

איך טיפול נולד...

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GALLSTONE DISEASE

Among the most common and costly digestive diseases:

- **Prevalence 10-20% of population**
- **#2 GI cause of hospitalization (US)**
- **~5% of the total health budget**



LAP CHOLECYSTECTOMY

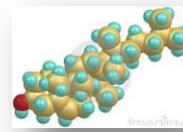
Morbidity 0.6-12% (major 2%)

Mortality (0.1%)

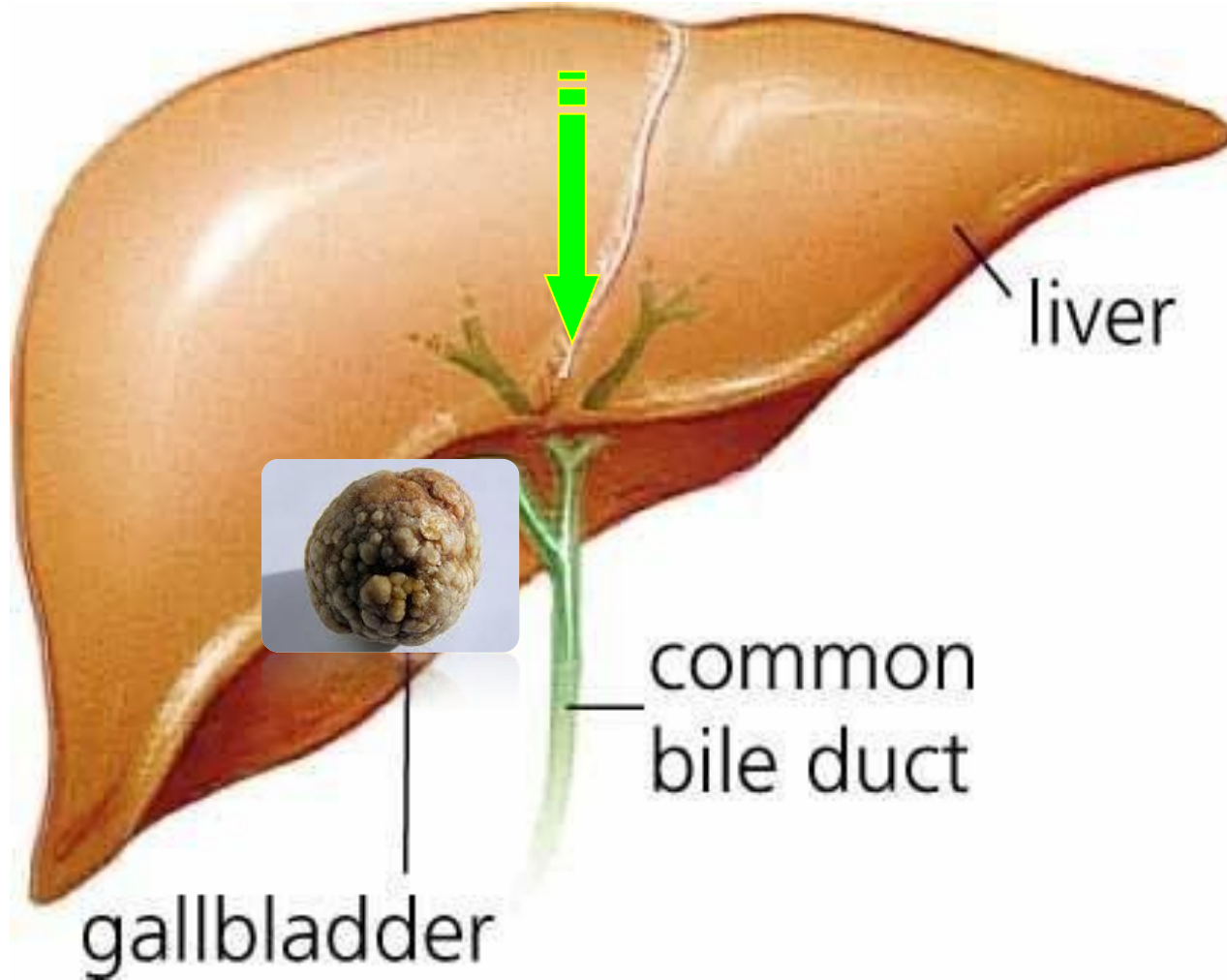
TREATMENT OF GALLSTONES

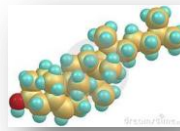
URSODEOXYCHOLATE (UDCA)

- **Only ~3% suitable patients**
- **Prolonged treatment (6-18mos)**
- **Recurrence 50% in 5 years**



cholesterol

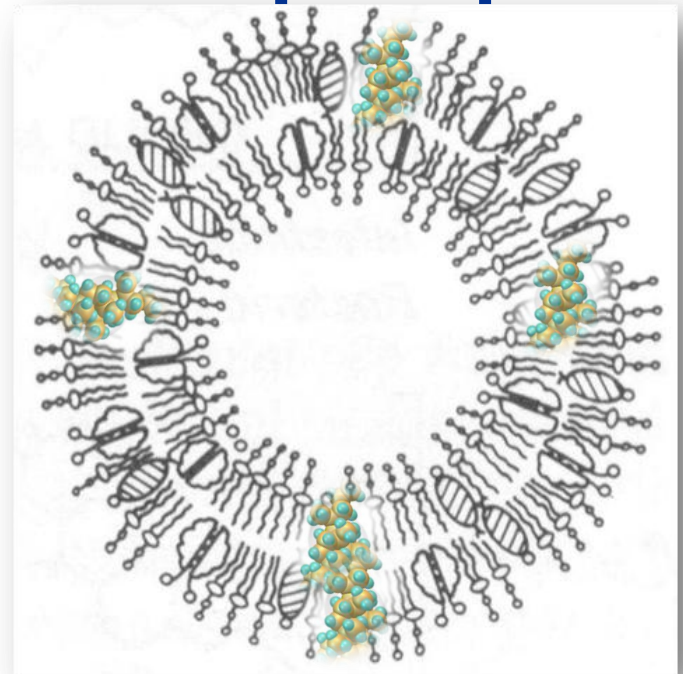
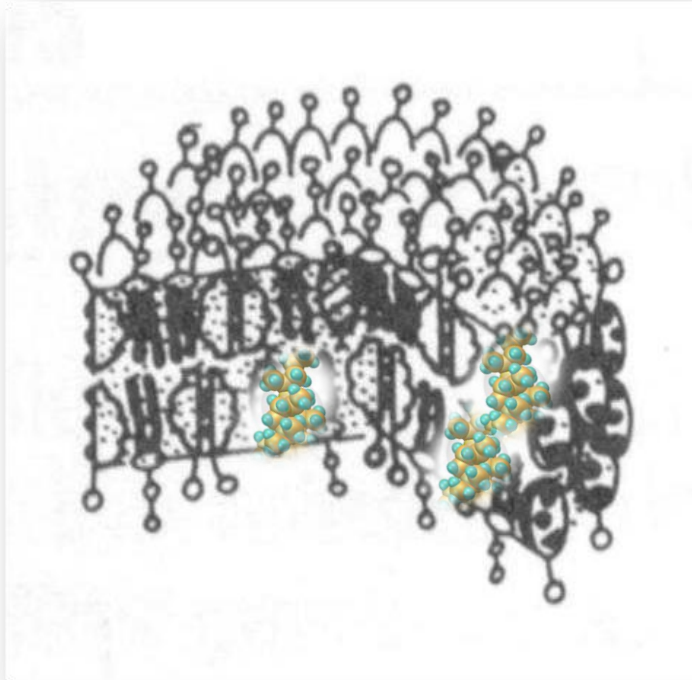




