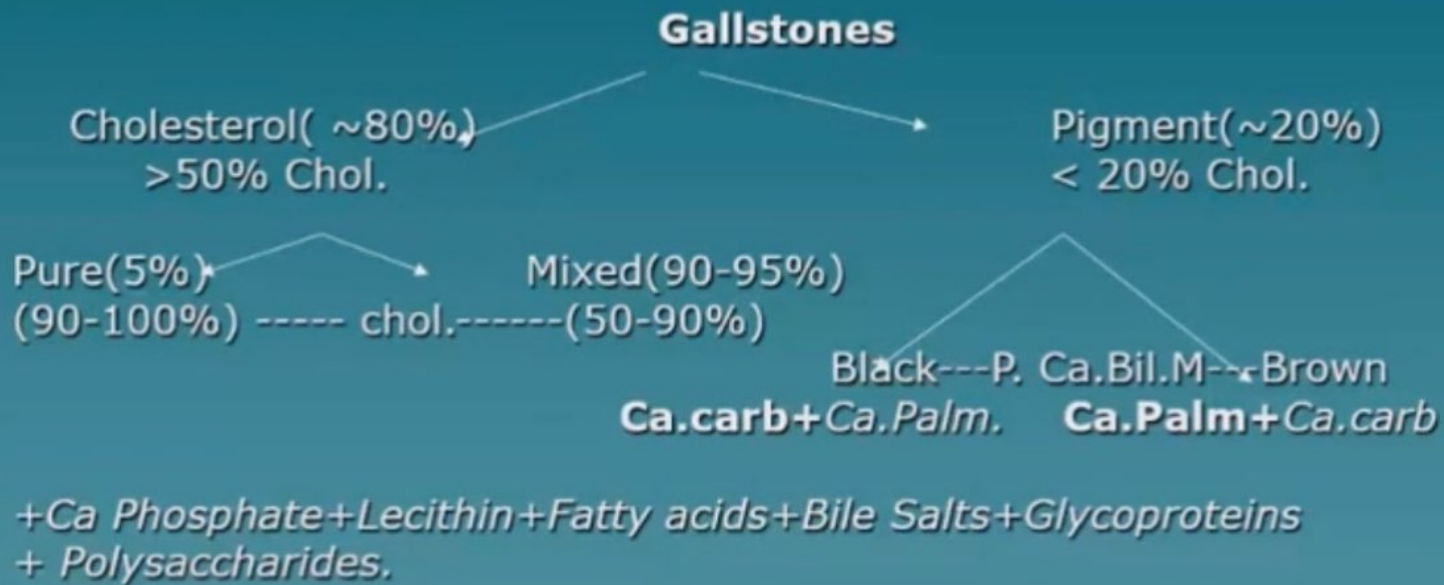
