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Carey M. C, and S. J. Robins. "Bile Production and Secretion." In *Internal Medicine*. Edited by J. H. Stein, et al. Boston, MA: Little, Brown and Company, 1983, pp. 25-30.

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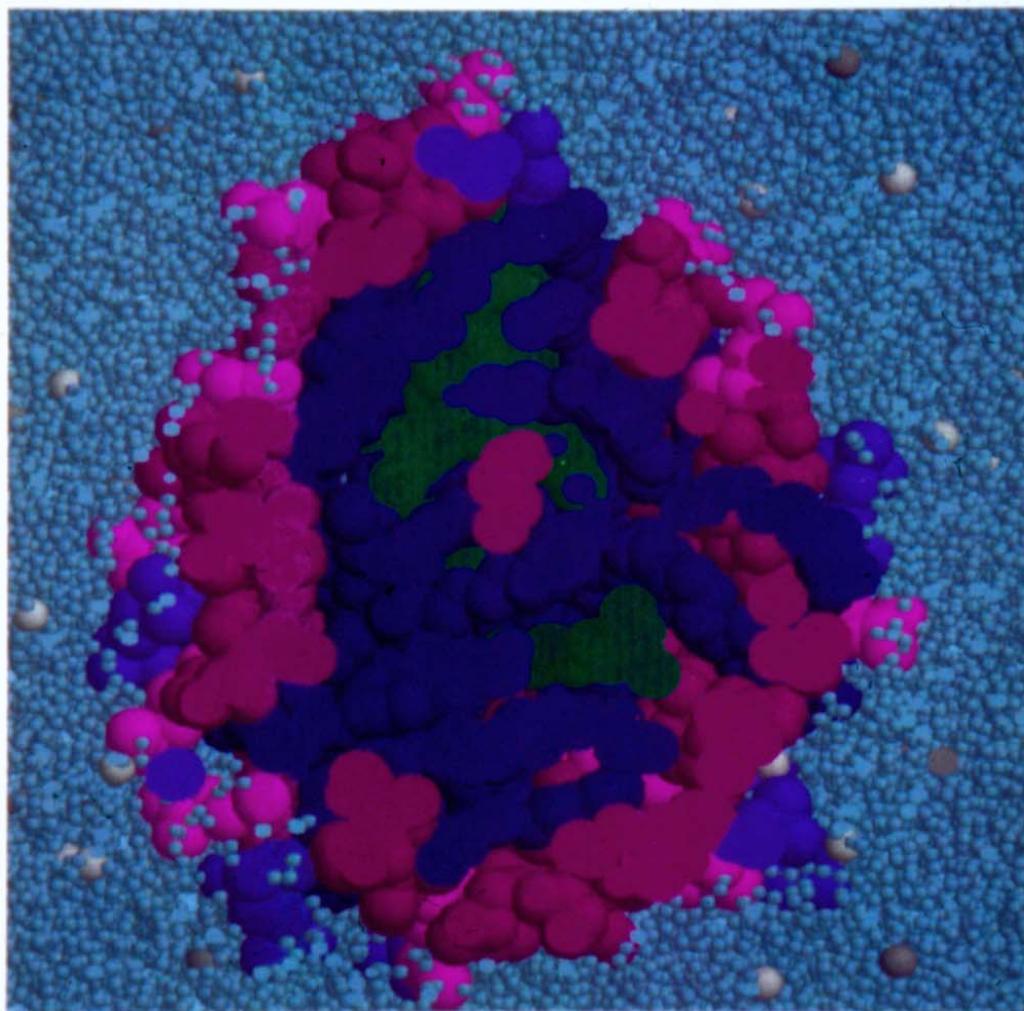
Figure 3e in Crawford, J. M., G. M. Mockel, A. R. Crawford, S. J. Hagen, V. C. Hatch, S. Barnes, J. J. Godleski, and M. C. Carey. "Imaging biliary lipid secretion in the rat: ultrastructural evidence for vesiculation of the hepatocyte canalicular membrane." *J Lipid Res* 36 (1995): 2147-2163.

## THE "SECRETORY" MIXED MICELLE



■ Phospholipid ■ Bile salt ■ Cholesterol  
■ Water ■ NaCl

## THE "SECRETORY" MIXED MICELLE



■ Phospholipid ■ Bile salt ■ Cholesterol  
■ Water ■ NaCl

# CHOLESTEROL ENRICHMENT OF BILIARY VESICLES BY BILE SALTS

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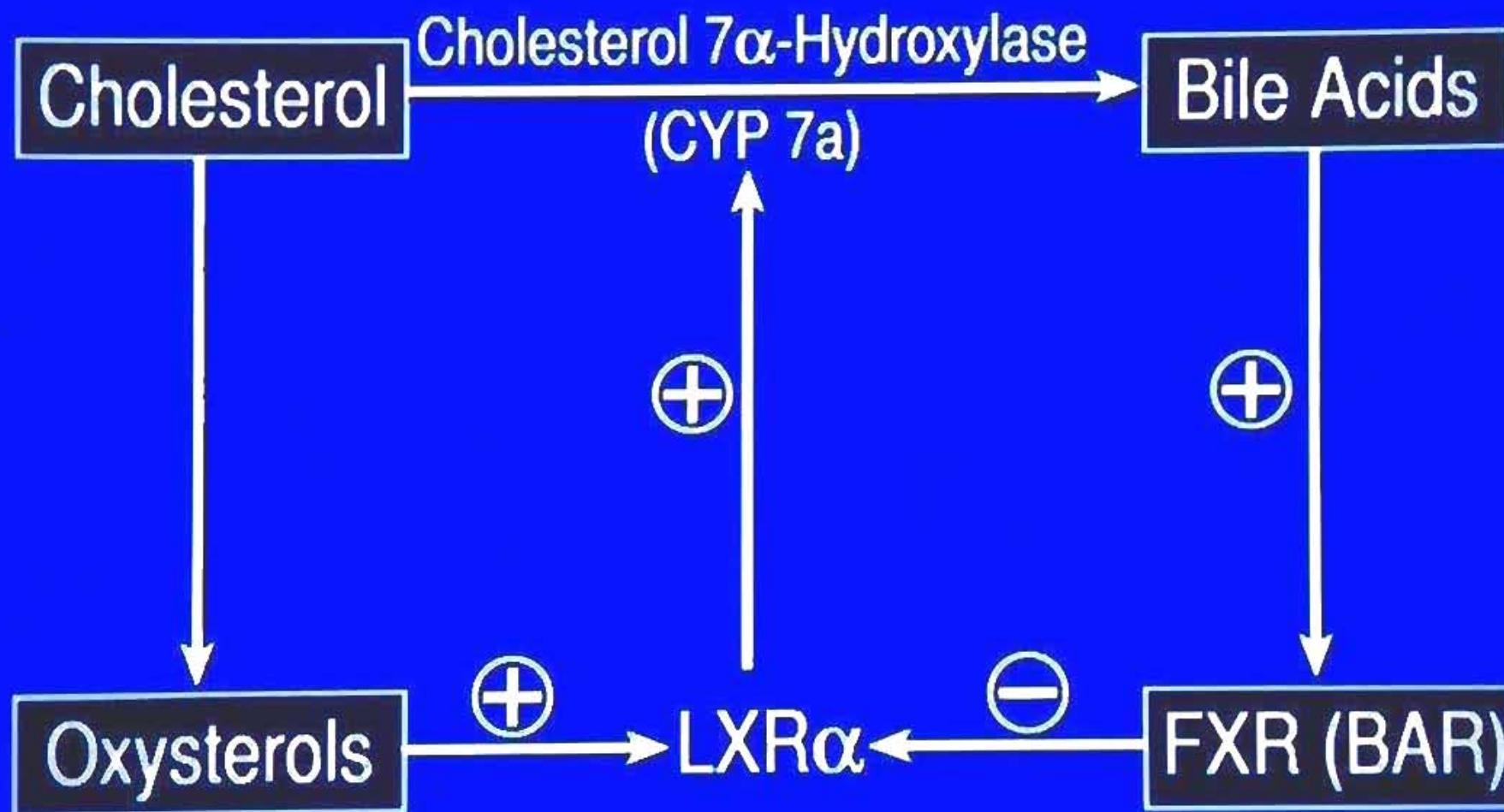
Carey, M. C. *New Trends in Hepatology*. Edited by W. Gerok, A. S. Loginov, and V. I. Pokrowskij.  
Dordrecht, The Netherlands: Kluwer Academic Press, 1996, pp. 64-83.