cholesterol

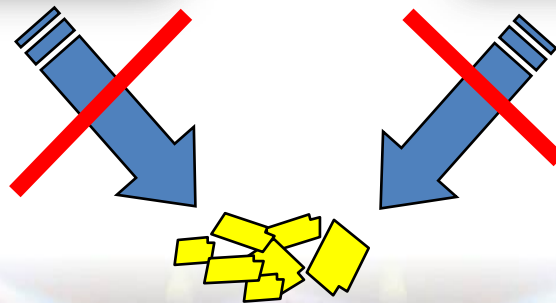
Bile Acids

Phospholipids



Micelles

Vesicles



Admirand WH, Small DM. J Clin Invest 1968,47:1043

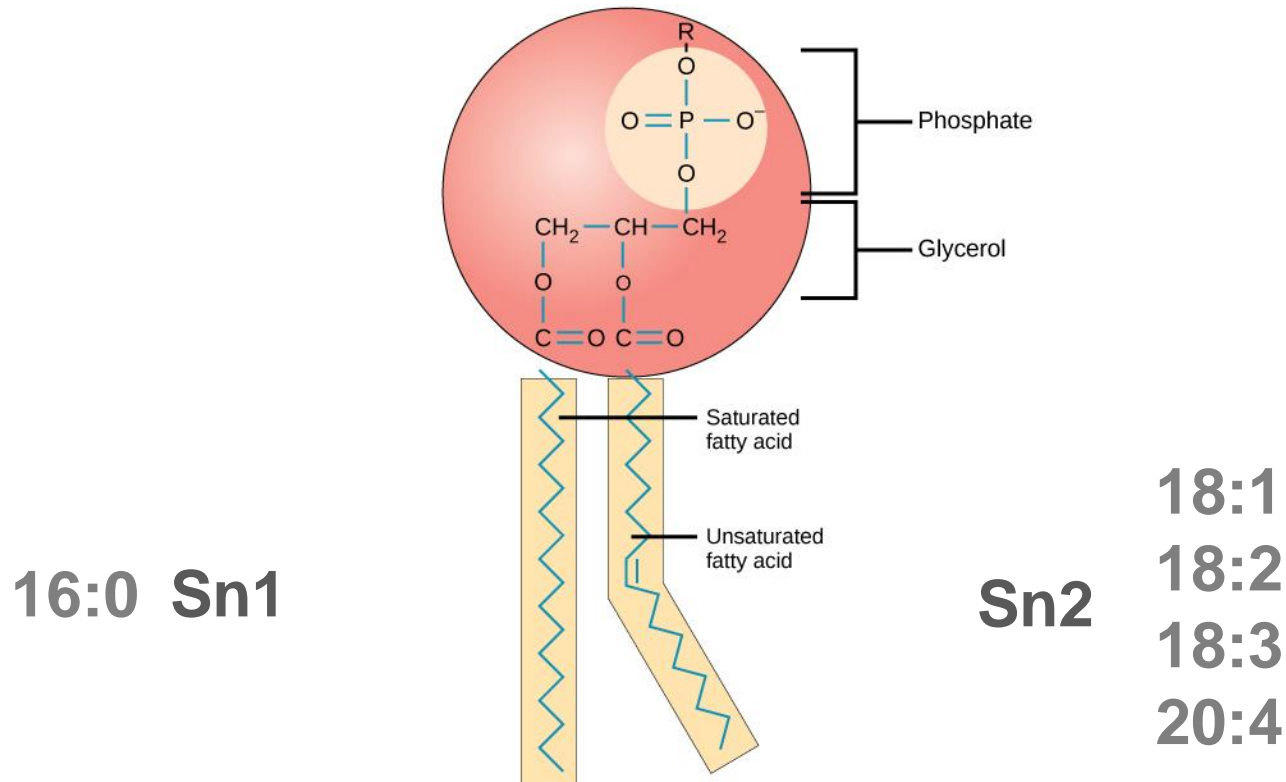
Peled Y, Halpern Z, Eitan B, Goldman G, Konikoff F, Gilat T. Biochim Biophys Acta 1989,1003:246

PHOSPHOLIPIDS

Candidates for gallstone treatment?

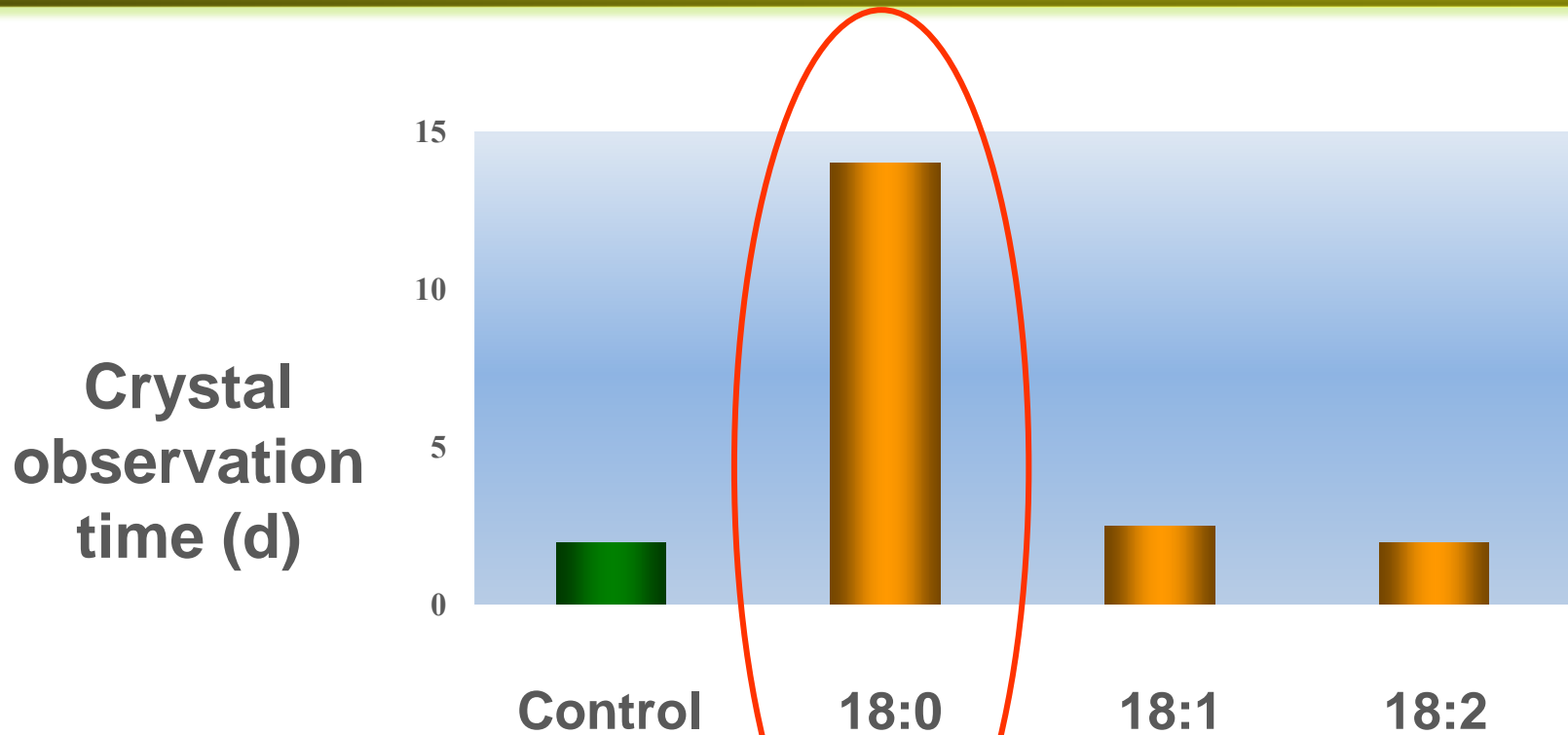
- **Broken by digestive enzymes**
- **Biliary phospholipids cannot be controlled by dietary ingestion**

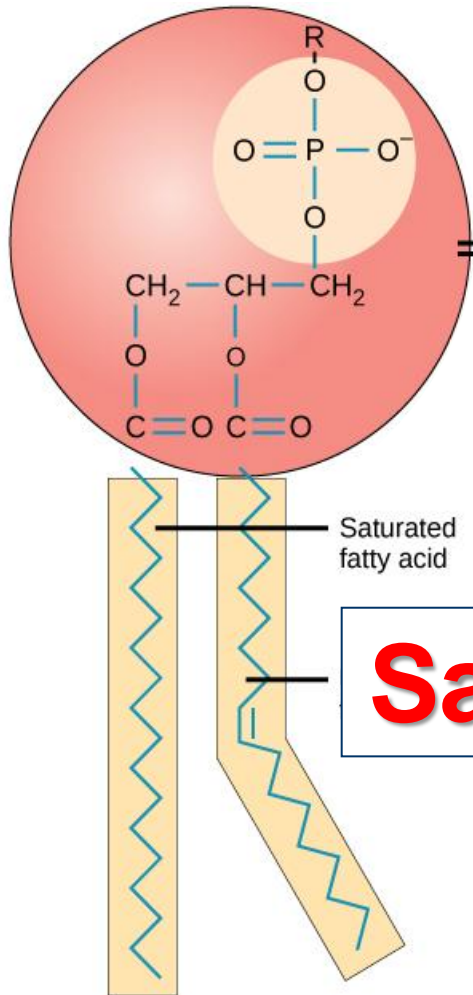
PHOSPHOLIPIDS IN BILE



Phosphatidylcholine (Lecithin)

Effect of Sn2 chain on cholesterol crystallization





Candidate for gallstone treatment?

