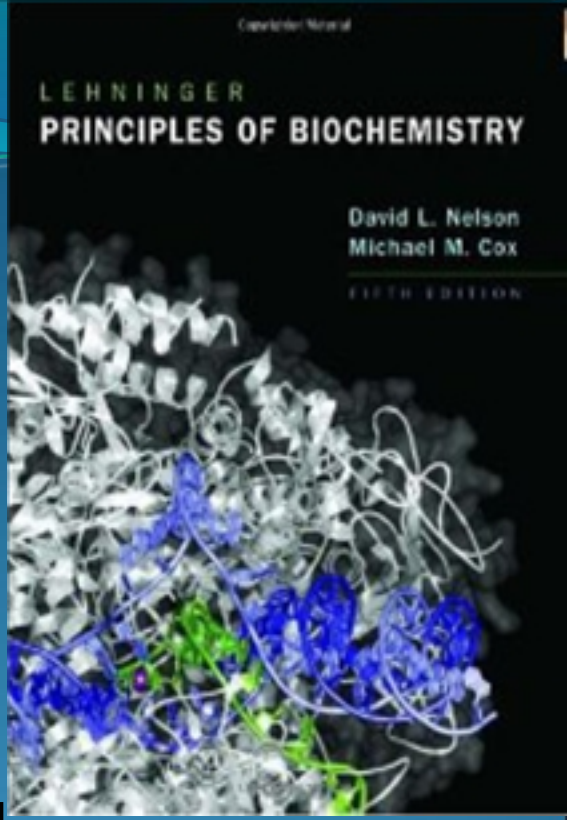


Lipids & Lipoprotien Metabolism

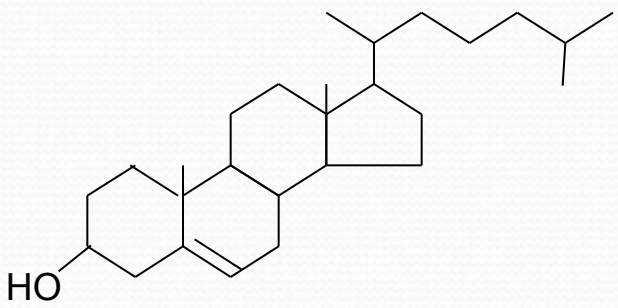
Dr. Alaa Kamal Jabbar Alhamd
M Sc. & Ph. D. In Clinical Biochemistry

Ph D. Course-Biology
Department of Chemistry
College of Sciences\ University of Almustansirya
2016-2017

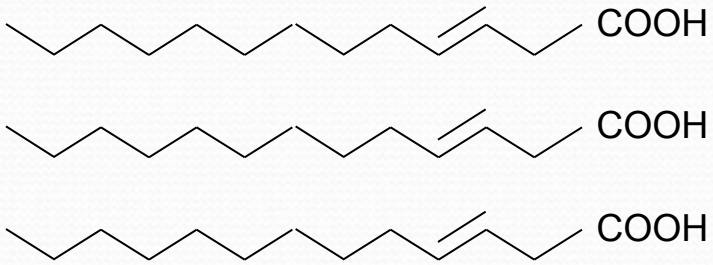
1. Lehninger Principle of Biochemistry , David Nelson , 4th Edition (2008).
2. Biochemistry , Lubbert Steryer,6th edition (2006).
3. Harpers Illustrated Biochemistry , Robbert Murray, 26th edition (2003).
4. The Chemical basis of Life , George Schimd , 2th edition (1985).