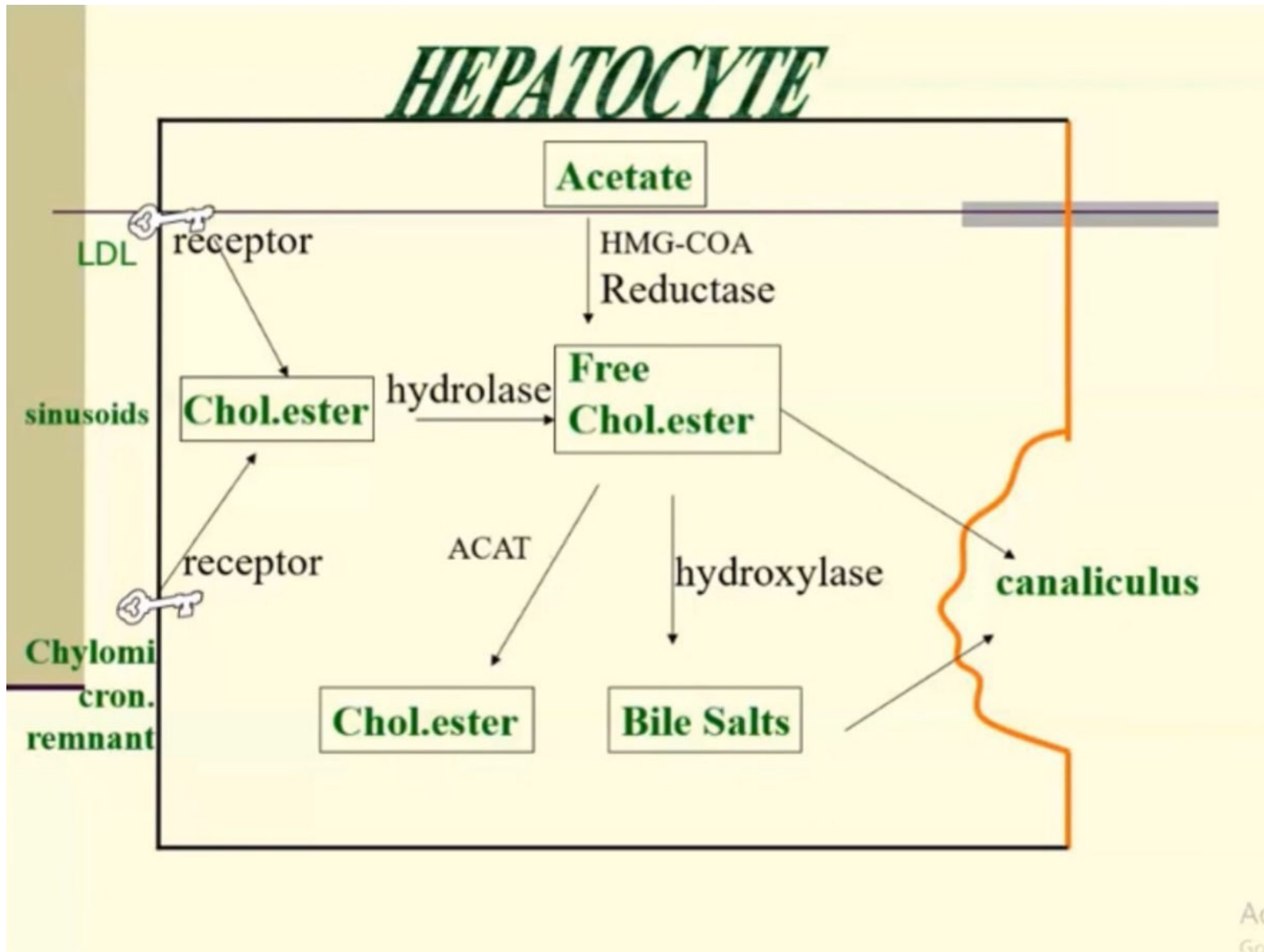


