CLASSIFICATION AND PATHOGENESIS OF GALLSTONES

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Classification

Gallstones

Cholesterol(~80%)
>50% Chol.

Pigment(~20%)
< 20% Chol.

Pure(5%)
(90-100%) ----- chol.------(50-90%)

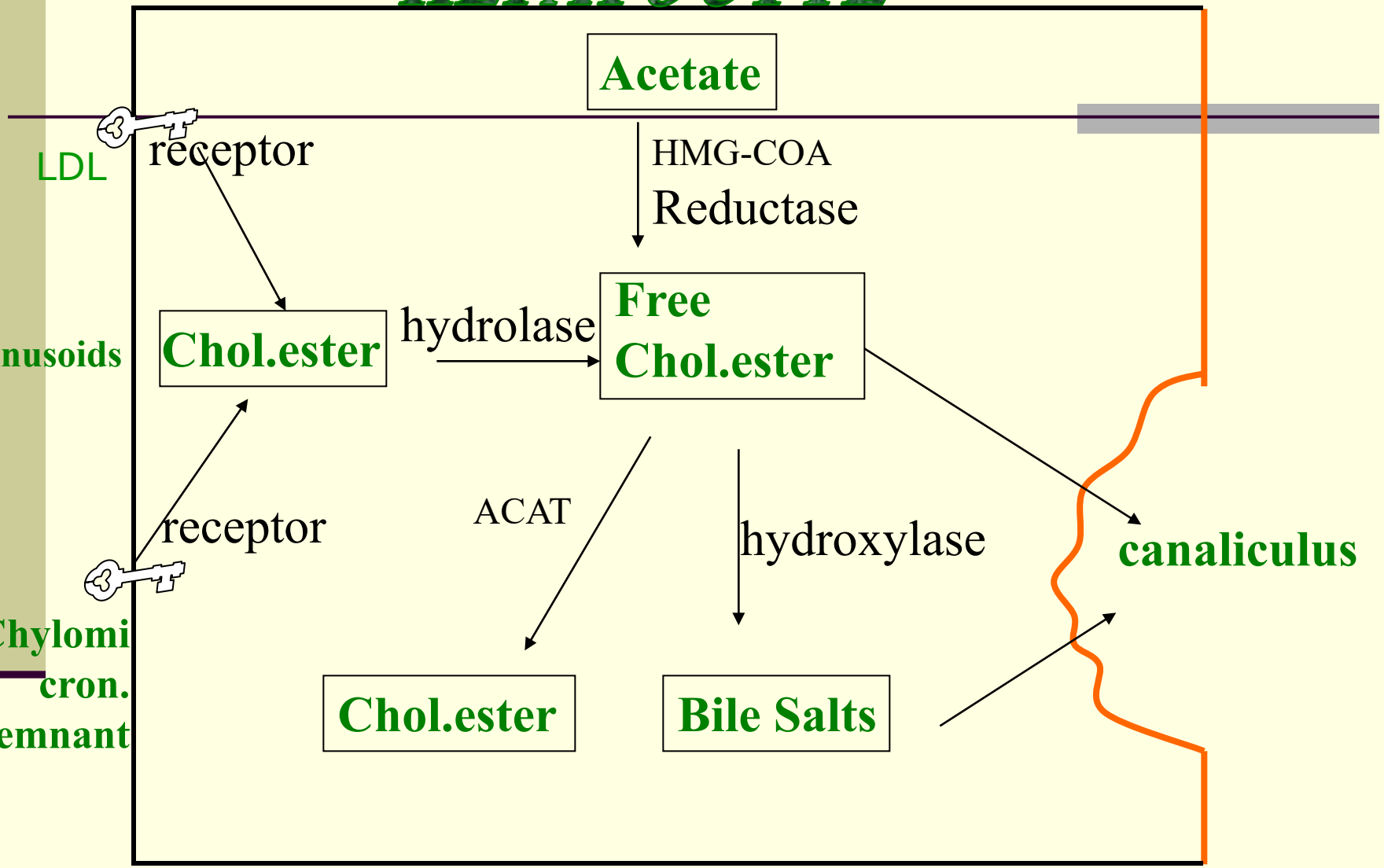
Mixed(90-95%)

Black---P. Ca.Bil.M---Brown

Ca.carb+*Ca.Palm.* **Ca.Palm+***Ca.carb*

+Ca Phosphate+Lecithin+Fatty acids+Bile Salts+Glycoproteins + Polysaccharides.