Lipid Structure

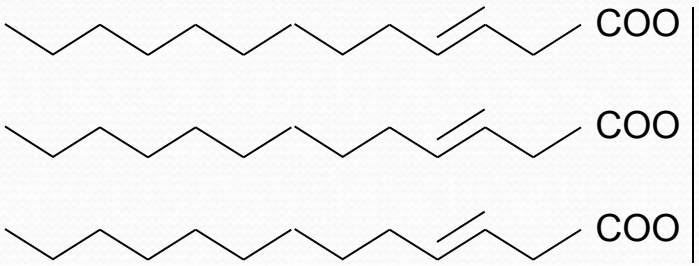
Cholesterol



Fatty Acids

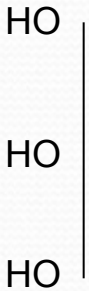


Triglycerides

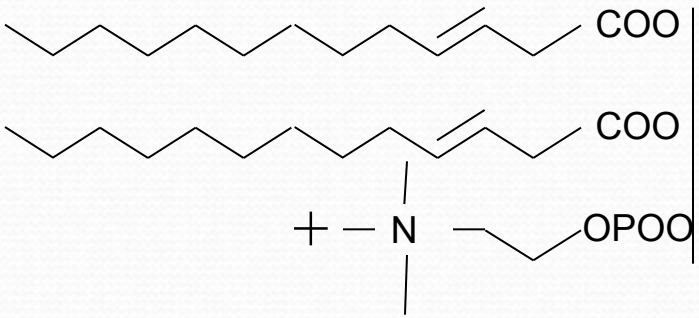


\+

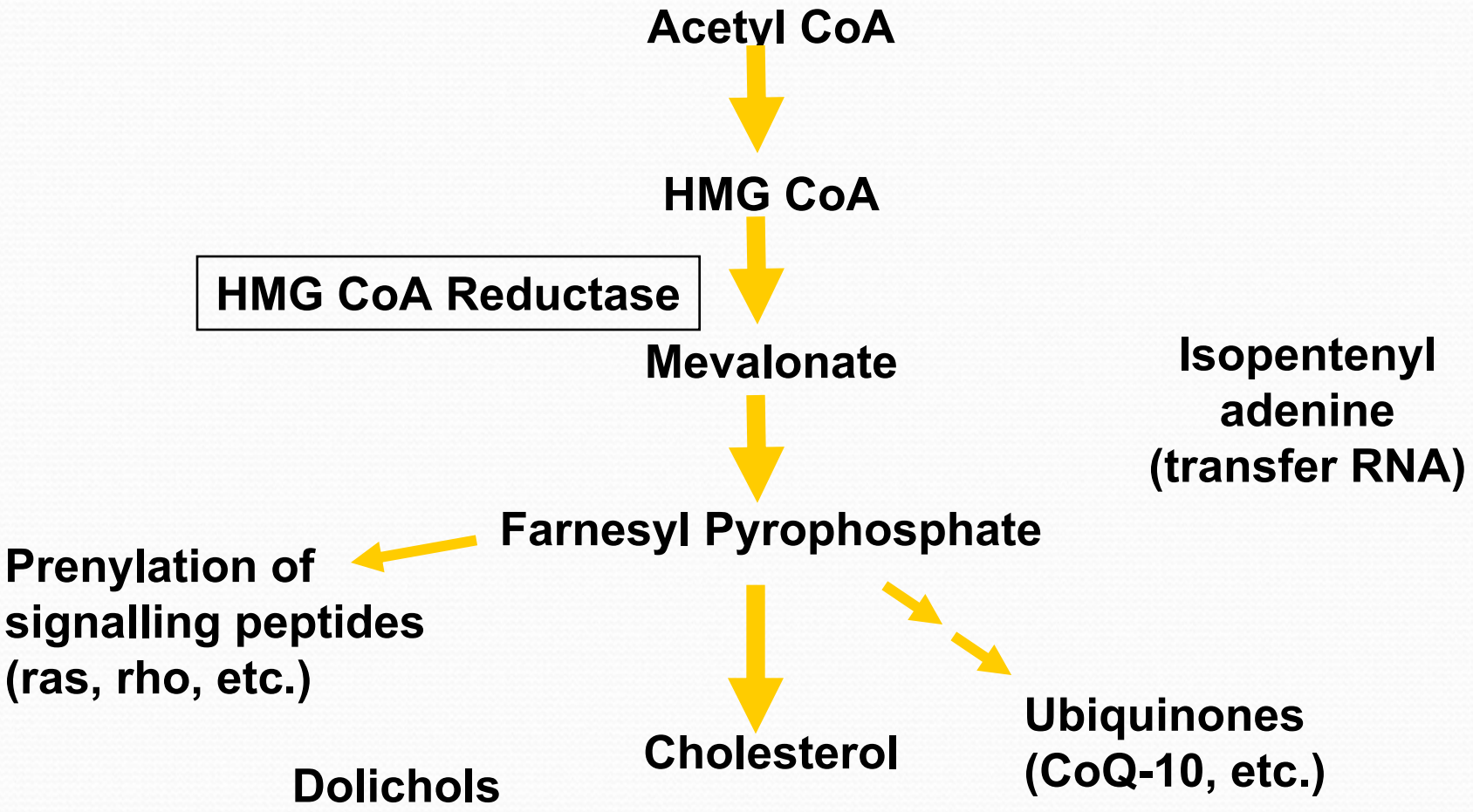
Glycerol



Phospholipid: Lecithin

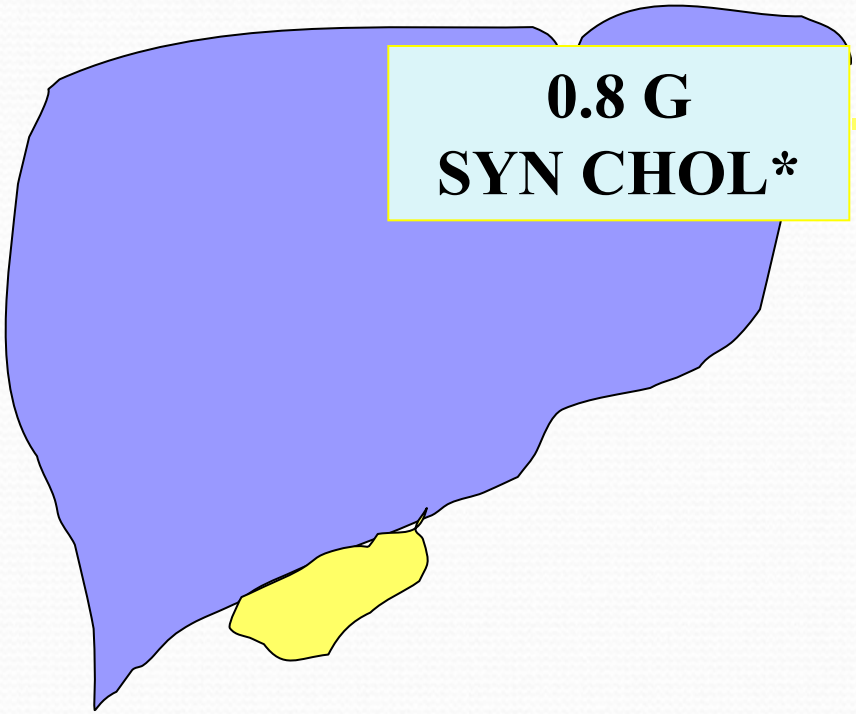


HMG CoA Reductase
(More Than Cholesterol Synthesis)



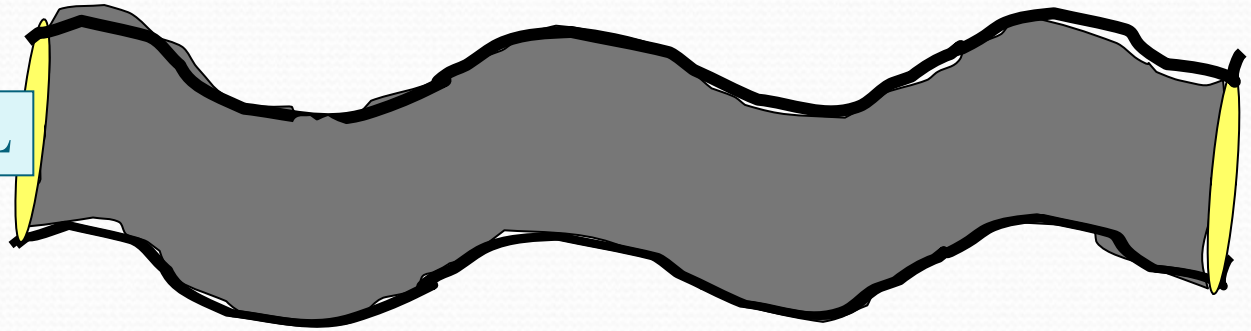
Inhibition of other key products of mevalonate may relate to nonlipid effects & rare side effects of statins.