# CLASSIFICATION AND PATHOGENESIS OF GALLSTONES

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# Classification





## Important Definitions

- **Cholelithiasis:** The presence of microscopic crystals or large stones in the gallbladder.
- **Biliary sludge:** Viscous mixture of mucin glycoproteins, calcium bilirubinate, and cholesterol crystals inside the gallbladder or biliary ducts.
- **Nucleation:** Precipitation of cholesterol crystals from saturated bile.

## Mechanism of formation: 1) Solubilization

- ◆ **Cholesterol is a hydrophobic lipid.**
- ◆ **Micelles:**
  - ✓ *Simple.*
  - ✓ *Mixed(multilamellar).*
  - ✓ *Vesicles.*



## Epidemiologic facts

- 30 million Americans (10% of US population)
- Women are diagnosed with gallstones 2-3x more often than men of the same age
- Gallstones are found in 50% women and 16% men in their 70s
- 80% of women and men in their 90s
- Two-thirds of gallstones are asymptomatic
- Incidentally found on imaging studies or postmortem

## Types of Gallstones

• Majority of Gallstones 70-80%

Cholesterol stones (contain >50% cholesterol)

20-30%

Black and Brown pigment stones (contain <20% cholesterol)

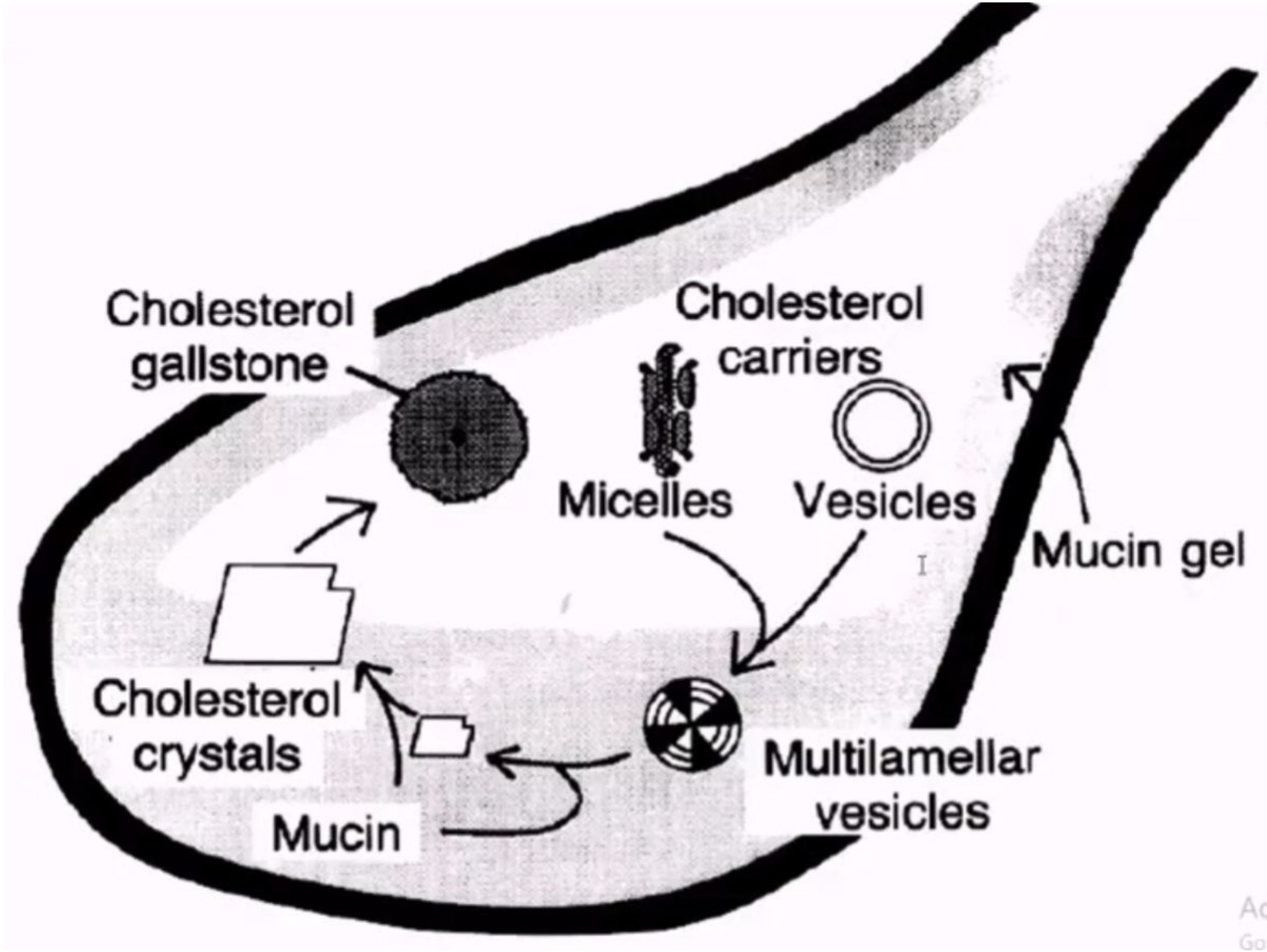
## Pathogenesis of Cholesterol Gallstone

- Cholesterol is carried in micelles and vesicles
- Micelles: An aggregate of phospholipid, bile salts, and cholesterol.
- Vesicle: Spherical bilayers of phospholipid with associated cholesterol.
- At higher cholesterol levels
  - ✓Increased amount of cholesterol are carried in vesicles
  - ✓Micelles and vesicles fuse to form Multilamellar vesicle.