Fatty Acid Bile Acid Conjugate (FABAC)

- Influence cholesterol solubility & crystallization

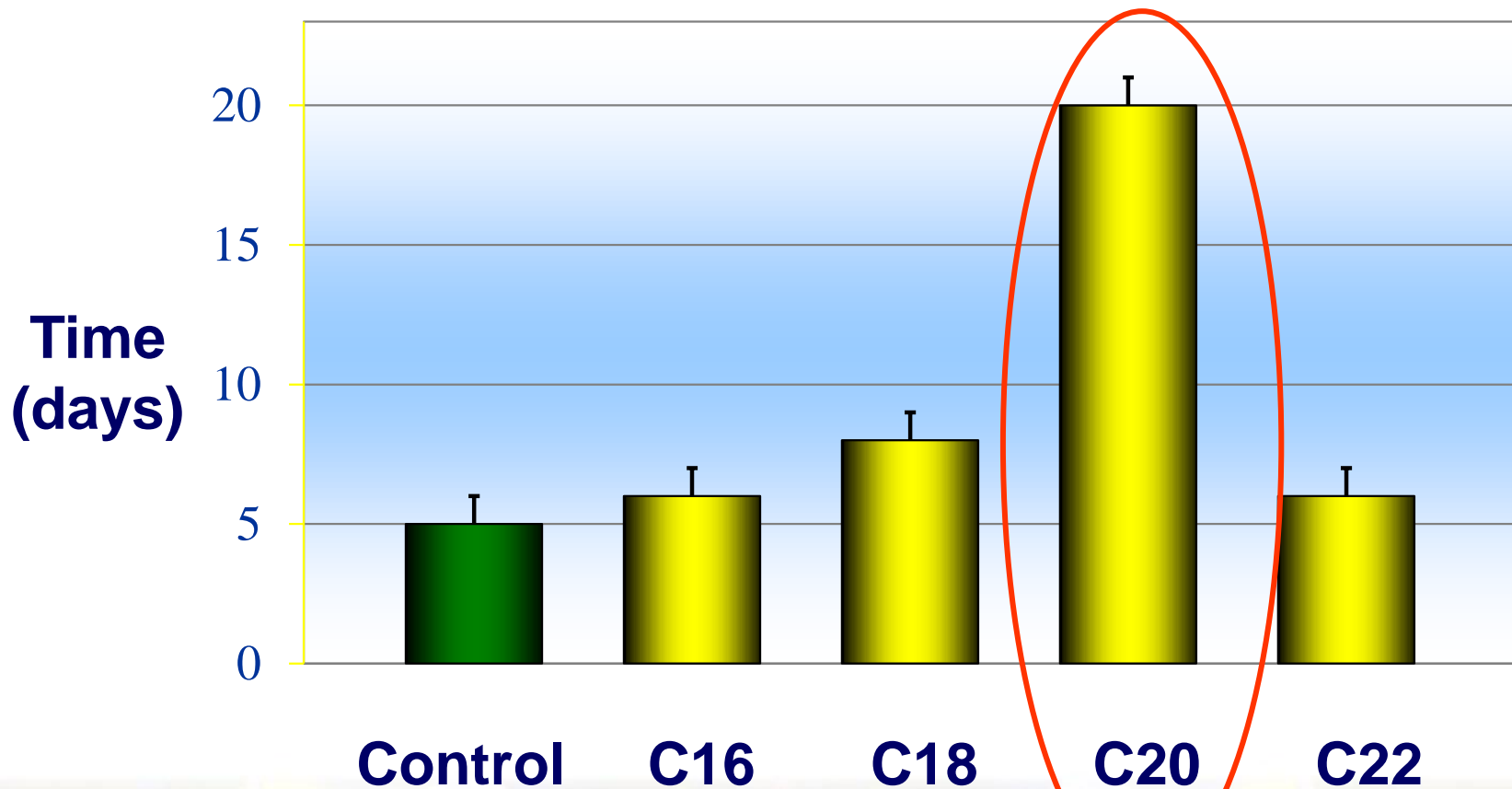
- Secreted into bile
- Enterohepatic circulation

Fatty Acid
SATURATED

Bile Acid

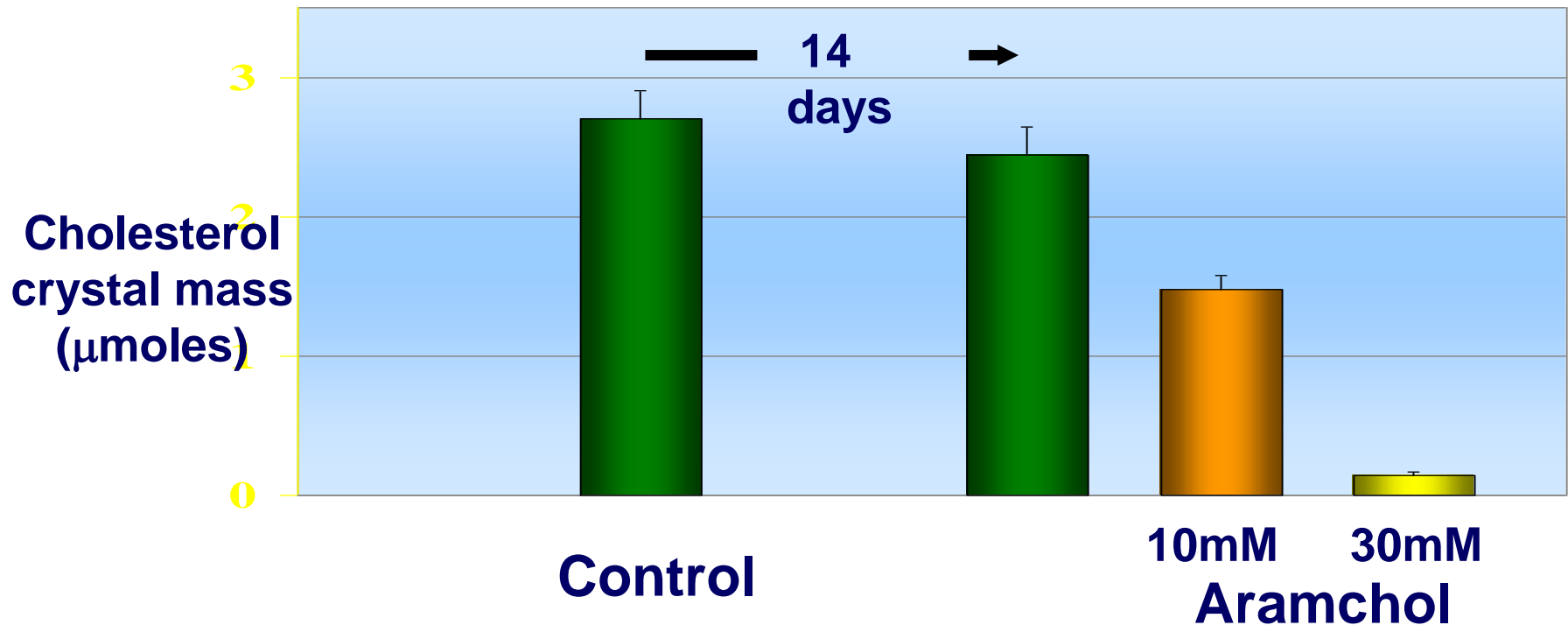
C20-FABAC = Aramchol

Crystal Observation Time



Dissolution of crystals by Aramchol

(human bile, *ex vivo*)