NORMAL CHOLESTEROL METABOLISM



0.8 G
SYN CHOL*

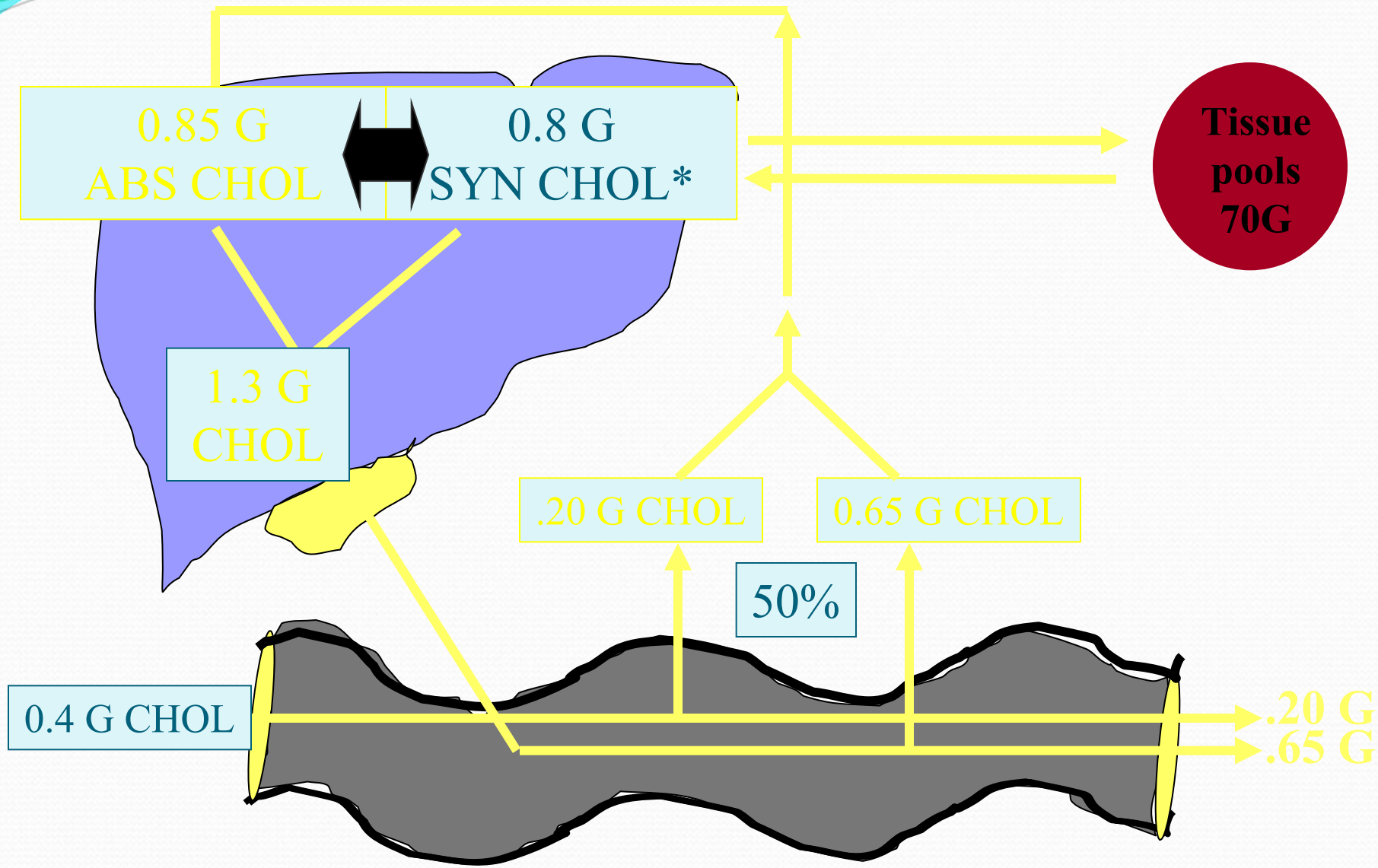
Tissue
pools
70G



0.4 G CHOL

*SYN CHOL = CHOLESTEROL SYNTHESIS

NORMAL CHOLESTEROL METABOLISM

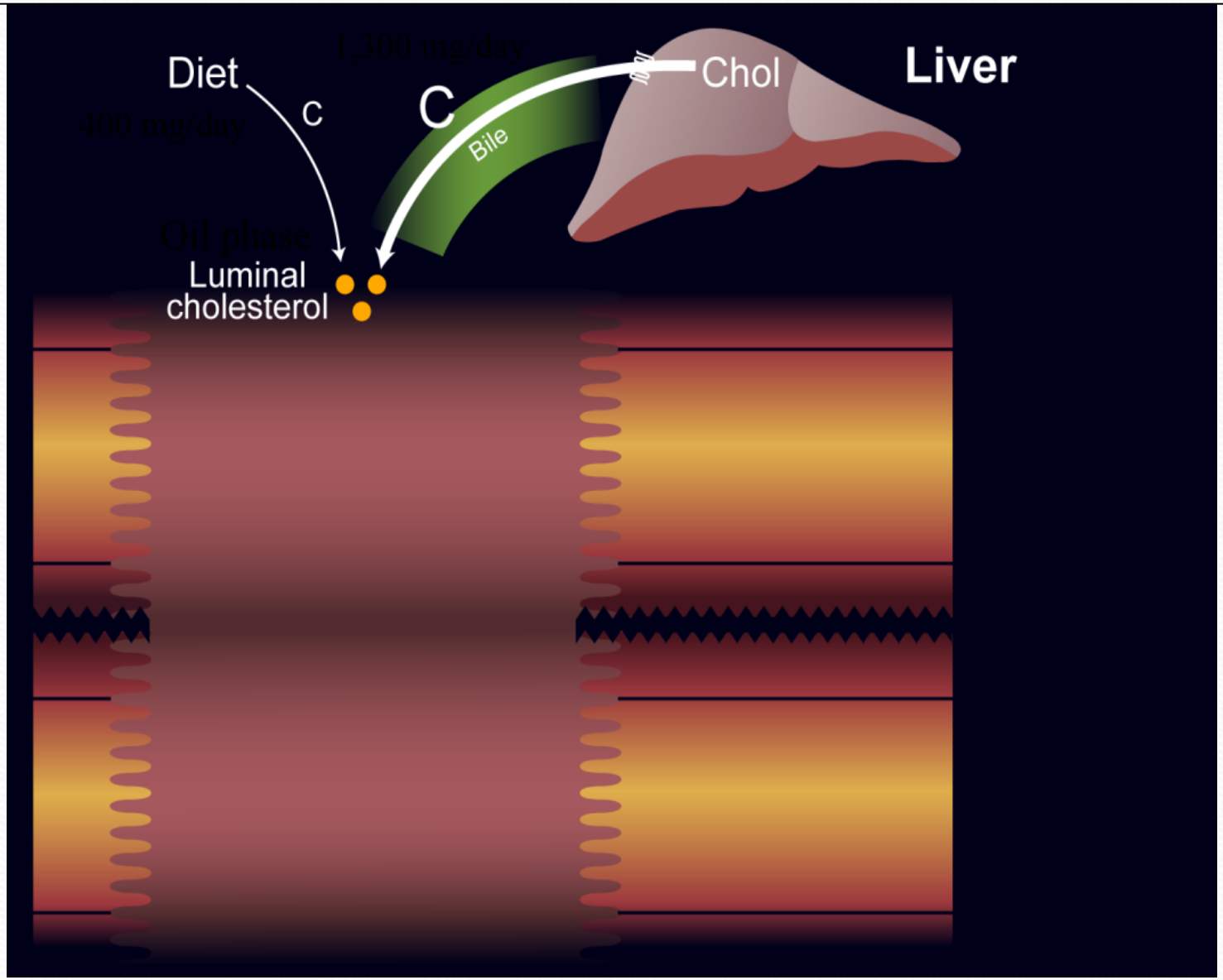


*SYN CHOL = CHOLESTEROL SYNTHESIS

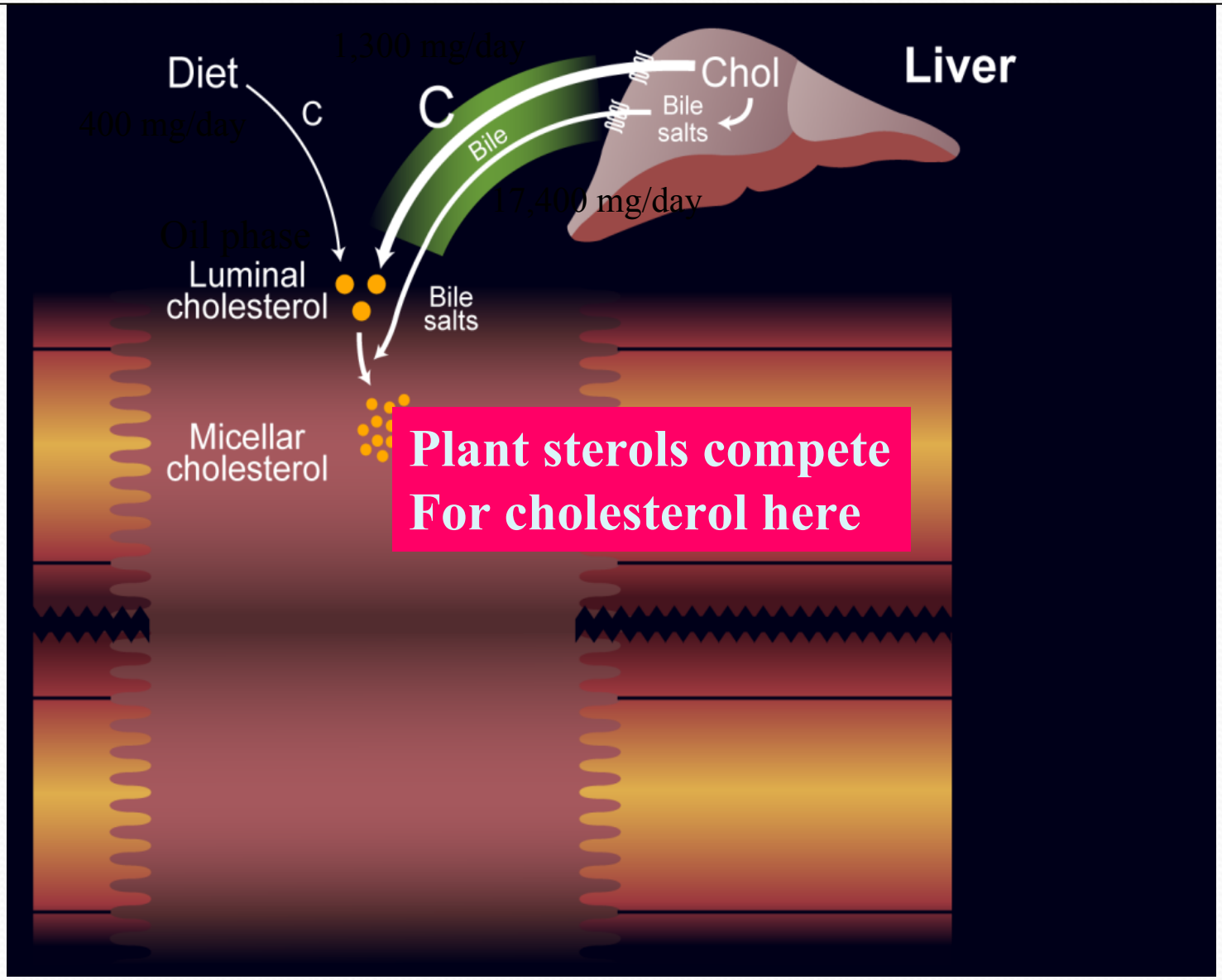
NORMAL CHOLESTEROL METABOLISM

- Key concepts: synthesis
  - Primary synthetic sites are extrahepatic, but liver is key regulator of homeostasis
- Key concepts: absorption
  - Largest source is biliary secretion, not diet.
  - Normal absorption: 50%
  - For cholesterol to be absorbed it must:
    - undergo hydrolysis (de-esterification by esterases)
    - be incorporated into micelles
    - be taken up by cholesterol transporter