## Pathogenesis of Cholesterol Gallstone

- *Multilamellar vesicle:*
  - ✓ Cholesterol crystals grow and agglomerate on vesicle membrane
  - ✓ Mucin Proteins entrap lipid vesicles and micelles forms multilamellar vesicles



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## 2)Cholesterol Saturation

- ◆ Increased secretion of cholesterol.
- ◆ Decreased secretion of bile salts.
- ◆ Decreased secretion of lecithin.

## 3)Nucleation

- Definition:
  - ✓ Is the emergence of solid crystals of cholesterol monohydrate from a saturated solution of cholesterol.
- Nucleation time.

## 4)Stone growth

Aggregation of crystals +calcium+mucous glycoproteins(1-2mm/year).

# Role of the Gallbladder

Form primarily in the GB ,rarely recurs following cholecystectomy.

- Impaired absorptive capacity :  
↑tendency of nucleation.
- Impaired secretion: lack of bile acidification→ precipitation of Ca palmitate+ Ca bilirubinate+Ca carbonate→Nidus.



# Role of the Gallbladder

## 3. Impaired motility:

- ✓ Impaired contraction: → ↑fasting volume → ↑residual volume → ↓rate of emptying → ► stasis. (obesity, pregnancy, DM, TPN, post-gastrectomy).
- ✓ Accelerated emptying → ► shrinkage of bile acid pool → saturated bile.

## Risk Factors

### **Elevated Estrogens:**

- ✓ *Increase biliary cholesterol saturation*
- ✓ *Endogeneous-puberty & pregnancy*
- ✓ *Exogeneous-OC &HRT*

### **Obesity:**

- ✓ *Increases activity of HMG-CoA reductase with expansion of the*
- ✓ *hepatic free cholesterol pool*
- ✓ *Hypersaturation of bile with cholesterol*

## Risk Factors

### **Rapid Weight loss:**

- ✓ *Increases cholesterol excretion in bile*
- ✓ *Gallbladder stasis secondary to fat restricting diet*

### **Spinal cord injury & disease with terminal ileum:**

- ✓ *Gallbladder stasis*



## Risk Factors

### Age

✓ *Decline in the activity of cholesterol 7-alpha hydroxylase*

*Leads to an increase in cholesterol saturation.*

### Hyperlipidemia.

### Intestinal hypomotility

✓ *Viral, drug induced, diabetes*

✓ *Increased production of lithogenic secondary bile acids*

*(deoxycholate)*

### Long term parenteral nutrition

✓ *Prolonged stasis of bile*

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## Risk Factors: Medications

- **Ceftriaxone(Rocephin)**

- ✓ *Precipitates with calcium in bile to form biliary sludge & stones*
- ✓ *25-46% pts develop sludge*
- ✓ *Biliary symptoms develop in 19% of pts*
- ✓ *Resolves in most cases after cessation of therapy*
- ✓ *Pts with Long term therapy (Lyme's) 1.8% developed GB dz*  
*(More than half underwent cholecystectomy)*
- ✓ *Dose of greater than 2g per day*



## Risk Factors: Medications

- **Octreotide:**

- ✓ *Treatment for Acromegaly*

- (67% noted to have gallbladder sludge after 1 yr of treatment)