HEPATOCYTE


Acetate
LDL
receptor
HMG-COA
Reductase
sinusoids
Chol.ester
hydrolase
Free
Chol.ester
receptor
ACAT
hydroxylase
canaliculus
Chylomi
cron.
remnant
Chol.ester
Bile Salts

Important Definitions

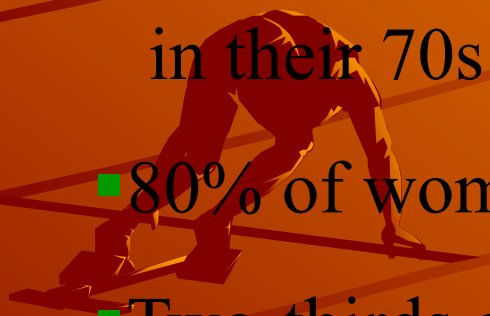
- Cholelithiasis: The presence of microscopic crystals or large stones in the gallbladder.
- Biliary sludge:Viscous mixture of mucin glycoproteins, calcium bilirubinate, and cholesterol crystals inside the gallbladder or biliary ducts.
- Nucleation: Precipitation of cholesterol crystals from saturated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



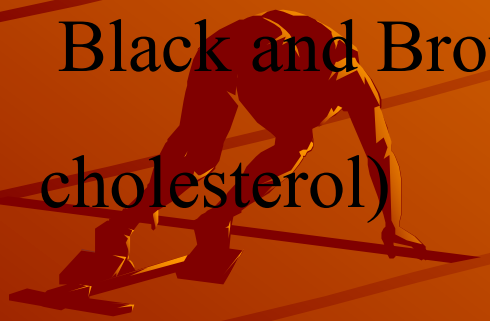
Types of Gallstones

- **Majority of Gallstones 70-80%**

  Cholesterol stones (contain >50% cholesterol)

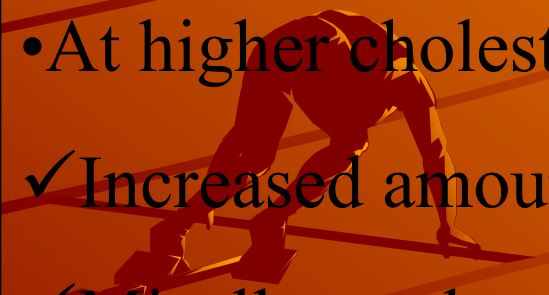
- **20-30%**

  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, cholesterol.
- Vesicle: Spherical bilayers of phospholipid with associated cholesterol.
- At higher cholesterol levels