## LIPID PARTICLES IN HUMAN BILES

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Carey, M. C. *New Trends in Hepatology*. Edited by W. Gerok, A. S. Loginov, and V. I. Pokrowskij.  
Dordrecht, The Netherlands: Kluwer Academic Press, 1996, pp. 64-83.

# Coordinate Regulation of Cholesterol Homeostasis (Nuclear Receptors)



Wang et al., 1999

# Membrane Transporter Defects in Hereditary Cholestatic Disorders

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# Membrane Transporter Defects in Acquired Cholestatic Disorders

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# Pathophysiology of Bile Secretory Failure (Cholestasis)

## Biliary Lipids in the Systemic Circulation:

- Bilirubin Conjugates (MRP1) → Icterus (Jaundice), Bilirubinuria
- Biliary Phospholipids (MDR3) → Lipoprotein X (LpX) – a vesicular LDL
- Biliary Cholesterol → LpX – Hypercholesterolemia
- Bile Salts (MRP3) → Cholemia, Choluria, Pruritus, Bradycardia

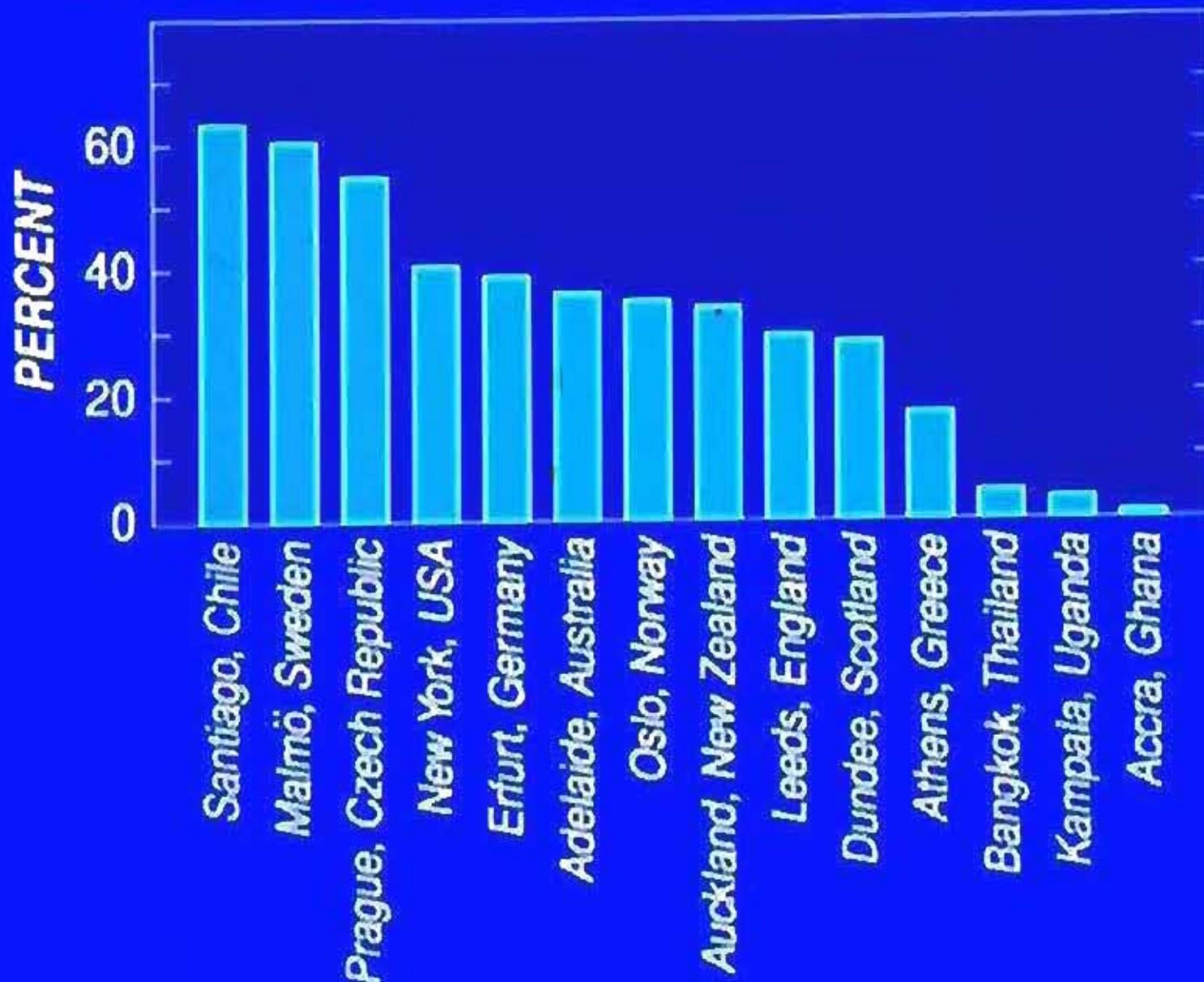
# **Pathophysiology of Bile Secretory Failure (Cholestasis)**