In vivo studies



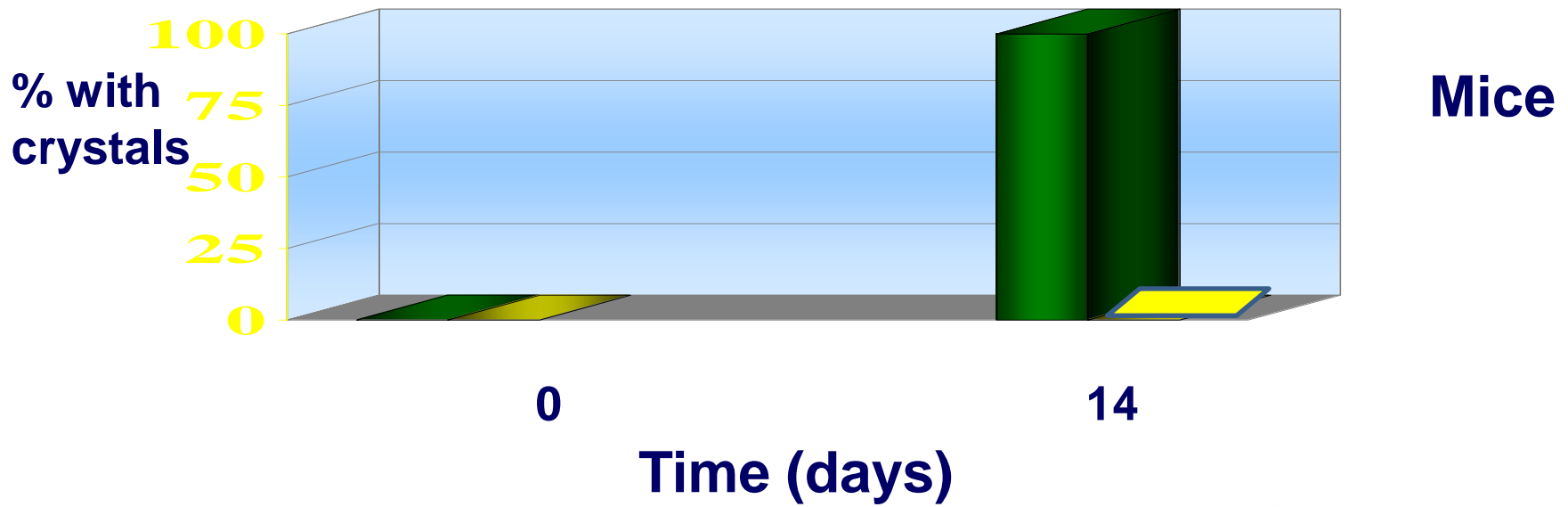
Prevention of crystallization

Lithogenic diet

Aramchol



150/mg/kg/d



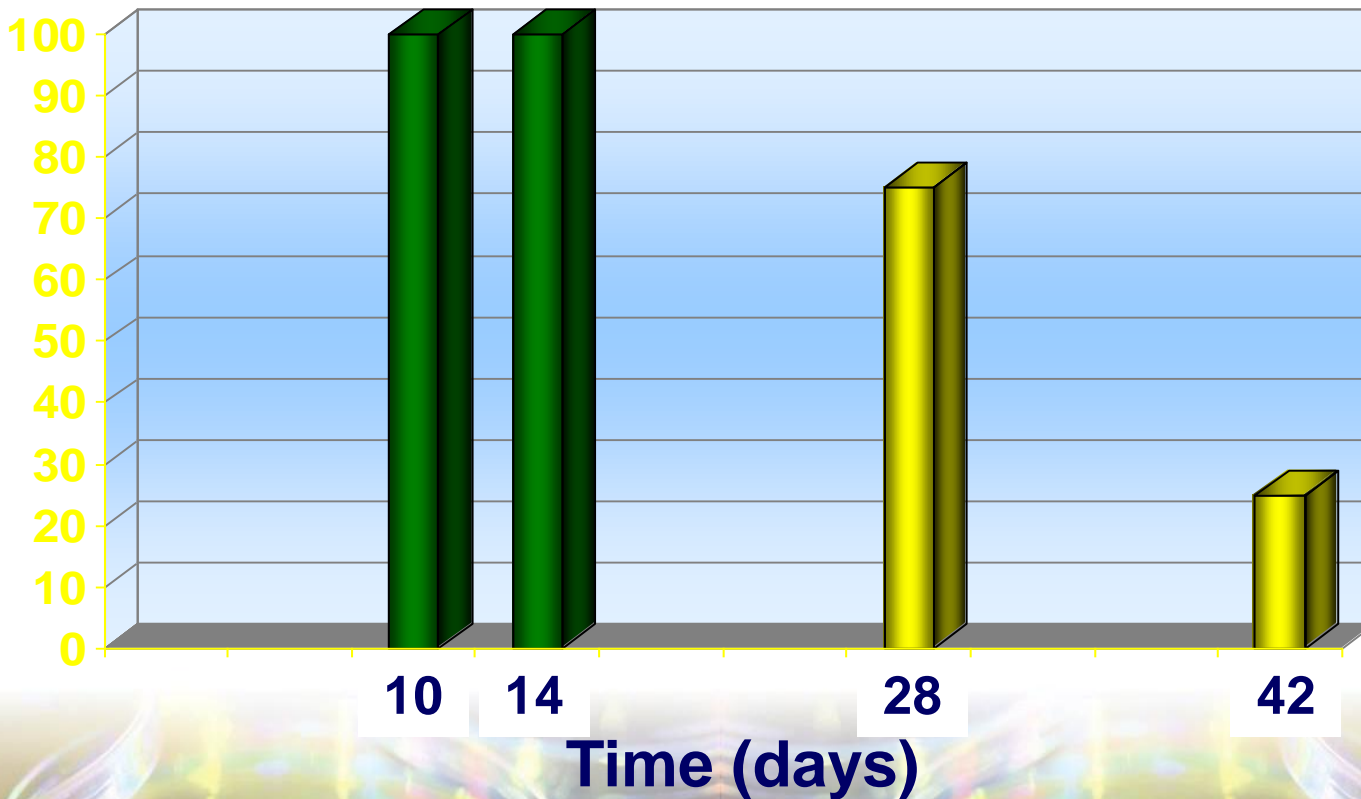
Dissolution of crystals

Lithogenic diet

Aramchol



150/mg/kg/d



Mice

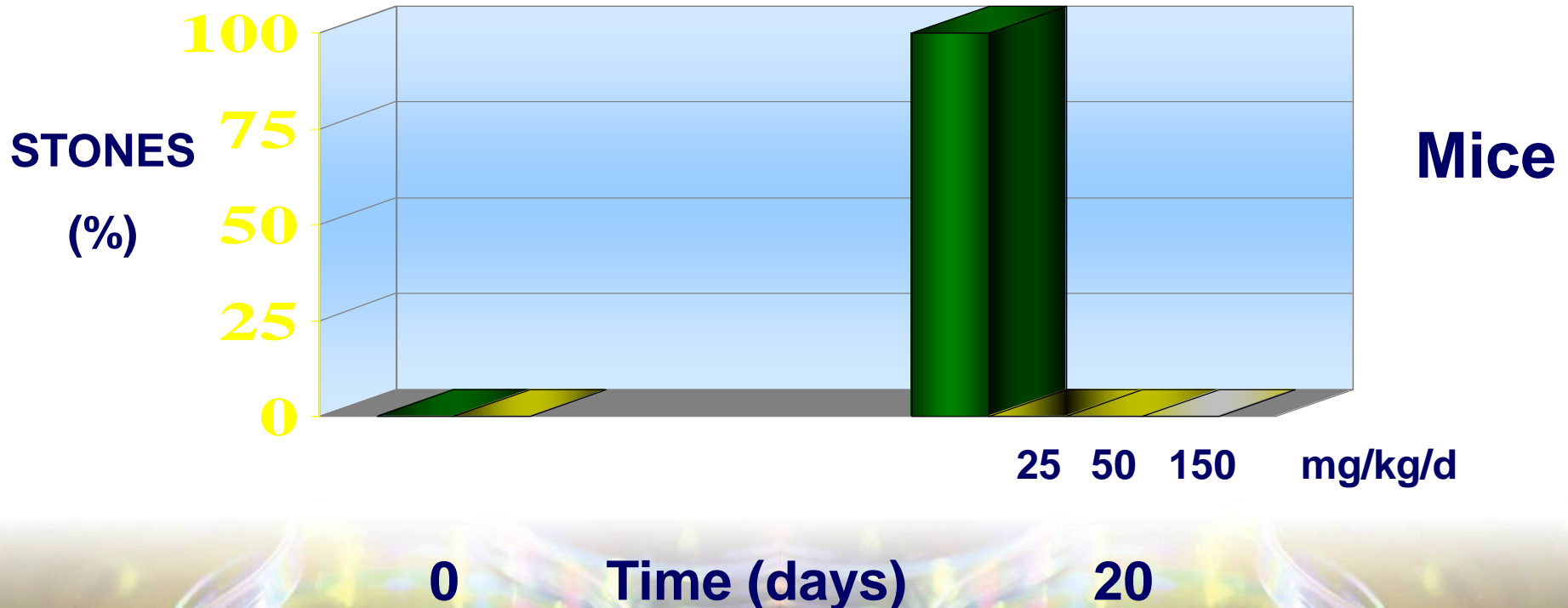
% with crystals

Prevention of gallstone formation

Lithogenic diet

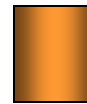
Aramchol

150/mg/kg/d



Gallstone Dissolution

Aramchol:



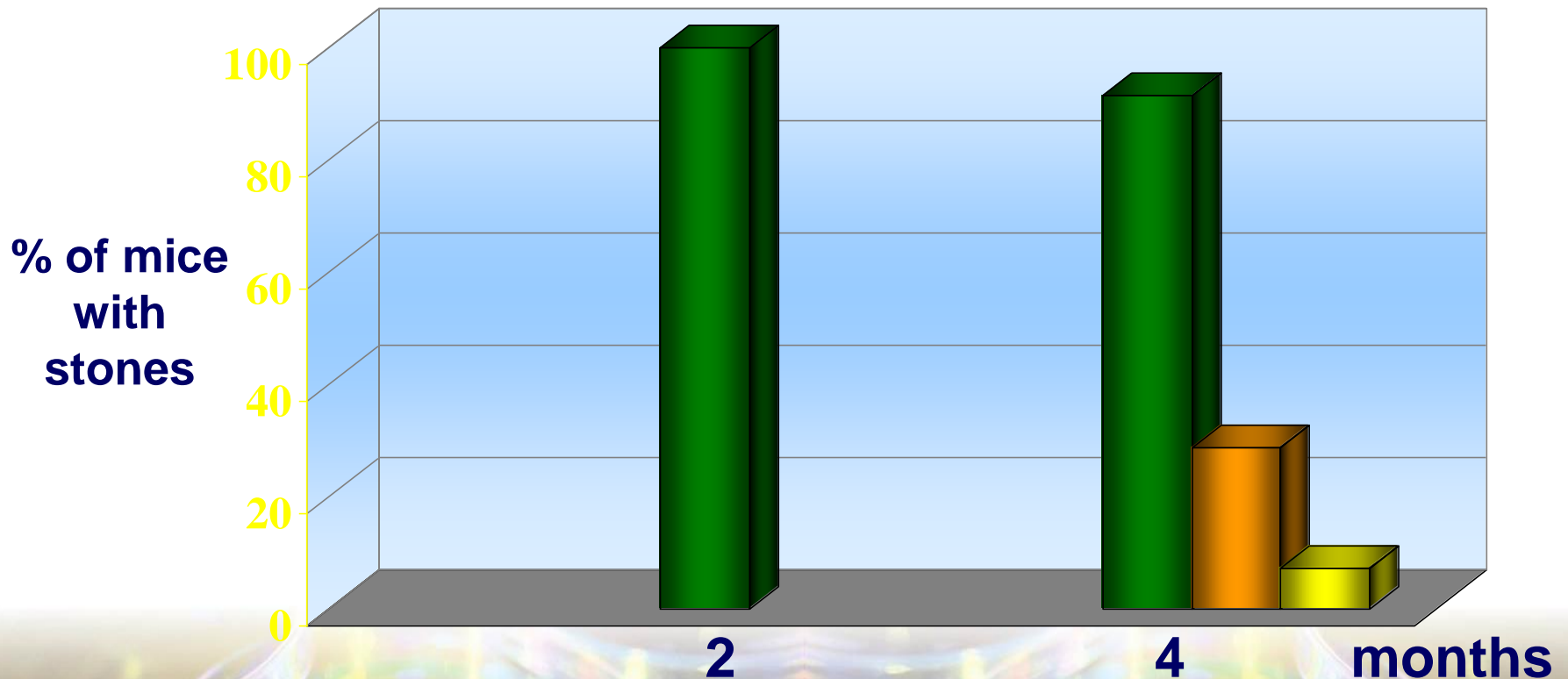
25mg/kg



150mg/kg

Lithogenic diet

Regular diet + Saline/Aramchol



Aramchol:

- Prevents cholesterol crystallization and gallstone formation
- Dissolves cholesterol crystals and gallstones

**Potential medical treatment
for gallstones!...**



Pharmacodynamics

(after 150mg/kg/d by gavage)