- ✓ *Alter bile flow*

- ✓ *Concentrate bile*

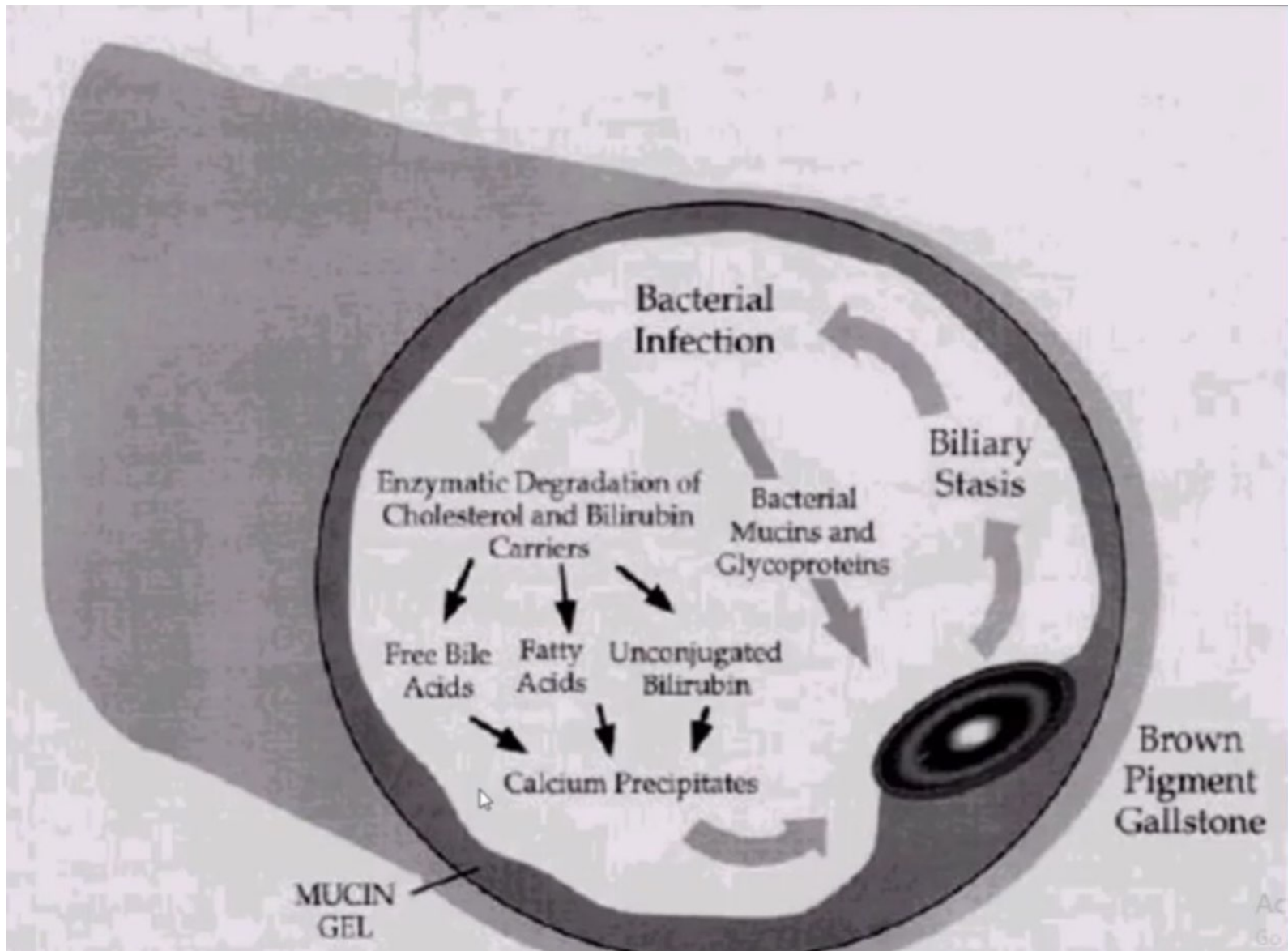
- ✓ *Inhibit postprandial bile secretion*

## Pathogenesis of Brown Pigmented Gallstone

- Increased Enzyme *Beta-Glucuronidase*
- ✓ Chronic low grade infection
- ✓ Inflammation of Biliary tree
- ✓ Formation of monoglucuronide and unconjugated forms  
Precipitates as Calcium salts
- 15% of these gallstones are calcified enough to be seen  
on plain abdominal film
- Primary bile duct stone

## Conditions predisposing to brown stones

- ◆ Oriental cholangiohepatitis.
- ◆ Choledochal cyst.
- ◆ B.strictures.
- ◆ Sphincterotomy.
- ◆ Periapillary diverticulum.
- ◆ Polycystic disease.