## **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

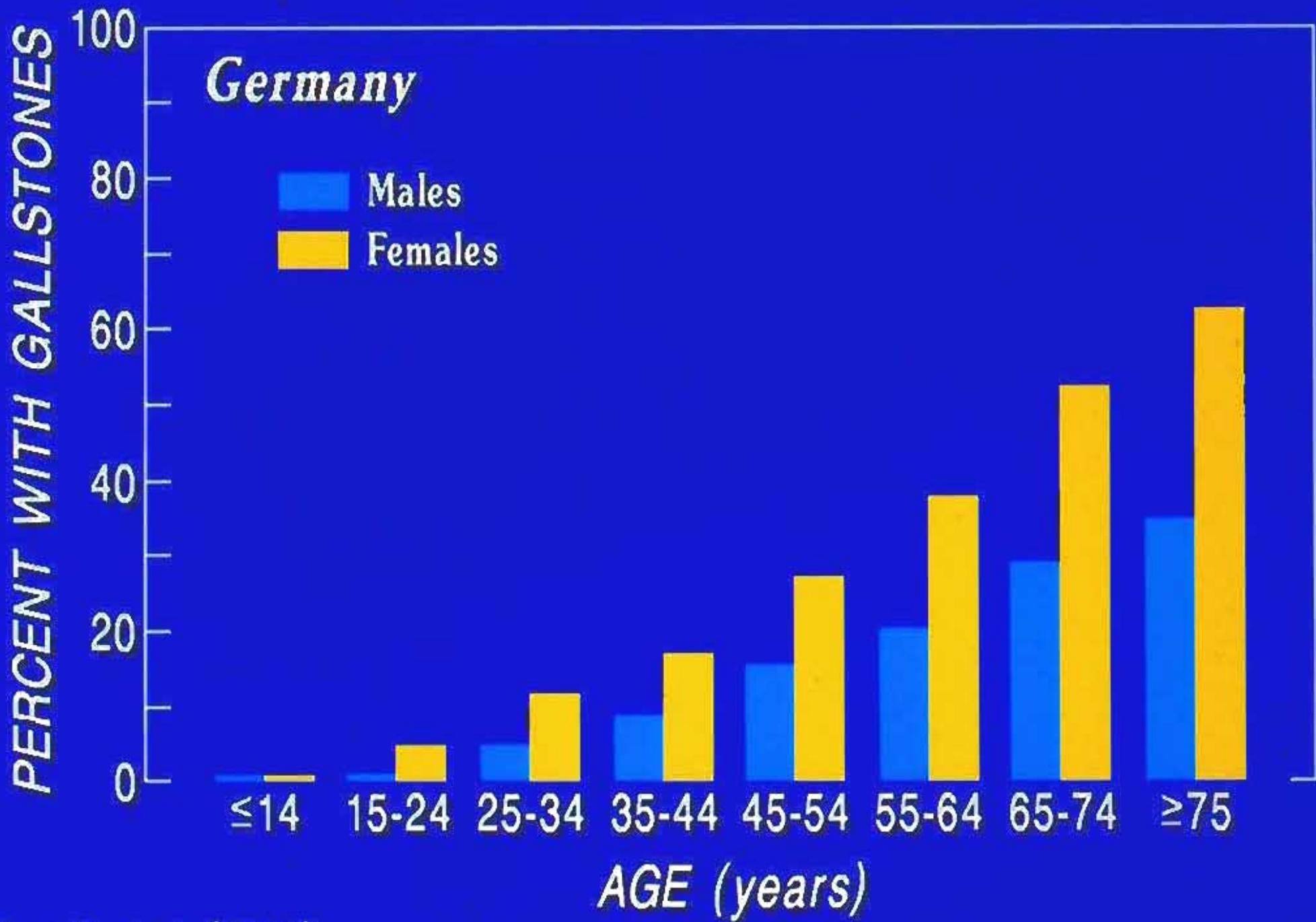
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# AUTOPSY PREVALENCE RATES OF GALLSTONES IN WOMEN (1951-1981)



Heaton, 1981

# PREVALENCE OF GALLSTONES



# FORMATION OF CHOLESTEROL GALLSTONES: KEY ELEMENTS

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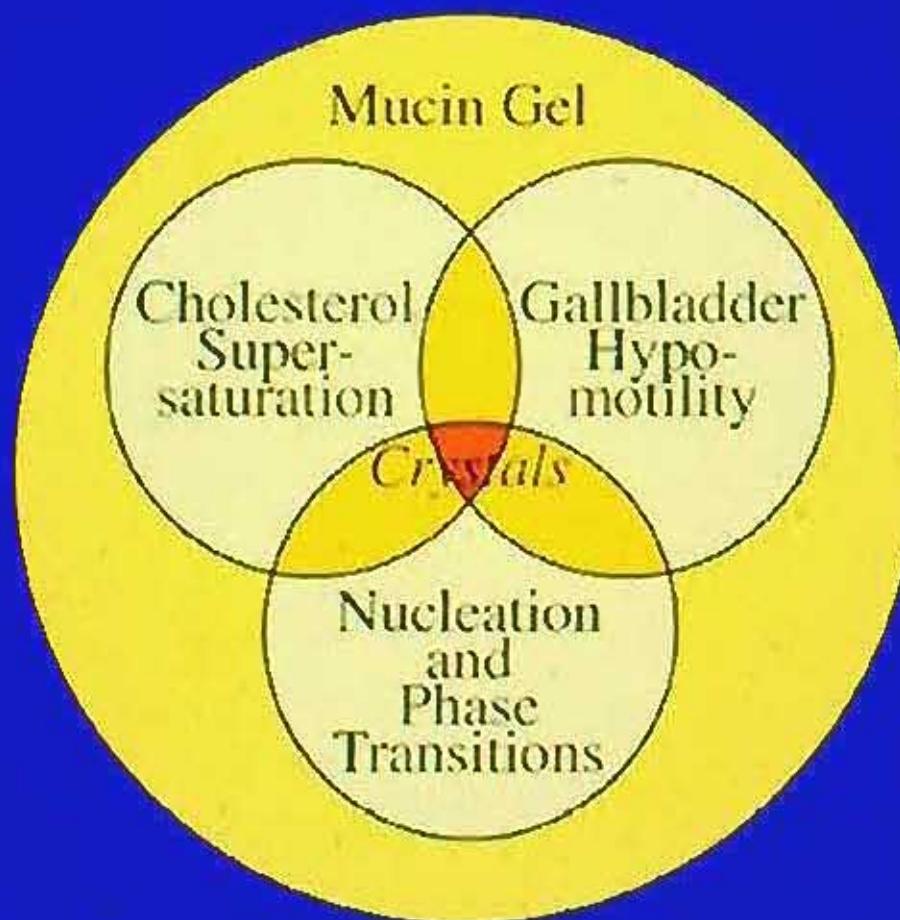


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Sömjén, G., and T. Gilat. "Cholesterol-phospholipid vesicles in human bile: an ultrastructural study." *Biochim Biophys Acta* 879 (1986): 14-21.