***In vivo* concentration of Aramchol:**

Bile:
1.0-5.2 $\mu\text{mol/l}$

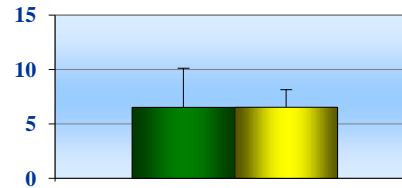
In vitro:
2-30mM

 **Mechanism of action?**

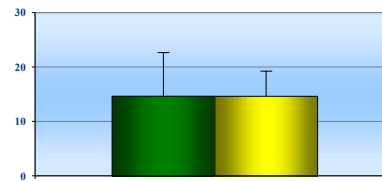
Effect on biliary lipids

■ Control ■ Aramchol

**Cholesterol
(mM)**

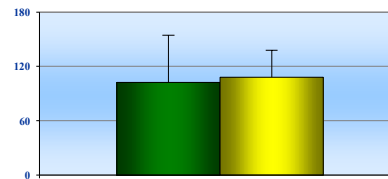


**Phospholipids
(mM)**

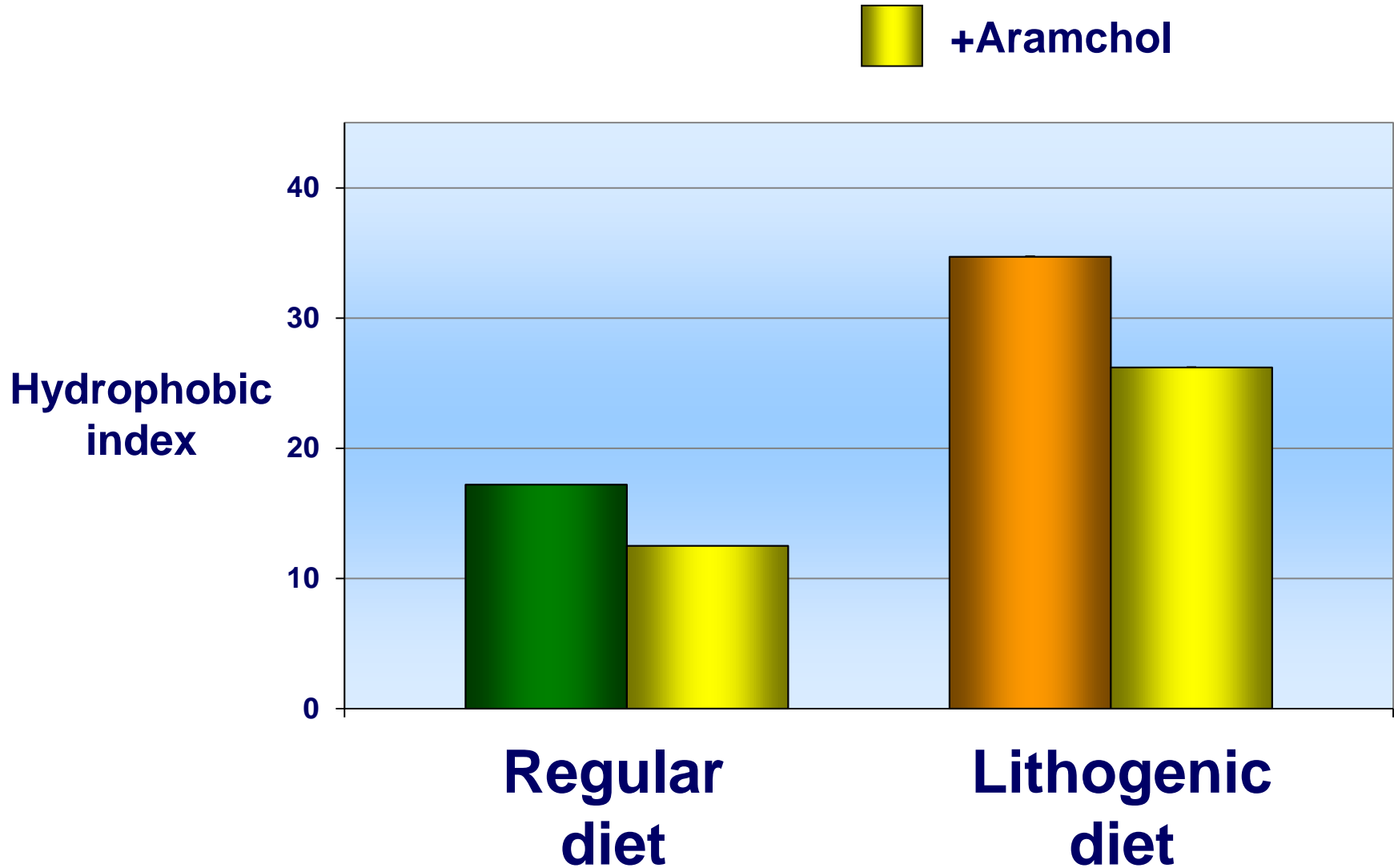


**C57L/J mice
8w**

**Bile salts
(mM)**

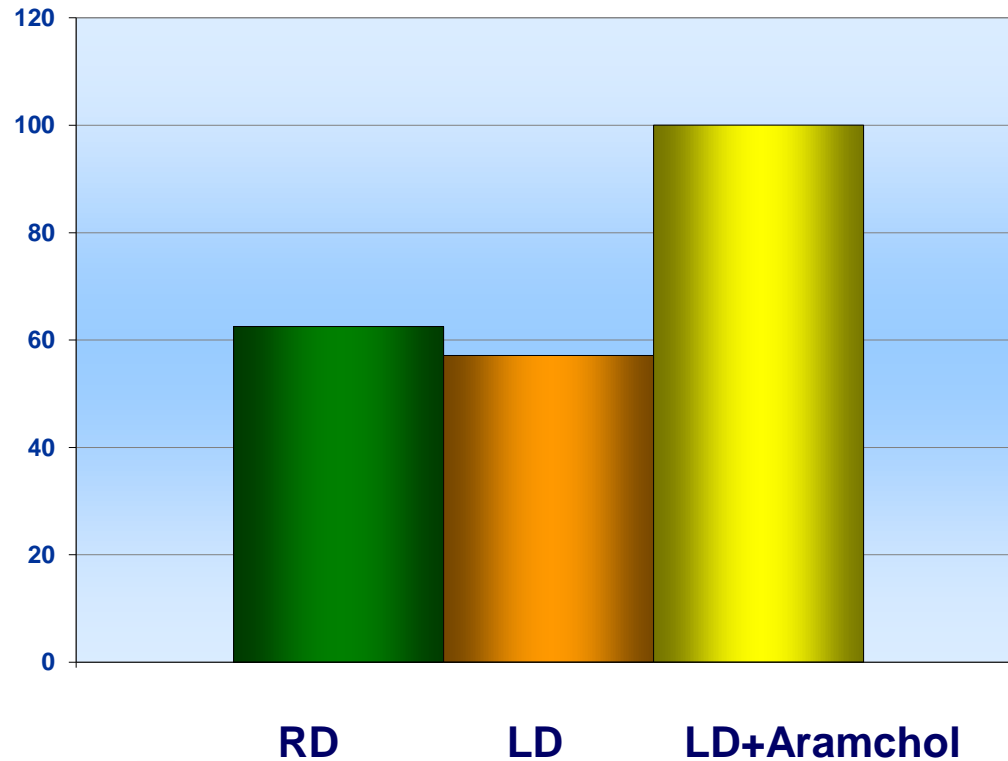


Bile acid composition

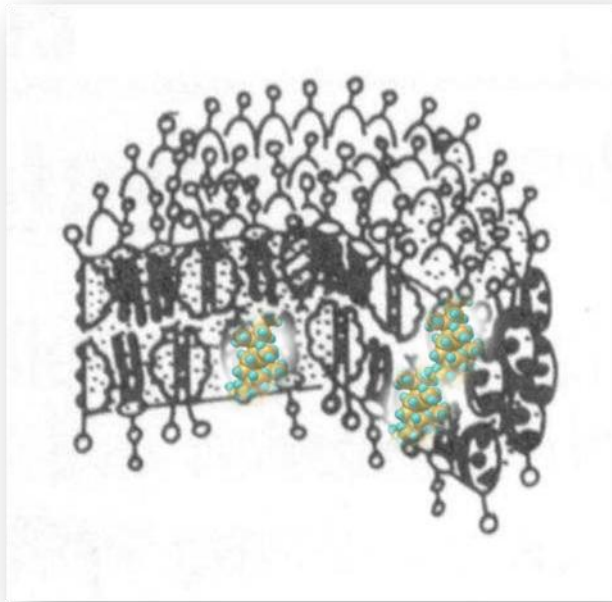


Phospholipid composition

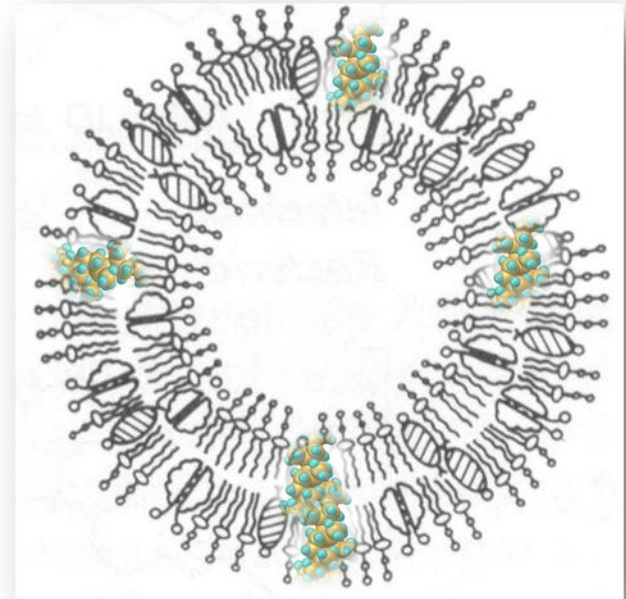
**Saturation
(16:0/16:1)**



Aramchol – MODE OF ACTION



**Bile salt
hydrophobicity**



**Phospholipid
saturation**



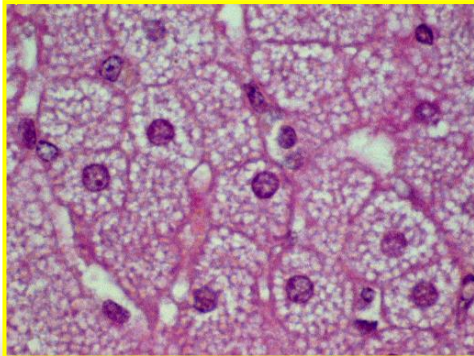
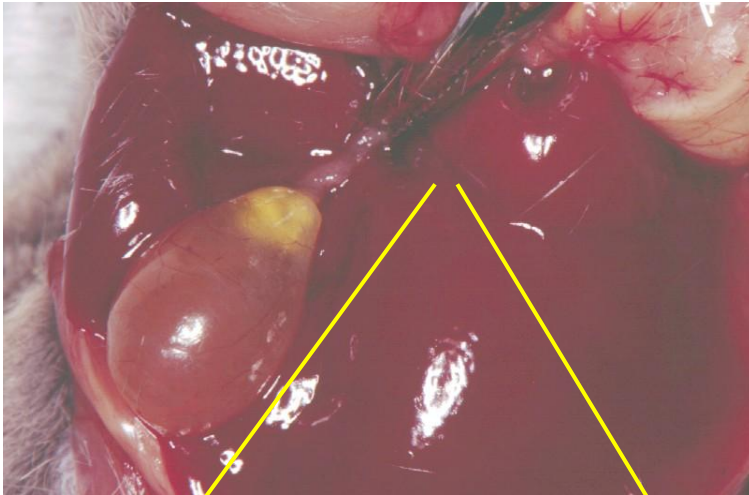
Cholesterol