✓Increased amount of cholesterol are carried in vesicles

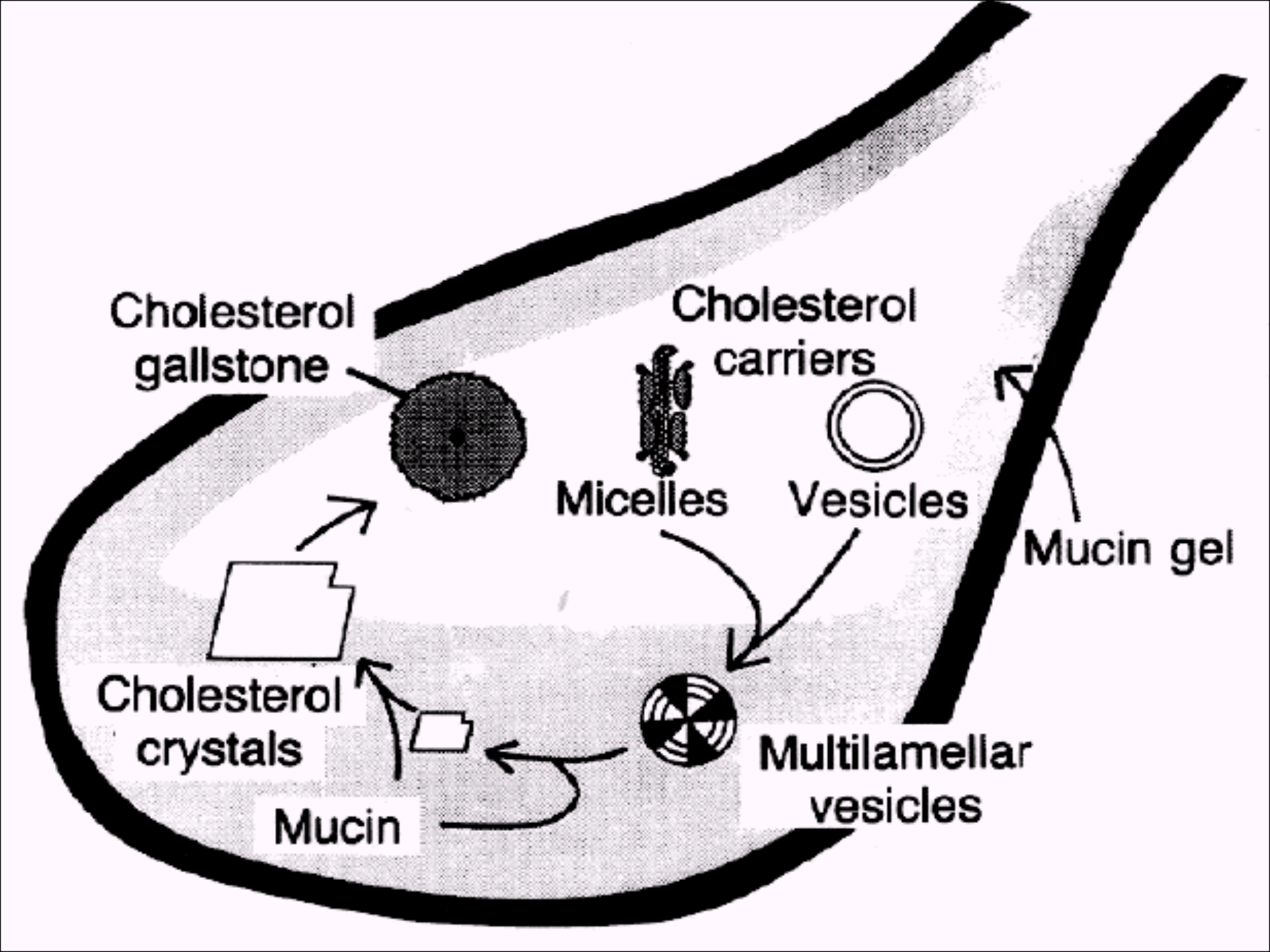
✓Micelles and vesicles fuse to form Multilamellar vesicle.

Pathogenesis of Cholesterol Gallstone

- ***Multilamellar vesicle***:

✓ Cholesterol crystals grow and agglomerate on vesicle membrane

✓Mucin Proteins entrap lipid vesicles and micelles forms multilamellar vesicles


Cholesterol gallstone
Cholesterol carriers
Micelles
Vesicles
Mucin gel
Cholesterol crystals
Multilamellar vesicles
Mucin

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***

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***

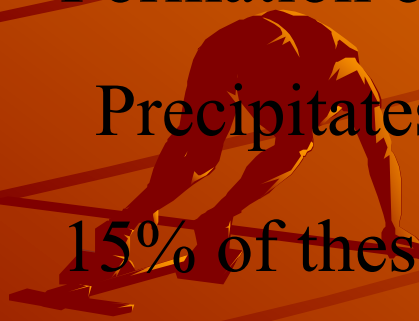
Pathogenesis of Brown Pigmented Gallstone