# Principles of Cholesterol Solubilization and Supersaturation in Bile

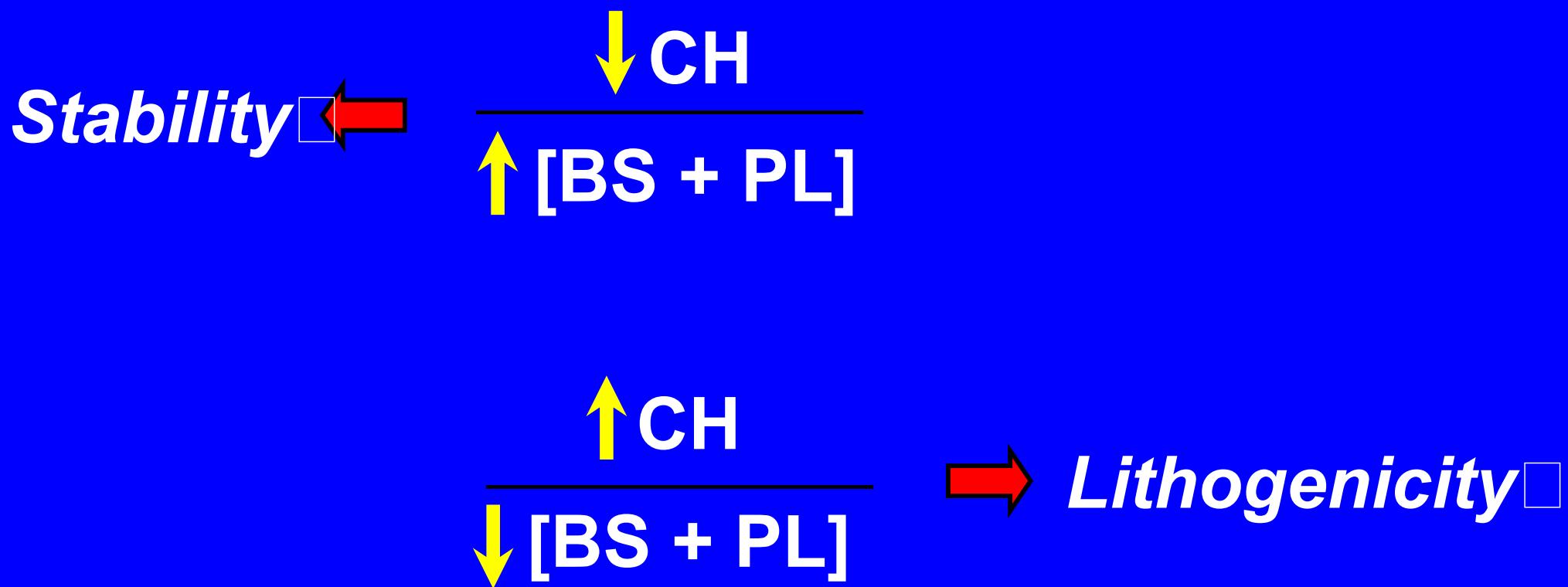


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Carey, M. C. *New Trends in Hepatology*. Edited by W. Gerok, A. S. Loginov, and V. I. Pokrowskij.  
Dordrecht, The Netherlands: Kluwer Academic Press, 1996, pp. 64-83.

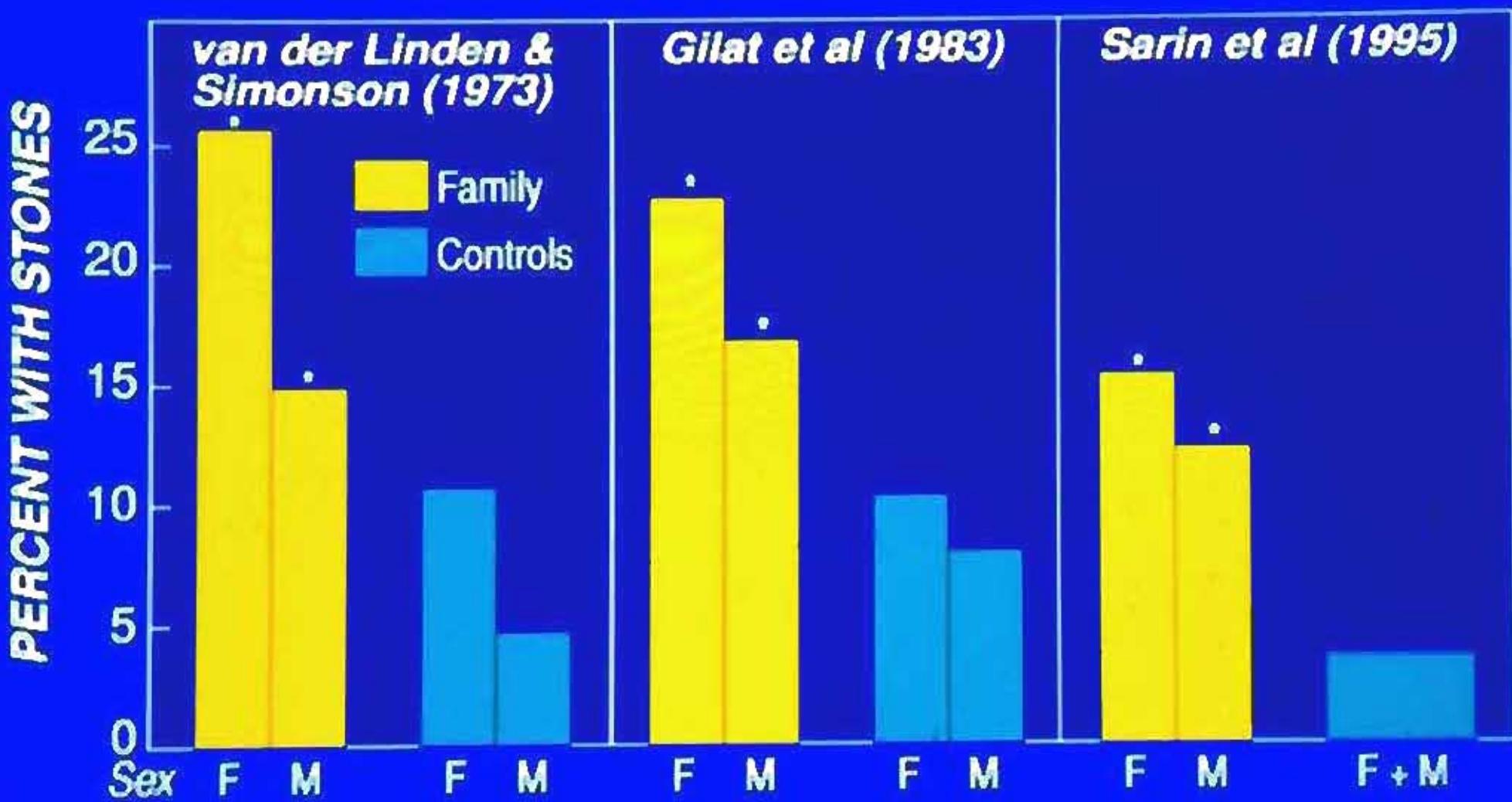
# Etiology of Cholesterol Cholelithiasis

- Genetic predisposition
  - Monogenic
  - Polygenic
- “Cholelithogenic” environment
  - Diet/ Drugs
  - Adiposity / Weight Loss
  - Gestation / Estrogens / Progestogens