NORMAL CHOLESTEROL ABSORPTION

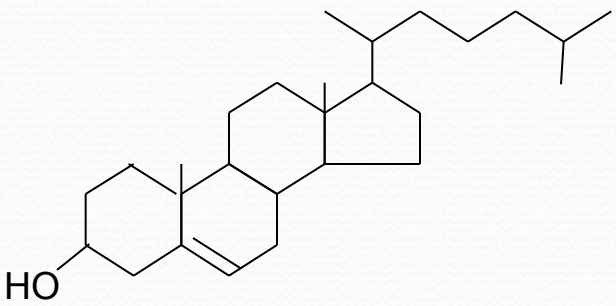


NORMAL CHOLESTEROL ABSORPTION

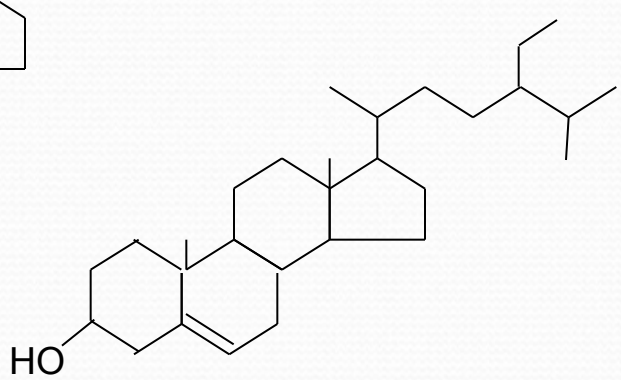


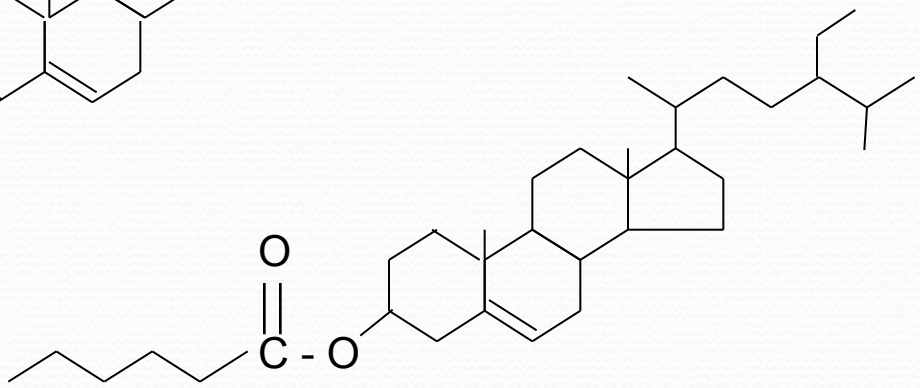
STRUCTURE OF PLANT STEROL ESTERS