- Increased Enzyme ***Beta-Glucuronidase***

✓ Chronic low grade infection

✓ Inflammation of Biliary tree

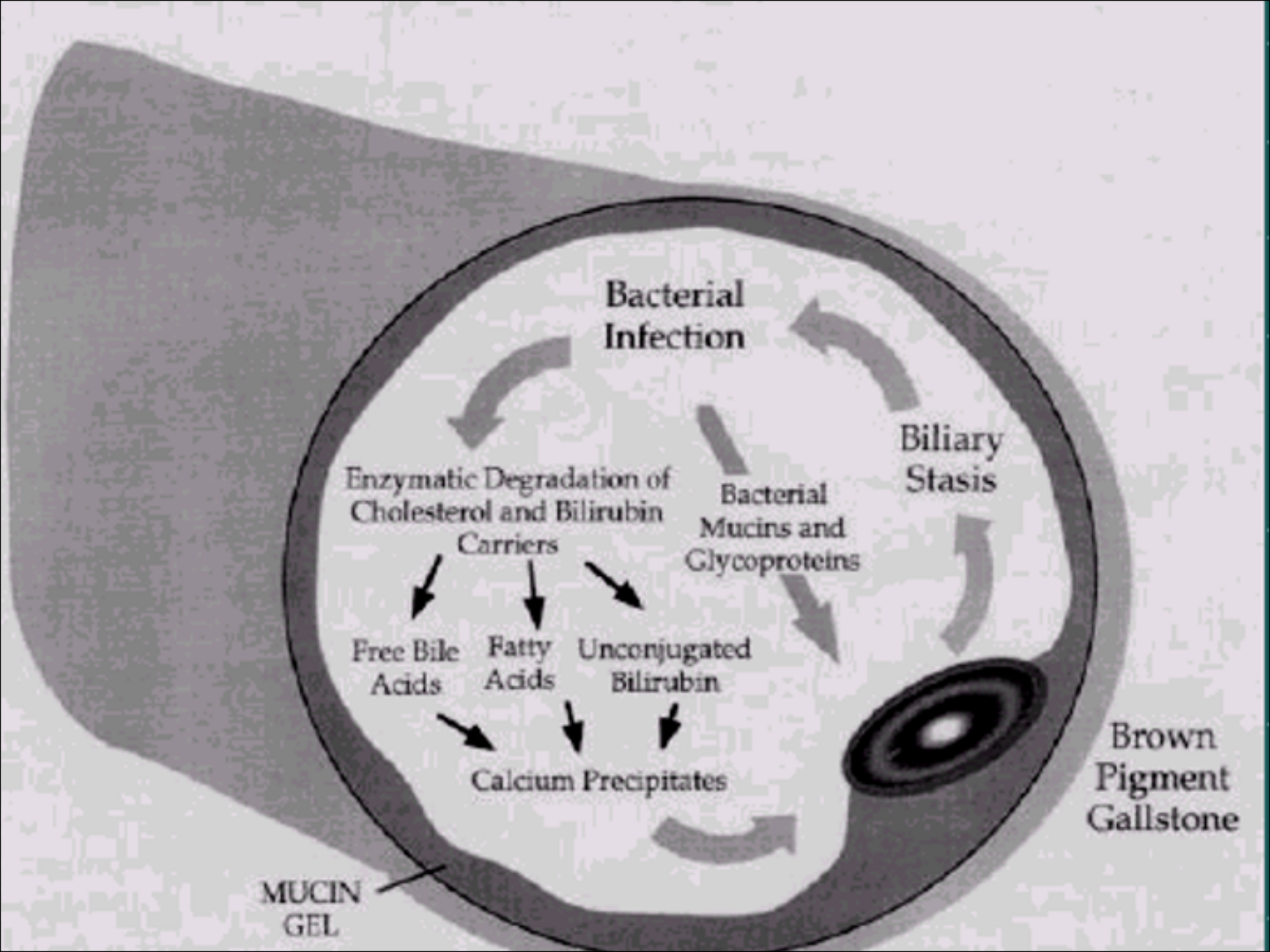
✓ Formation of monoglucuronide and unconjugated forms Precipitates as Calcium salts



- 15% of these gallstones are calcified enough to be seen on plain abdominal film
- Primary bile duct stone