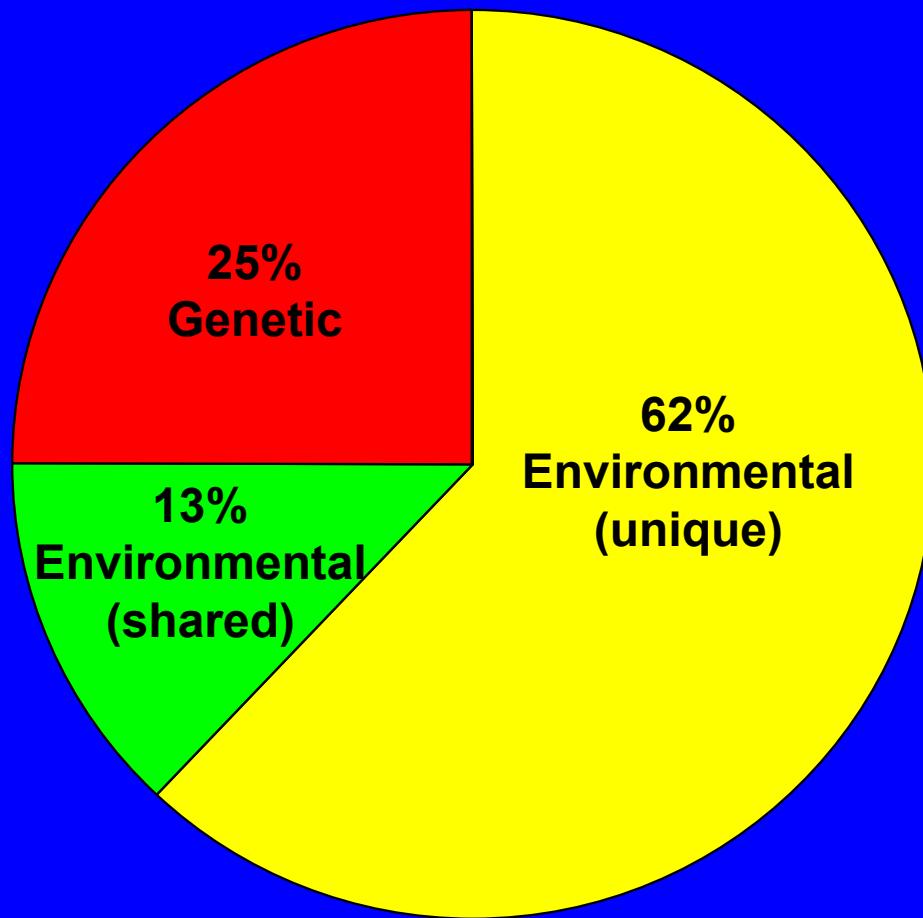
# The Genetic Factor in Human Cholesterol Gallstone Disease

- □ 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



# Genetic and Environmental Influences on Symptomatic Gallstone Disease\*



\*Katsika et al, Hepatology 2005; 41:1138-43. "A Swedish Study of 43,141 Twins"

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

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

\* J.V. Solnick & D. B. Schauer, Clin Microbiol Rev 2001; 14:59-97

## *Helicobacter hepaticus* in Liver

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# C57L Murine Cholesterol Gallstone Model: Lithogenic Diet Feeding