Cholesterol



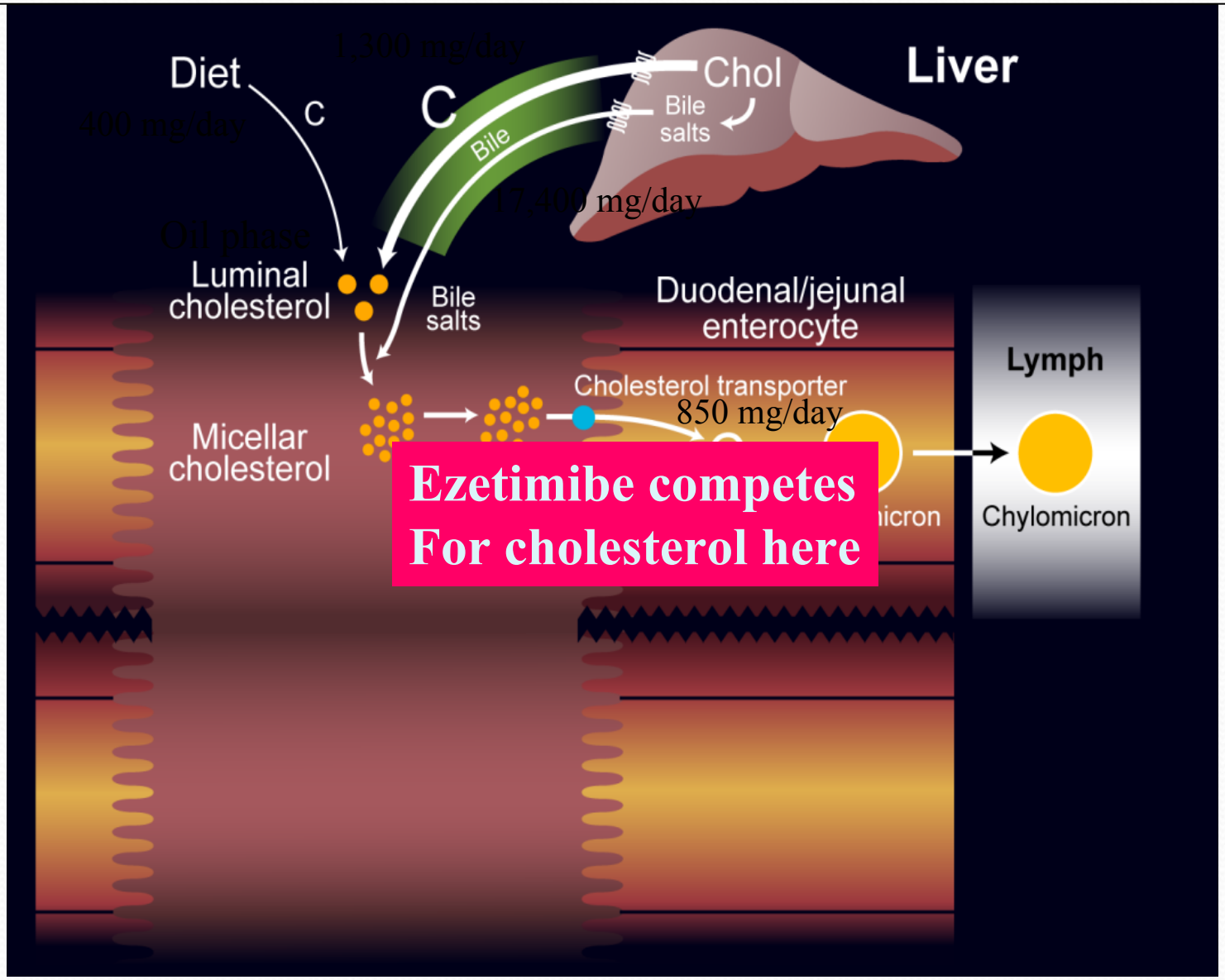
Sitosterol



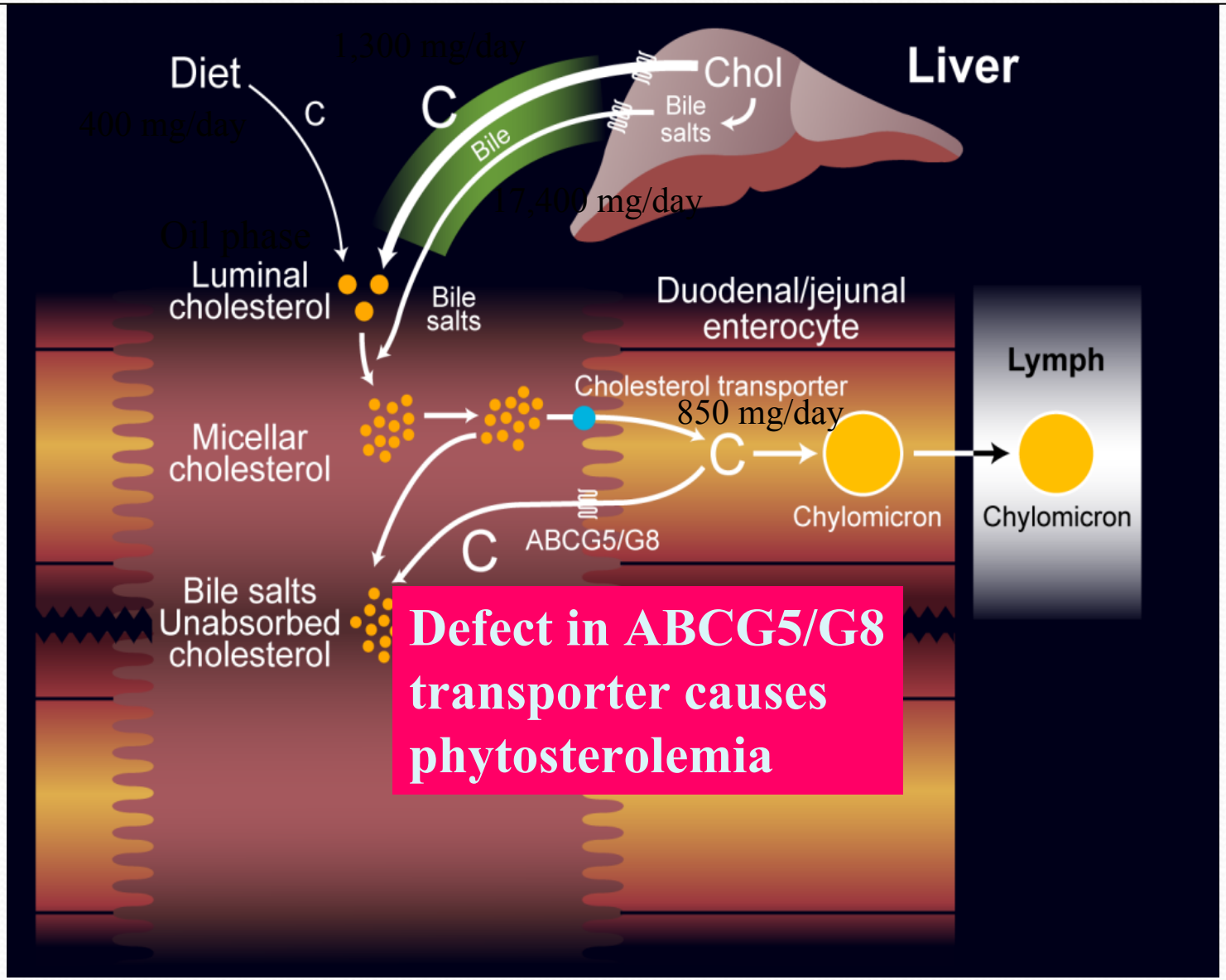


Sitosterol Ester

NORMAL CHOLESTEROL ABSORPTION



NORMAL CHOLESTEROL ABSORPTION

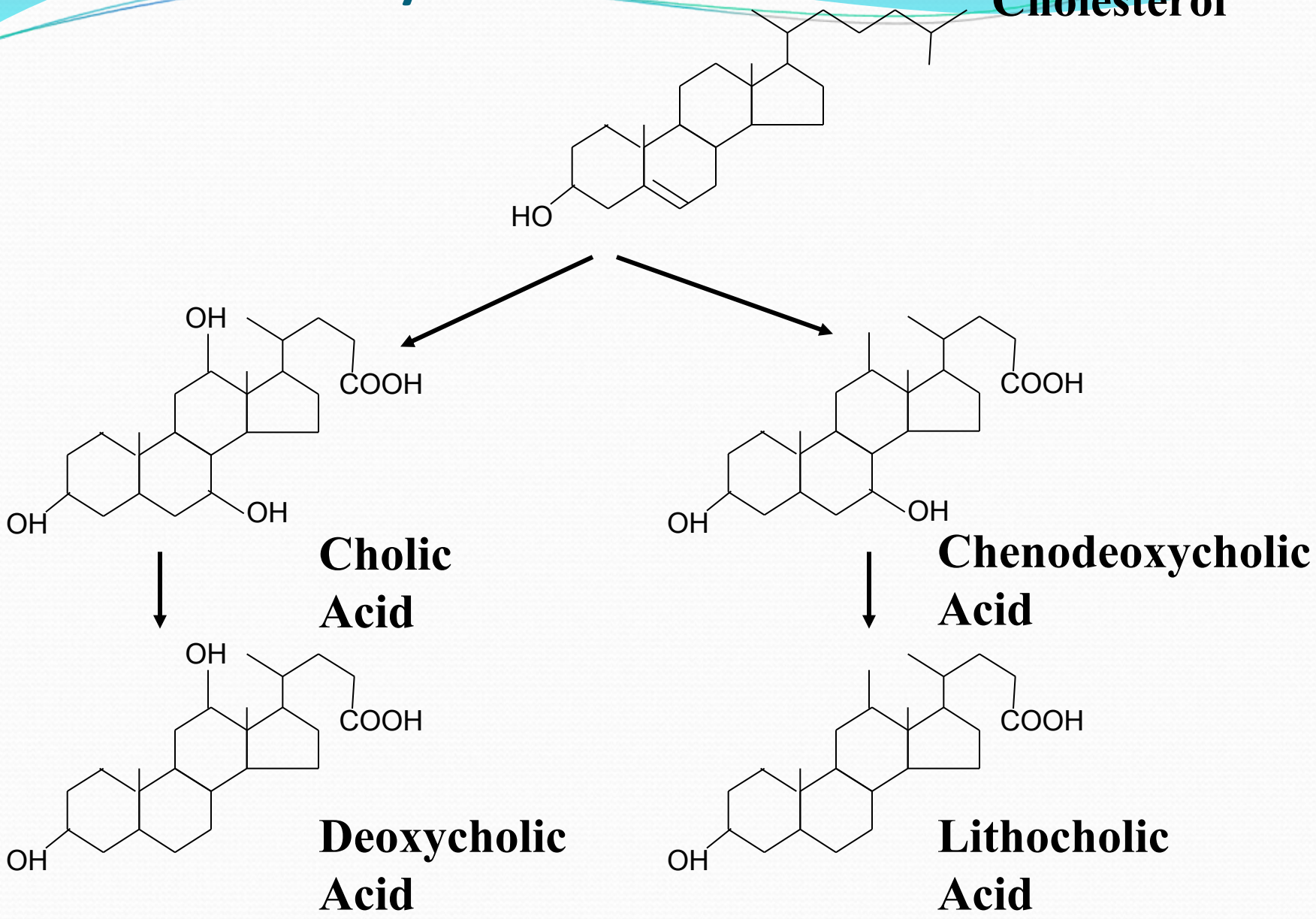