Conditions predisposing to brown stones

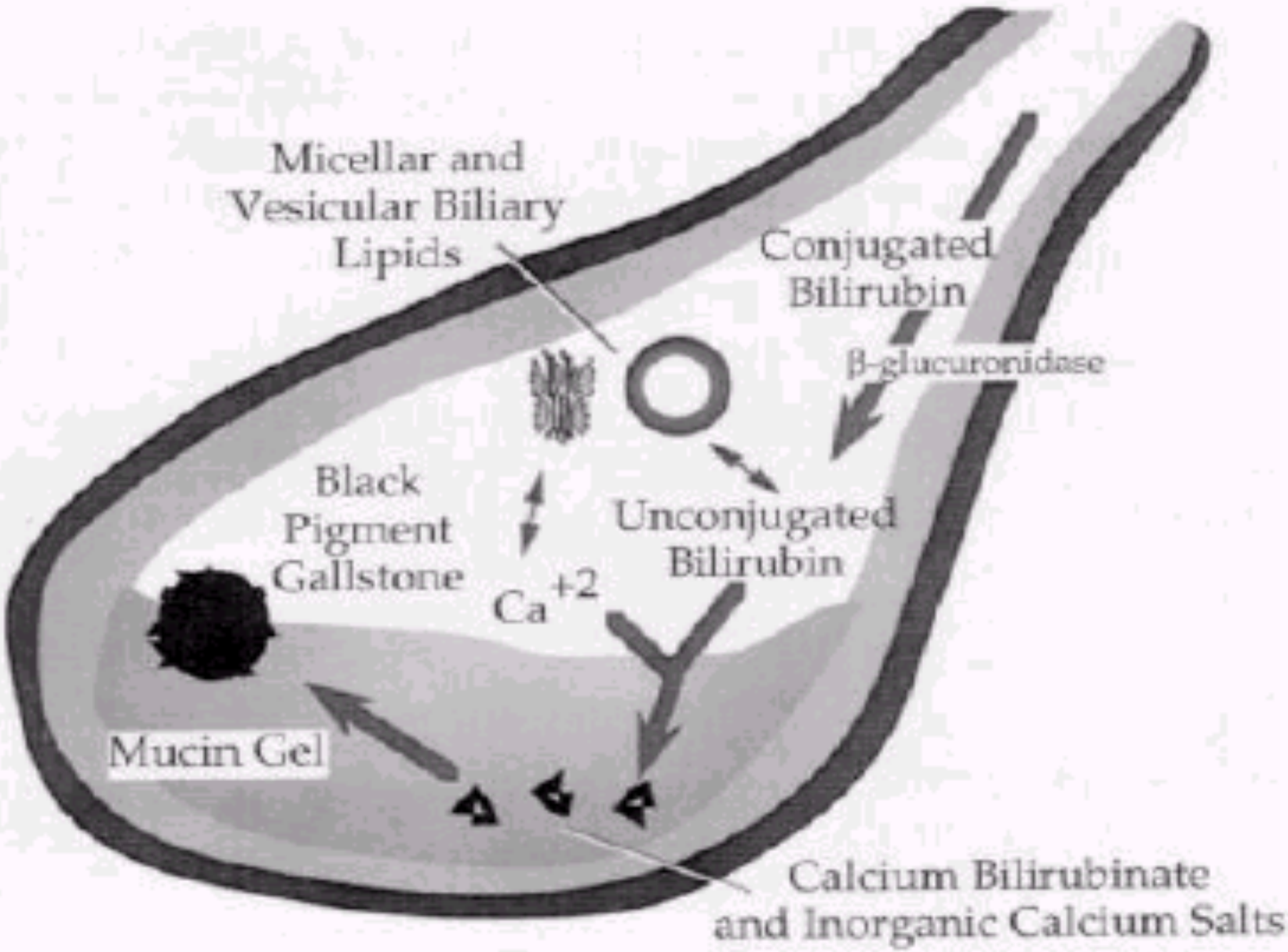
- Oriental cholangiohepatitis.
- Choledochal cyst.
- B.strictures.
- Sphincterotomy.
- Periampullary diverticulum.
- Polycystic disease.