Crystallization

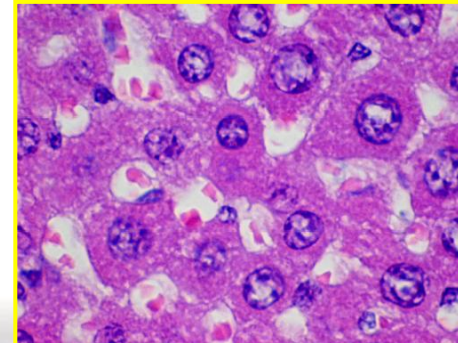
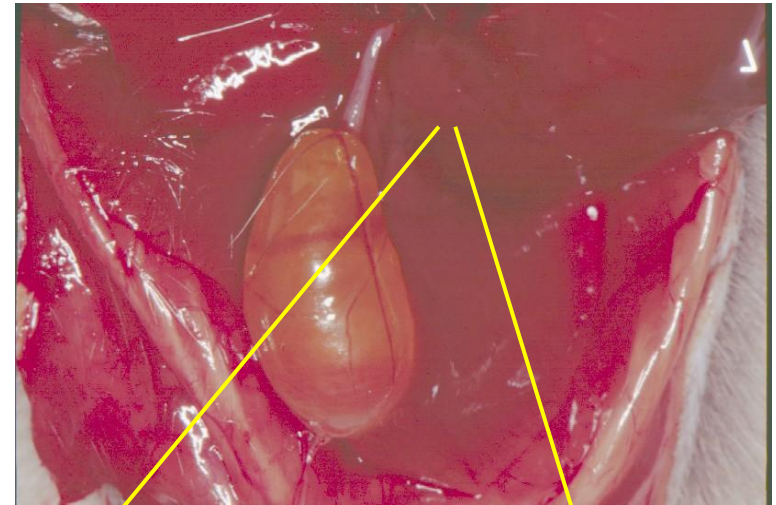
Mice on a high fat diet