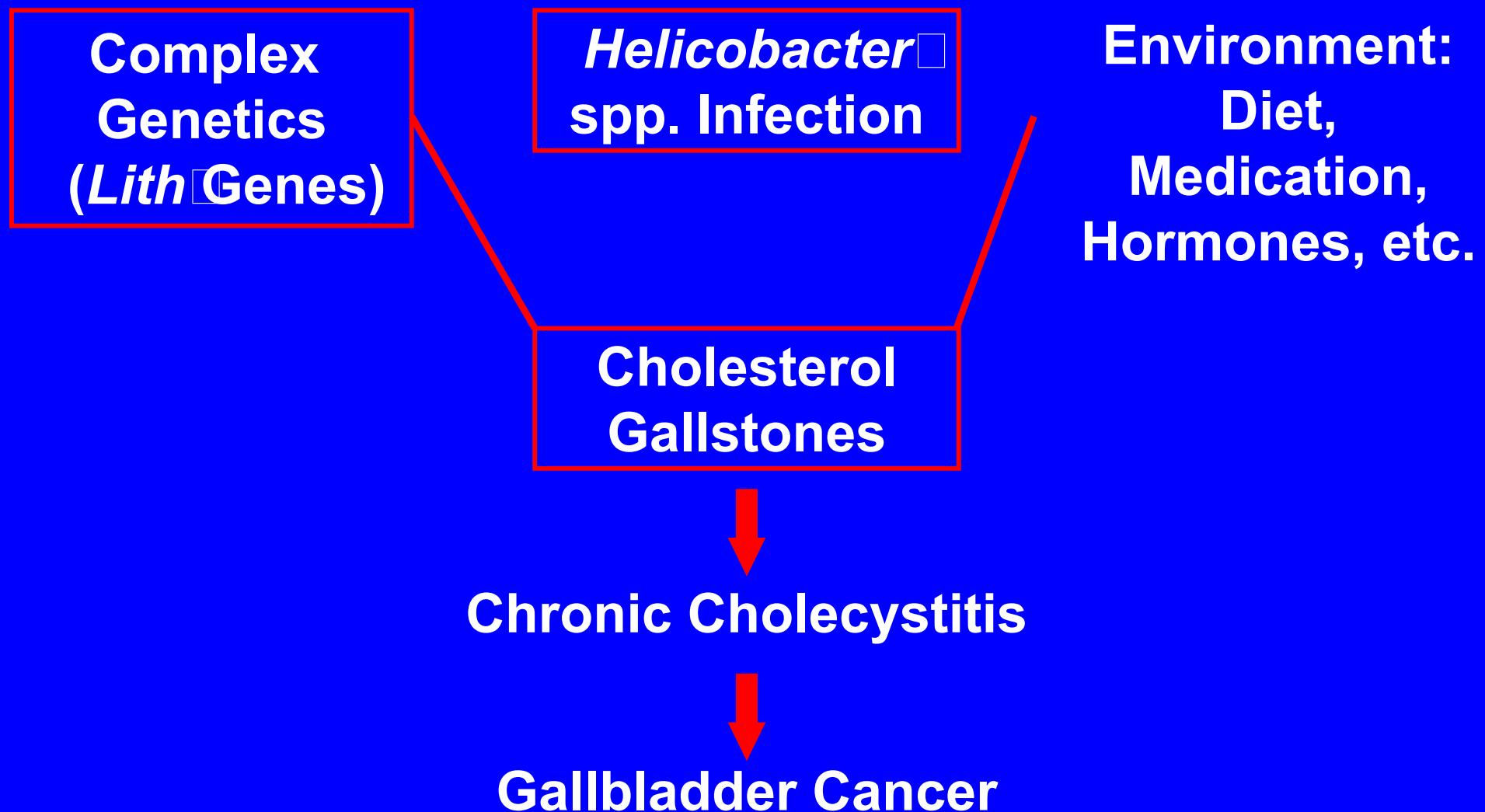
- With *Helicobacter*spp. infection



- Without *Helicobacter*spp. infection

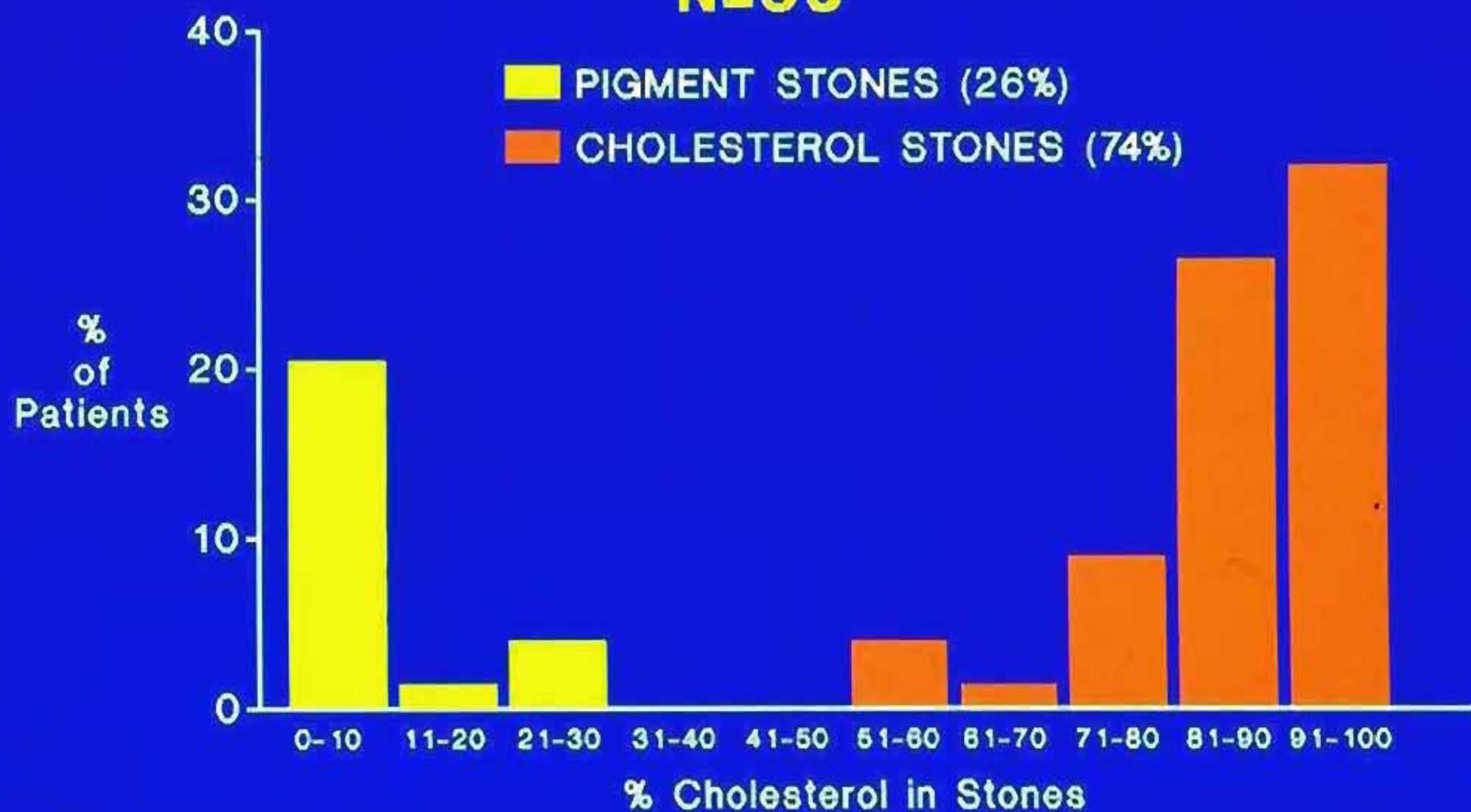


# Proposed New Paradigm for Cholesterol Gallstone Formation and Perhaps Biliary Cancer



# Frequency Distribution of Cholesterol in Gallstones

N=53



## TYPICAL ANATOMIC LOCATIONS OF PIGMENT GALLSTONES

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Cahalane, M. J., et al. "Physical-chemical pathogenesis of pigment gallstones." *Semin Liver Dis* 8 (1988): 317-28.

# CHEMICAL COMPOSITIONS OF PIGMENT GALLSTONES

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Cahalane, M. J., et al. "Physical-chemical pathogenesis of pigment gallstones." *Semin Liver Dis* 8 (1988): 317-28.

# FORMATION OF BILIRUBIN

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Ostrow, J. D., et al. In: "Hepatic Excretory Function." American Gastroenterological Association Teaching Project, Unit 1. Timonian, MD: Miller-Fenwick, 1975.

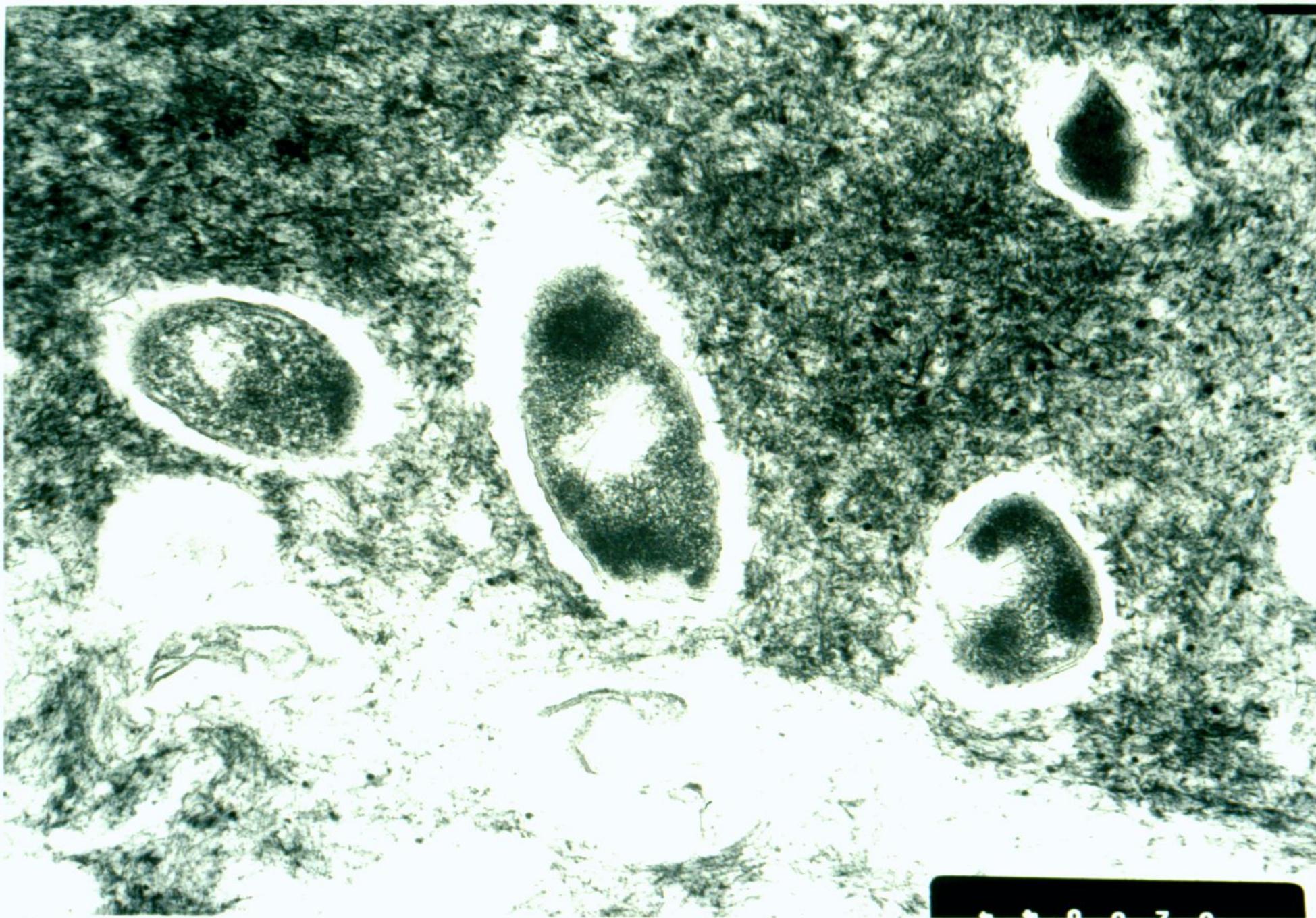
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Cahalane, M. J., et al. "Physical-chemical pathogenesis of pigment gallstones." *Semin Liver Dis* 8 (1988): 317-28.