NORMAL CHOLESTEROL METABOLISM

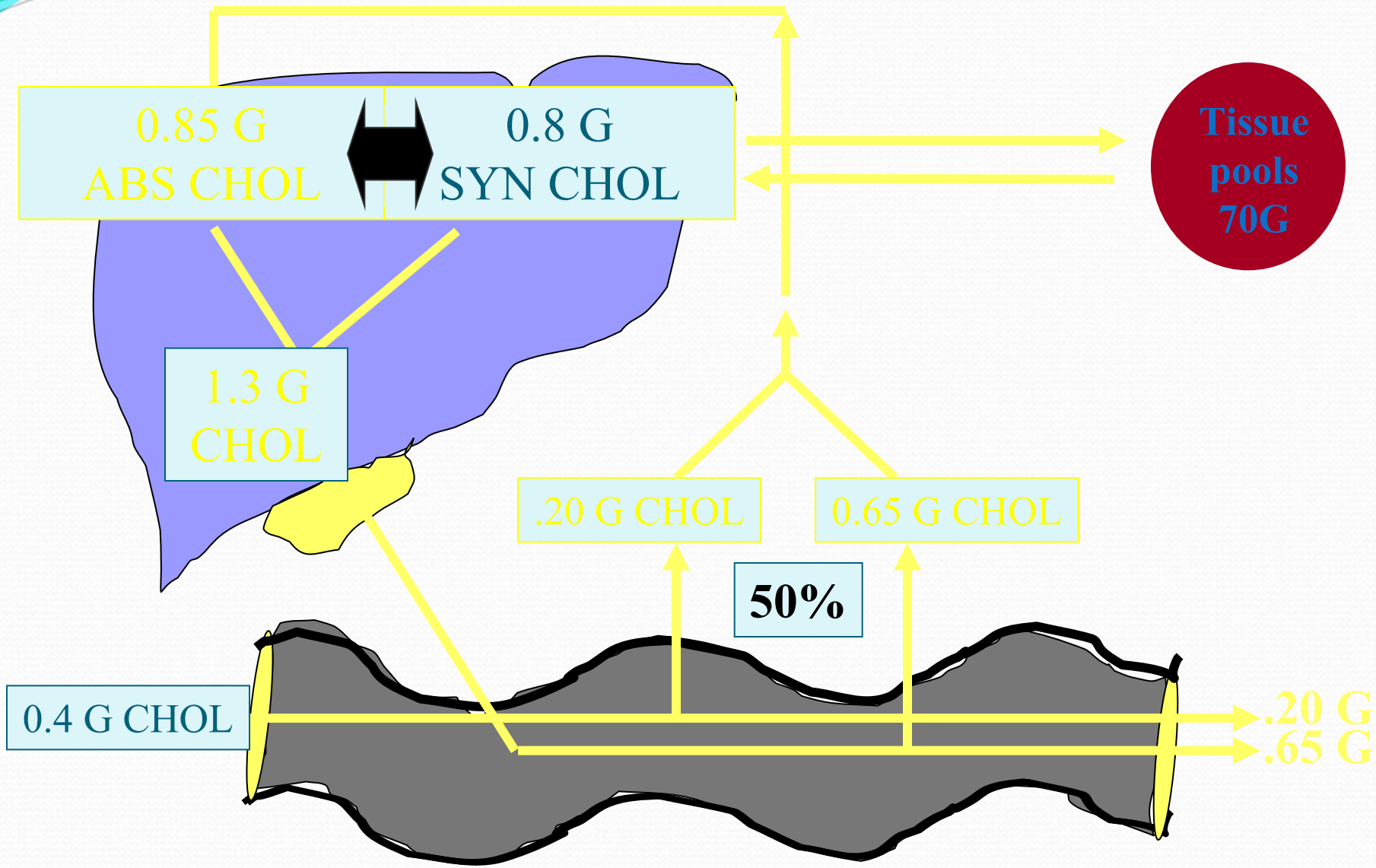
- Role of Bile Salts, cholesterol, phospholipids in gall stone formation.
- Importance of Bile Salts for cholesterol absorption