Control



Fatty Liver

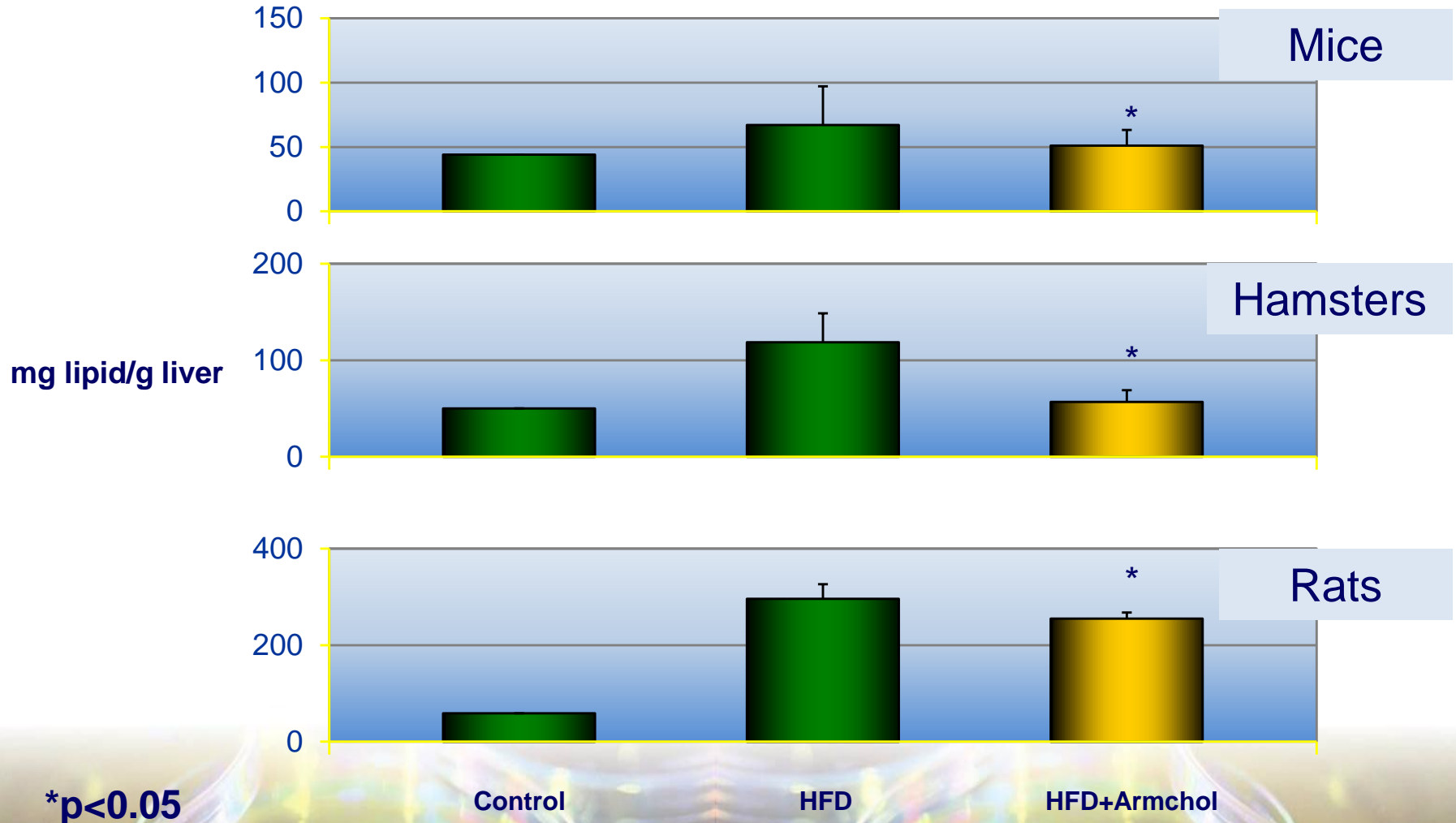
Aramchol+



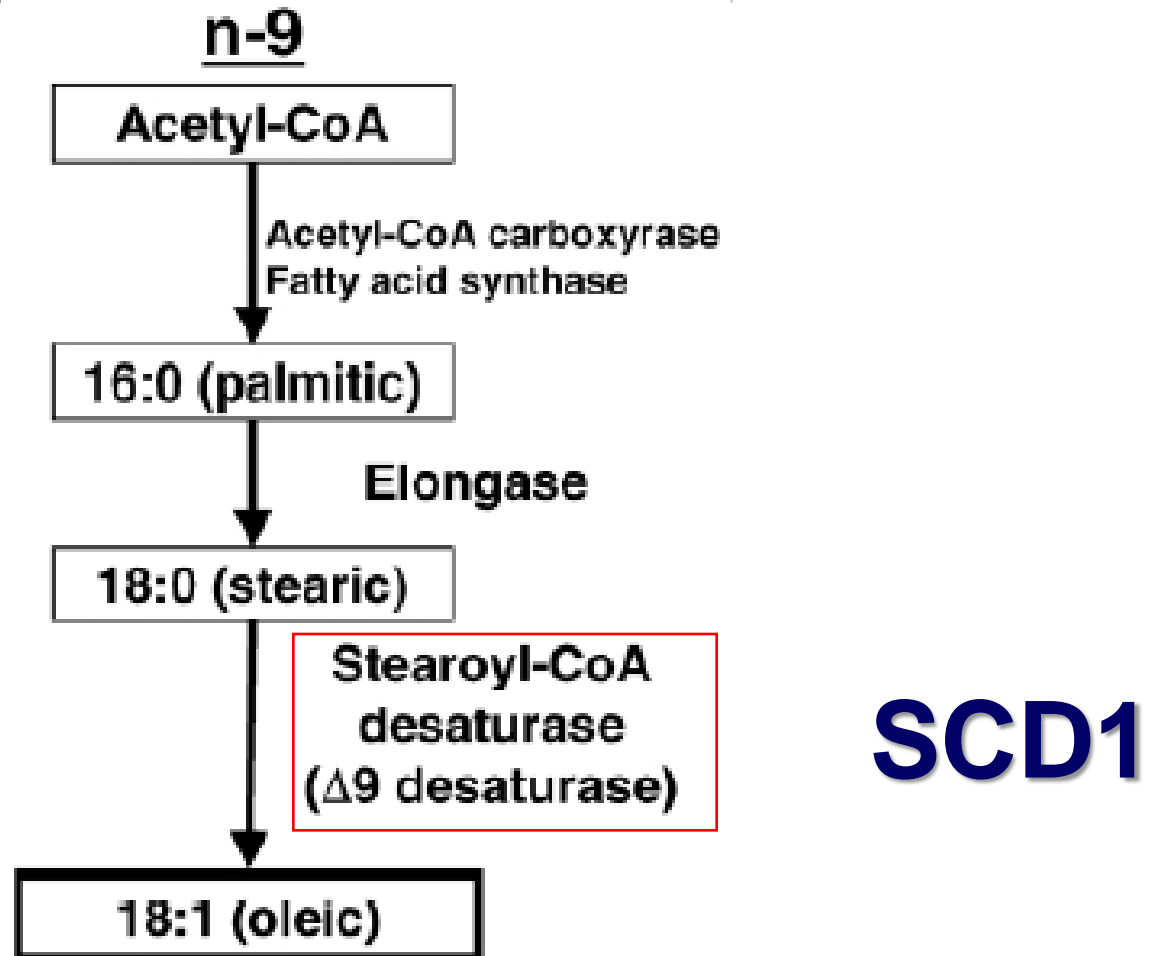
Normal Liver

LIVER LIPID CONTENT

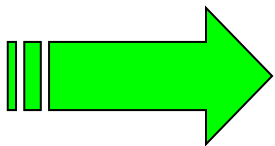
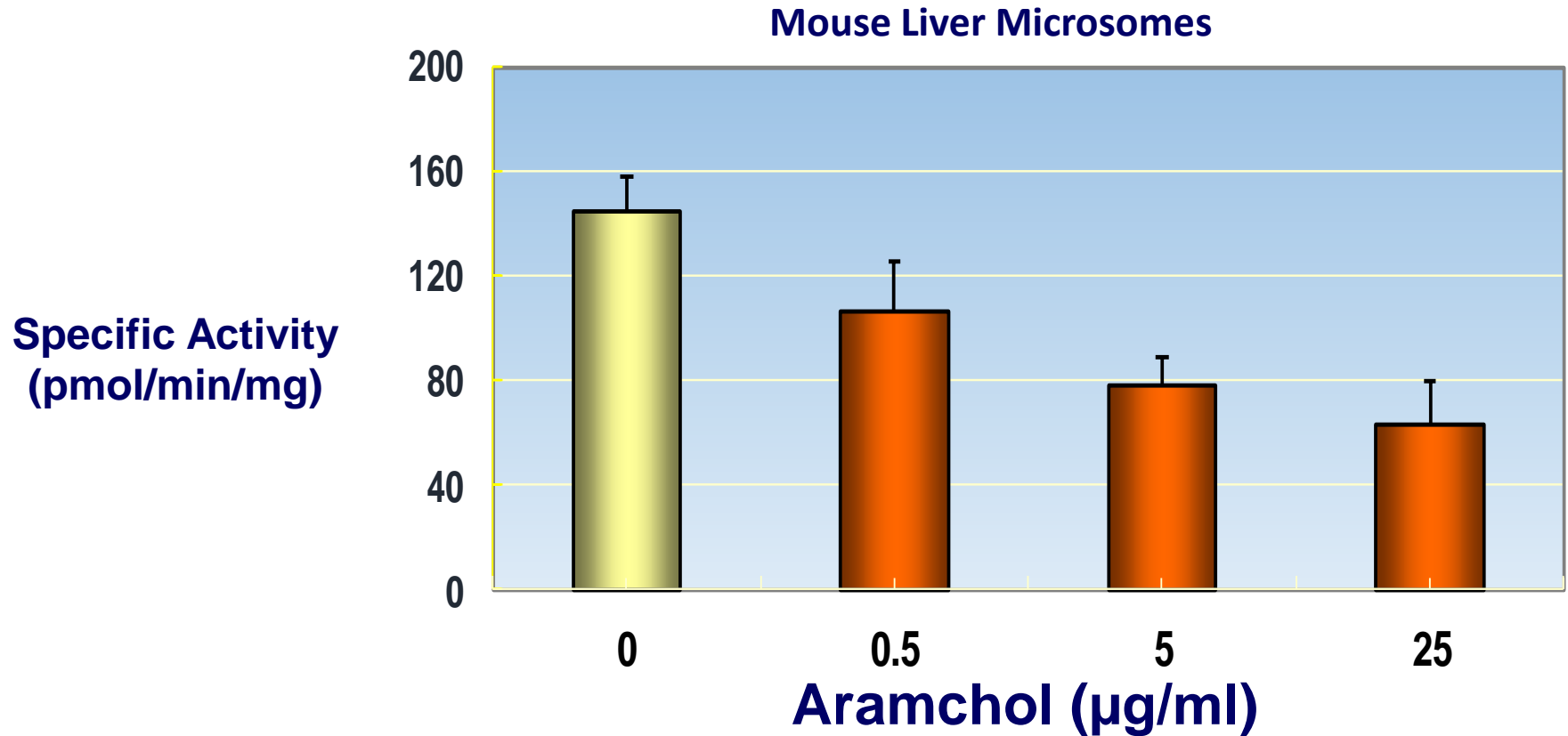
(21 days)



Fatty acid synthesis in the liver



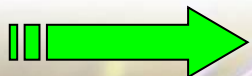
Effect of Aramchol on SCD1



Inhibition of SCD1

Aramchol:

- **Decreases bile lithogenicity via Bile acid & Phospholipid composition**
- **Effective for cholesterol gallstones**
- **Effective for fatty liver**
- **Inhibits SCD1**

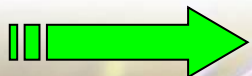


Therapeutic agent...

Human trials

Phase I:

- 41 healthy volunteers
- Single dose up to 900mg
- Repeated doses of 300mg

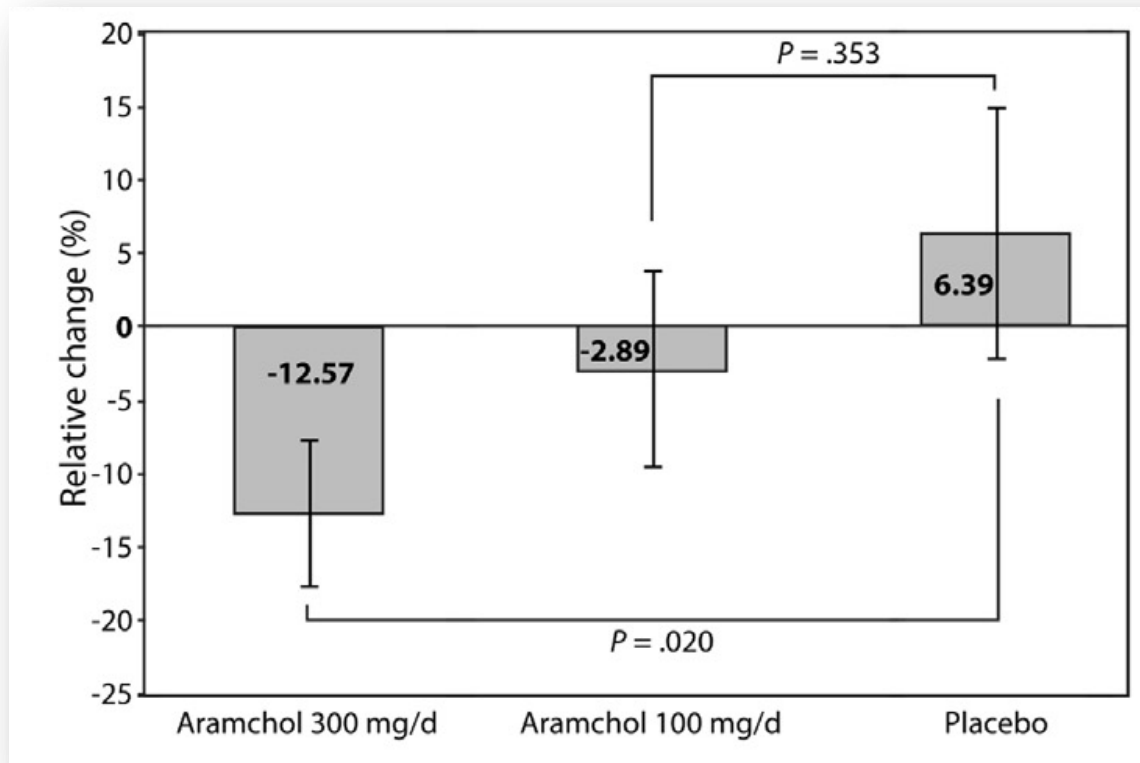


No toxic effects

Phase II trial

- Randomized, double blind, placebo controlled
- 60 pts with Bx proven NAFLD
- Aramchol: 100mg/d, 300mg/d, Placebo – 3mos
- Liver fat assessed by MR spectroscopy

Change in liver fat content (after 3 mos of treatment)



No adverse effects

Ongoing studies...

- **Multicenter International Phase II b fatty liver study (NASH)**
- **Gallstone prevention study after bariatric surgery (proof of concept)**

Conclusions

- **Observations on cholesterol crystallization in bile...**
- **Importance of Bile acids and Phospholipids**
- **Aramchol - therapeutic potential for:**
 - **Gallstones**
 - **Fatty liver**

...by a different mechanism than originally planned...

Israel

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