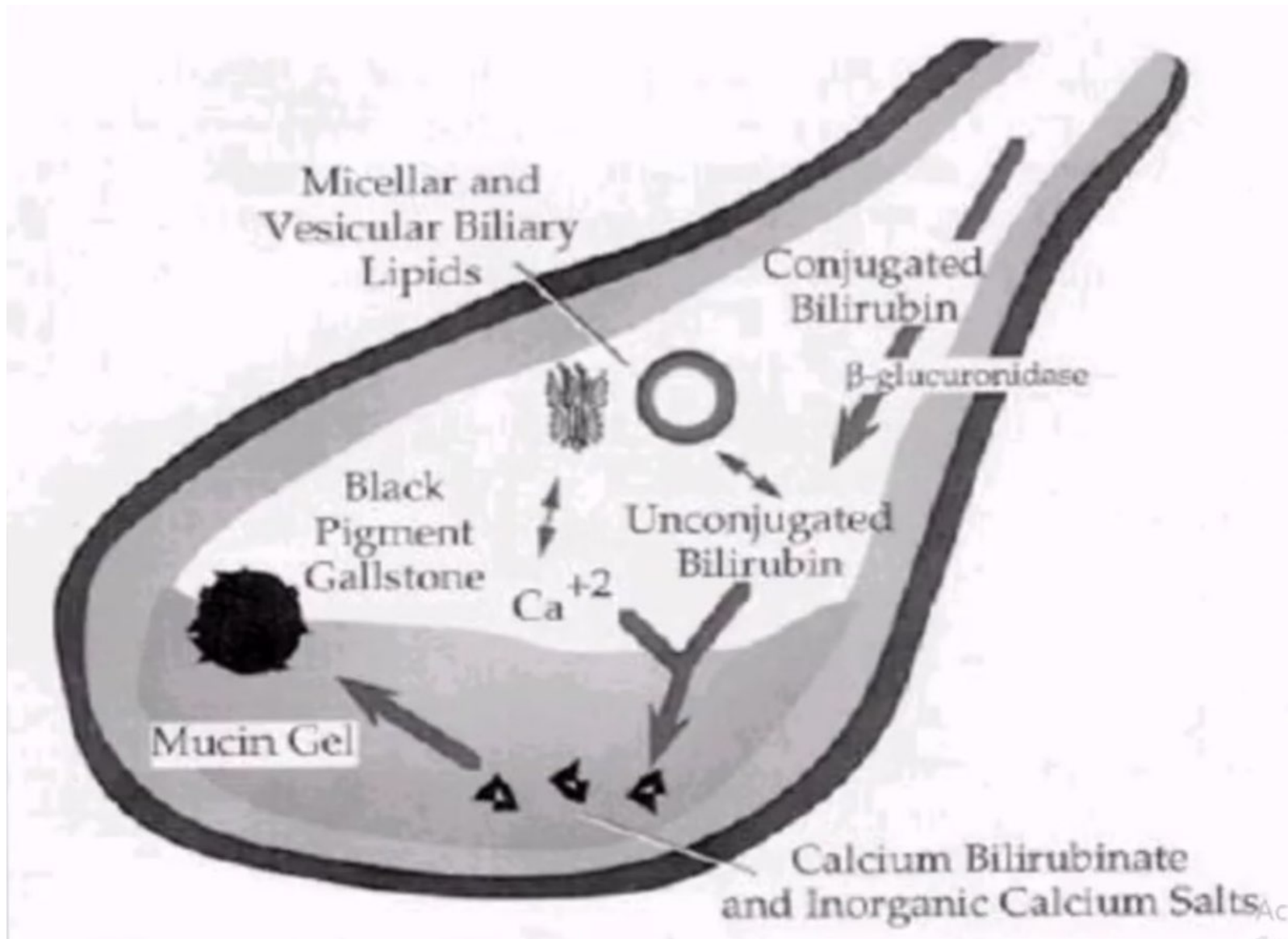


# Pathogenesis of Black Pigment Gallstones

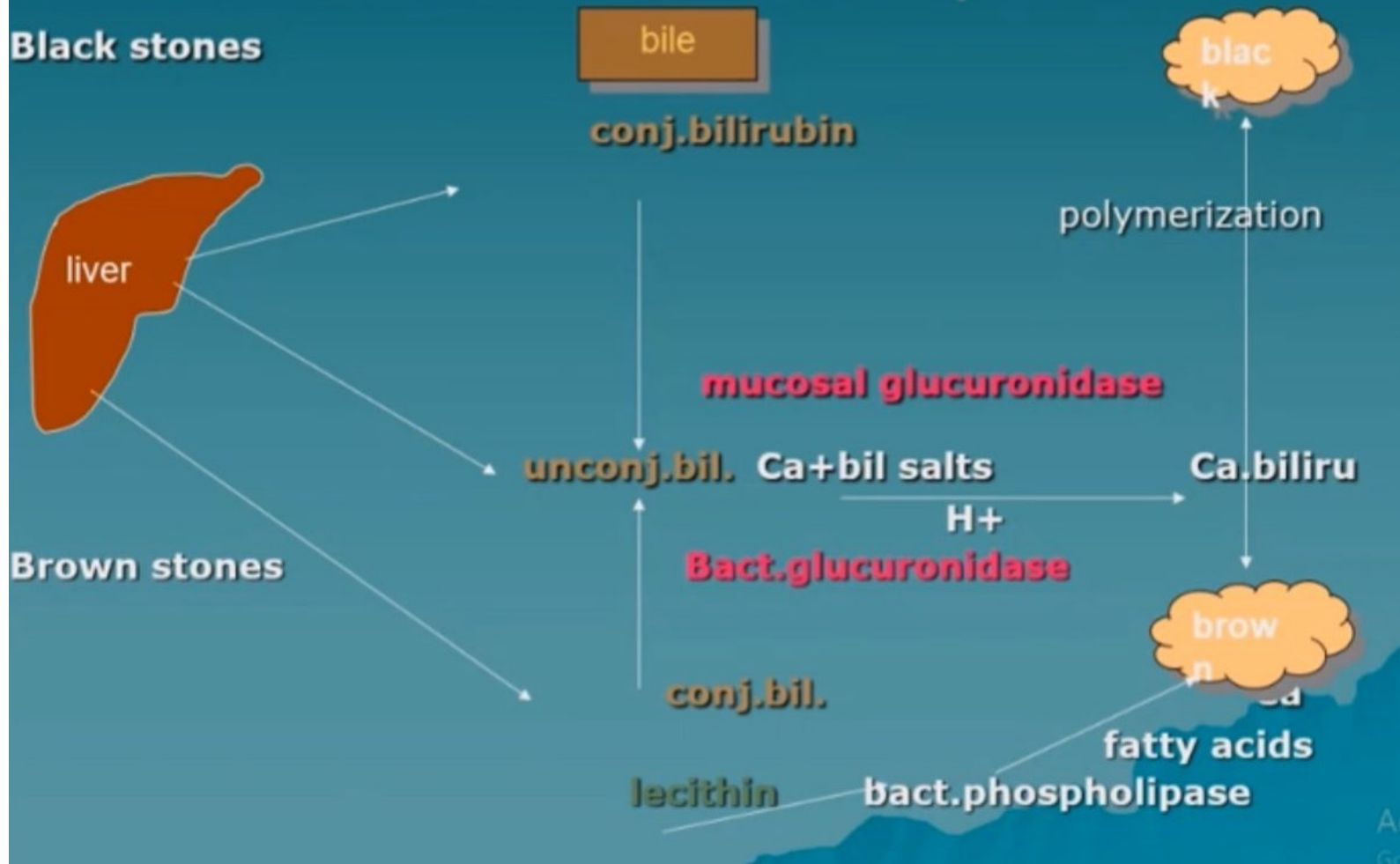
## *High levels of Bilirubin:*

- Cirrhosis
- Chronic Hemolytic diseases
  - Sickle cell anemia
  - Thalassemia
- Ileal resection





# Pathogenesis of Pigment stones



## Metabolic & Physiological Factors

- ***Cholesterol hypersecretion:***

- ✓ *Gallbladder hypomotility*

- ✓ *Increased mucin secretion*

- ***Hypersaturation of bile:***

- ***Increased activity of pronucleating factors:***

*N-aminopeptide, phospholipase C, fibronectin, immunoglobulins*

*G&M, alpha1 acid glycoprotein, haptoglobin,*

*alpha1 antichymotrypsin, apo A-1*

- ***Diminished gallbladder contractility***

- ***Delayed intestinal transit time***