Bacterial Infection
Biliary Stasis
Enzymatic Degradation of Cholesterol and Bilirubin Carriers
Bacterial Mucins and Glycoproteins
Free Bile Acids
Fatty Acids
Unconjugated Bilirubin
Calcium Precipitates
Brown Pigment Gallstone
MUCIN GEL

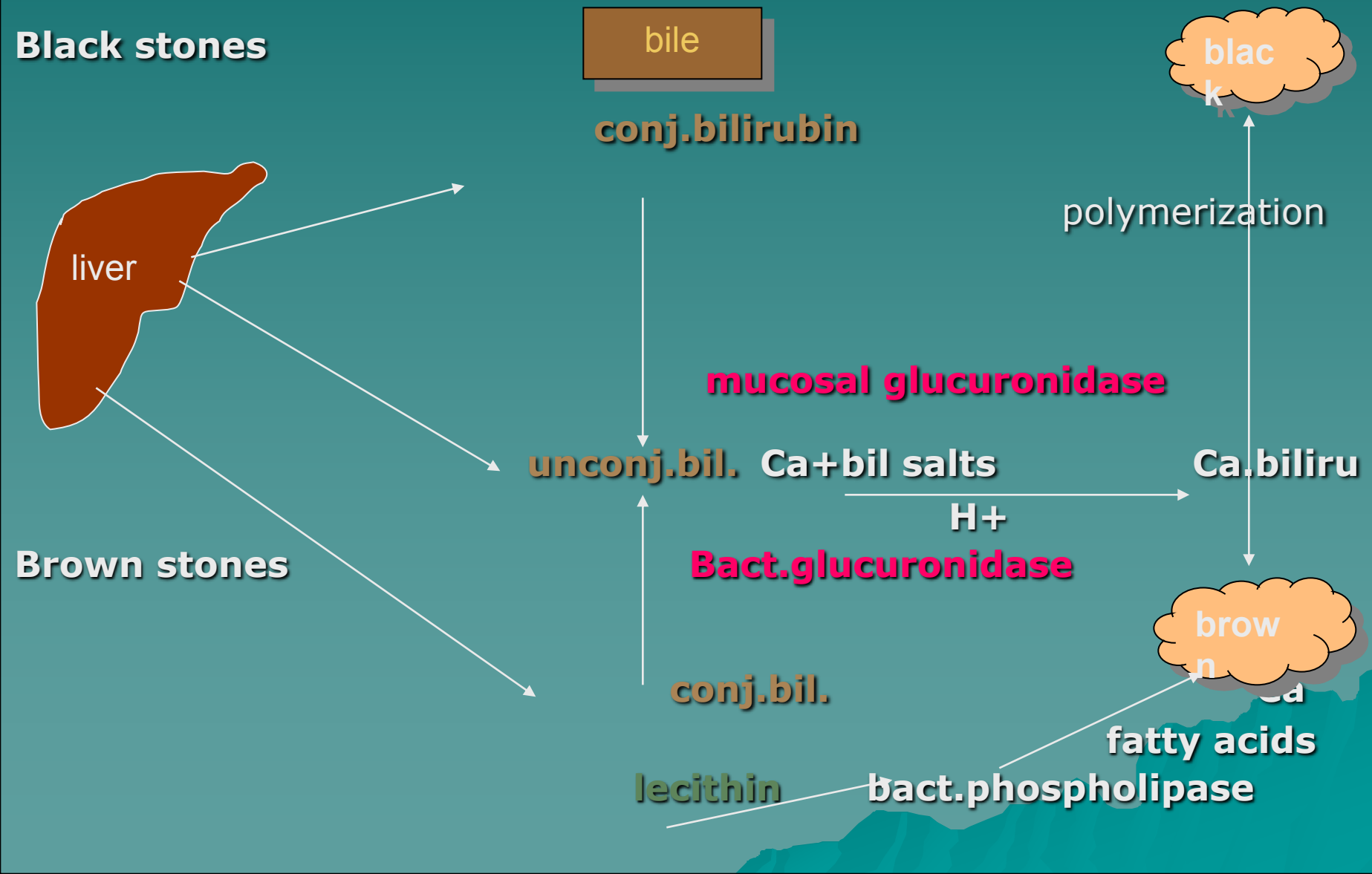
Pathogenesis of Black Pigment Gallstones

High levels of Bilirubin:

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


Micellar and
Vesicular Biliary
Lipids
Conjugated
Bilirubin
β-glucuronidase
Black
Pigment
Gallstone
Ca+2
Unconjugated
Bilirubin
Mucin Gel
Calcium Bilirubinate
and Inorganic Calcium Salts

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, alpha1antichymotrypsin,apo A-1

- ***Diminished gallbladder contractility***

- ***Delayed intestinal transit time***