## BROWN PIGMENT STONE FORMATION

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Cahalane, M. J., et al. "Physical-chemical pathogenesis of pigment gallstones." *Semin Liver Dis* 8 (1988): 317-28.

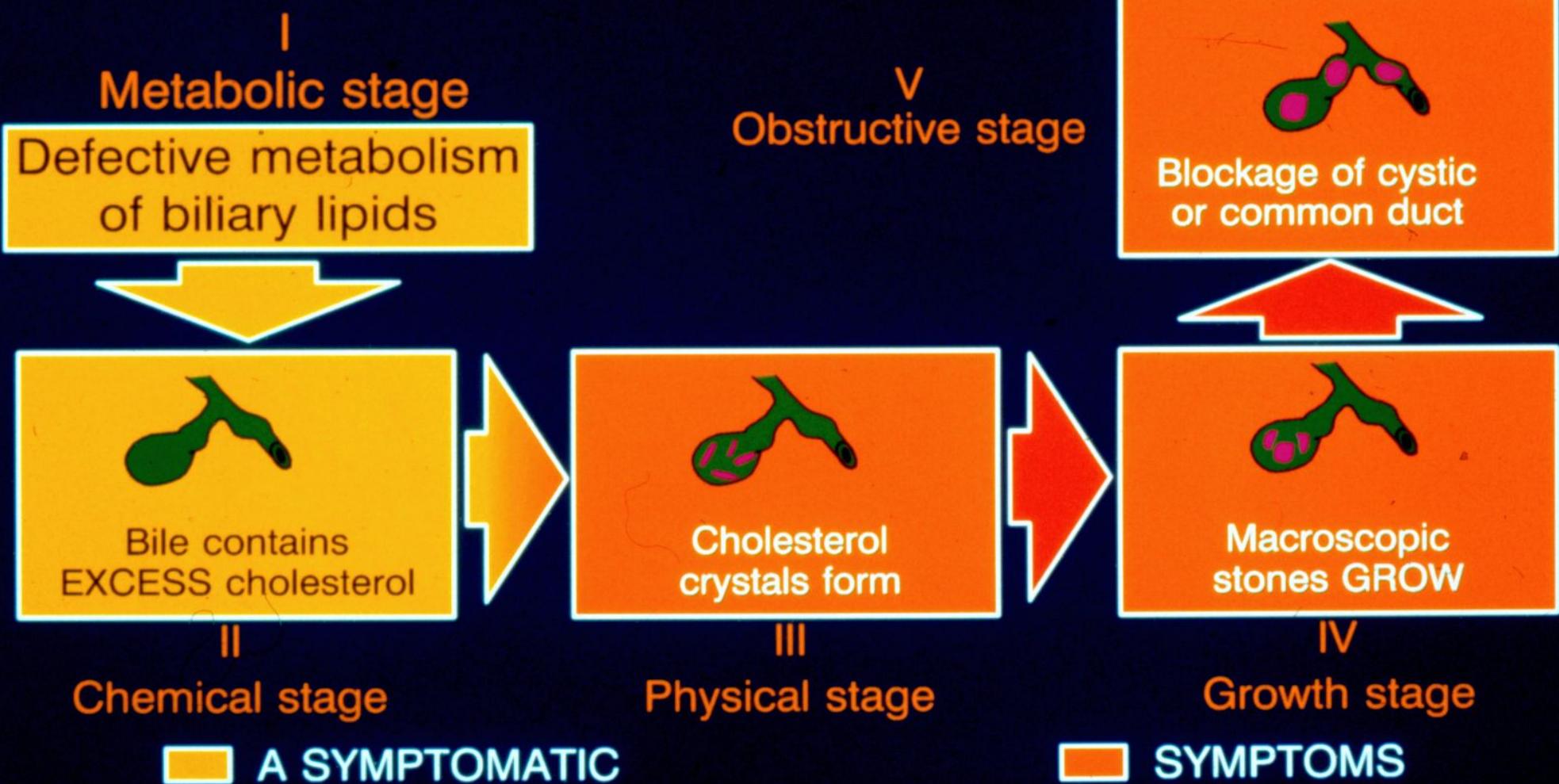


(Courtesy of Drs. Carlos Pellegrini and Lawrence Way. Used with permission.)

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# Evolution of Cholesterol Gallstones (As Currently Conceived)



(Courtesy of Professor Donald M. Small. Used with permission.)

## CHRONOBIOLOGY OF BILIARY PAIN (ITALY)

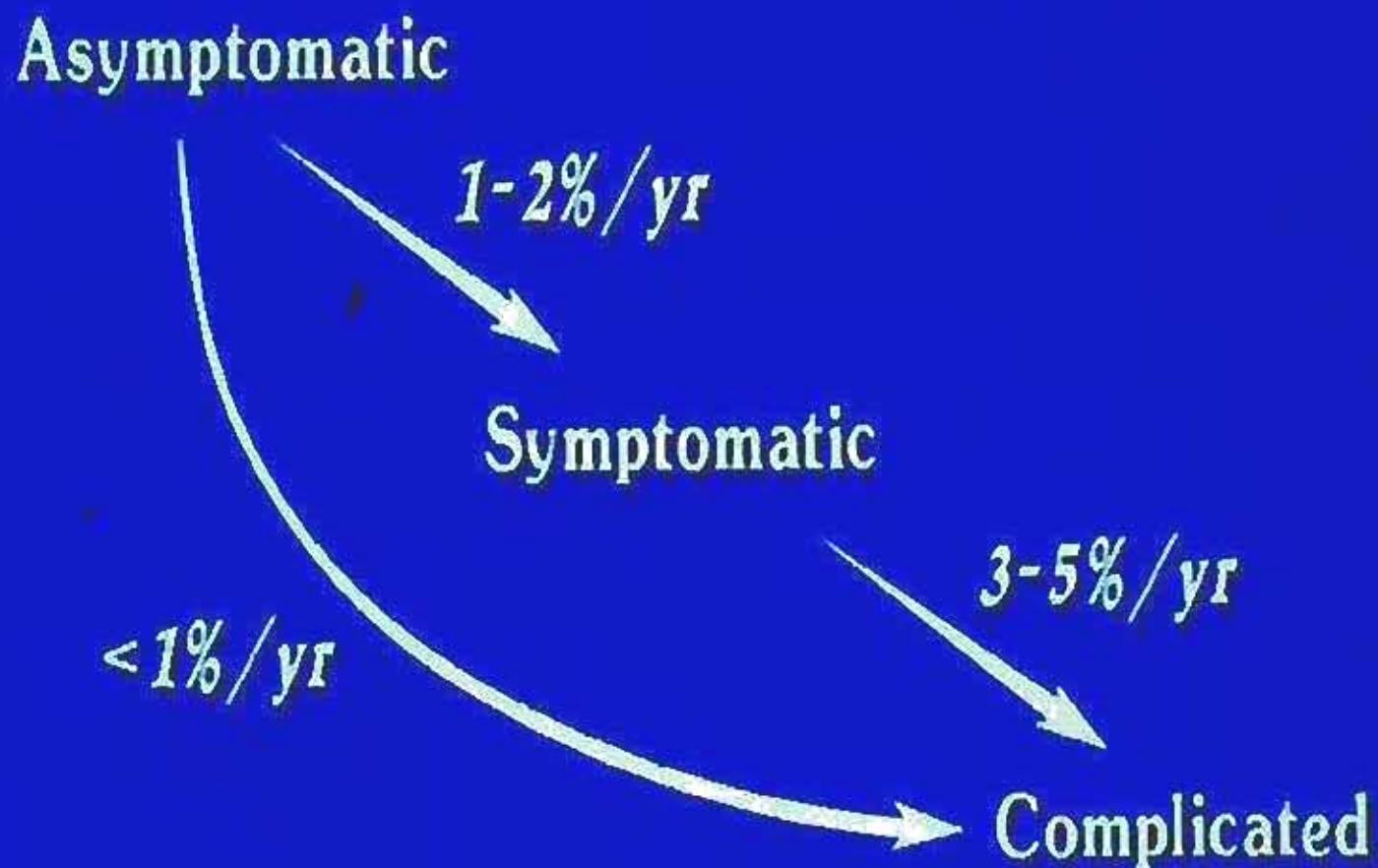
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Minoli, G., et al. "Circadian periodicity and other clinical features of biliary pain." *J Clin Gastroenterol* 13 (1991): 546-8.

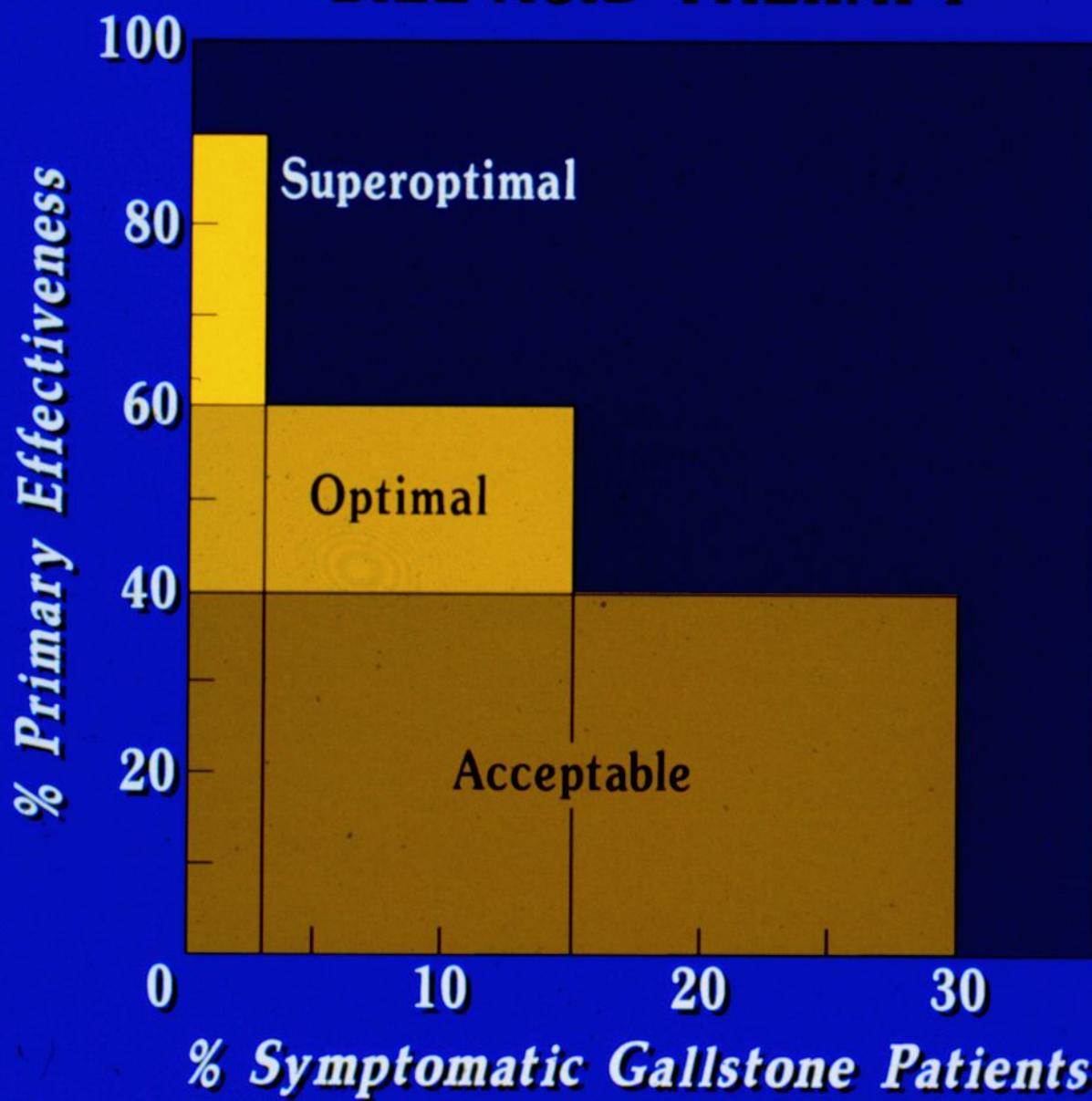
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Paigen, B., and M. C. Carey. *Genetic Basis of Common Diseases*. Edited by R. A. King, J. I. Rotter, A. G. Motulsky. 2nd ed. New York, NY: Oxford University Press, 2002, pp. 298-335.

# GALLSTONES



## BILE ACID THERAPY



Strasberg and Clavien (1992)

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

# TO AVOID GALLSTONES, A WOMAN SHOULD

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Heaton, K. W. "Cholesterol-rich gallstones." *Mol Aspects Med* 9 (1987): 89-96.



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