- Key concepts: bile salt absorption inhibitors
  - Bile acid binding compounds:
    - Welchol
    - Cholestyramine
    - Colestipol
    - Fiber
  - Surgery: Partial ileal bypass.

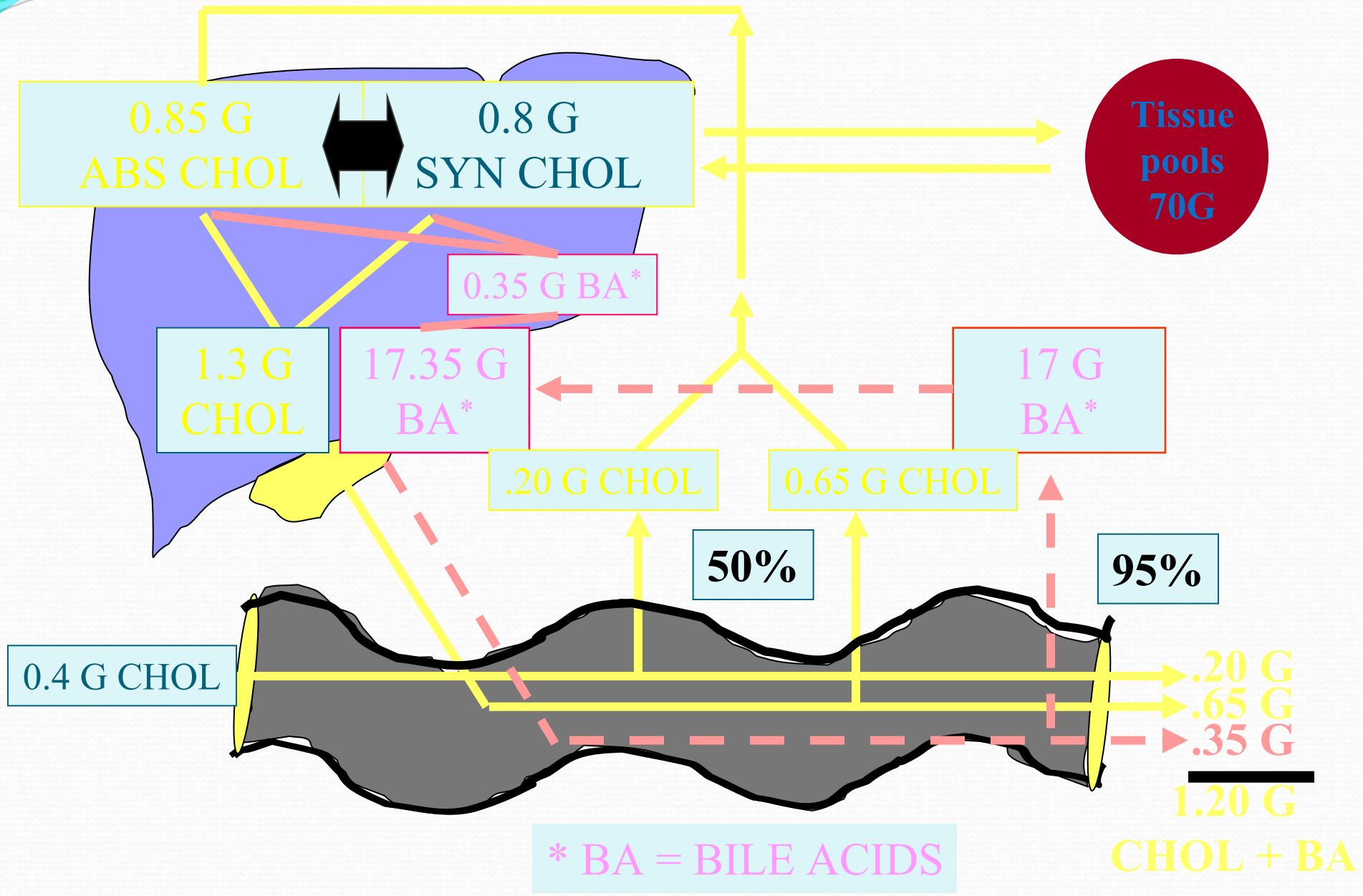
Bile Acid Synthesis



NORMAL CHOLESTEROL METABOLISM



NORMAL CHOLESTEROL METABOLISM



NORMAL TRIGLYCERIDE METABOLISM

- Key concepts: absorption
  - Triglyceride (i.e. energy) assimilation is key to the survival of the organism.
  - Dietary triglyceride must be hydrolyzed to fatty acids, mono-glycerides and glycerol prior to absorption.
  - Fatty acids must partition to micellar phase for absorption.
  - For transport, triglyceride must be reconstituted from glycerol and fatty acid and incorporated into chylomicrons.

Structures of Fatty Acids

18:0

cis-18:1 ω-6

trans-18:1 ω-6

18:2 ω-6

18:3 ω-3

Structures of Fatty Acids

16:0 (palmitic)

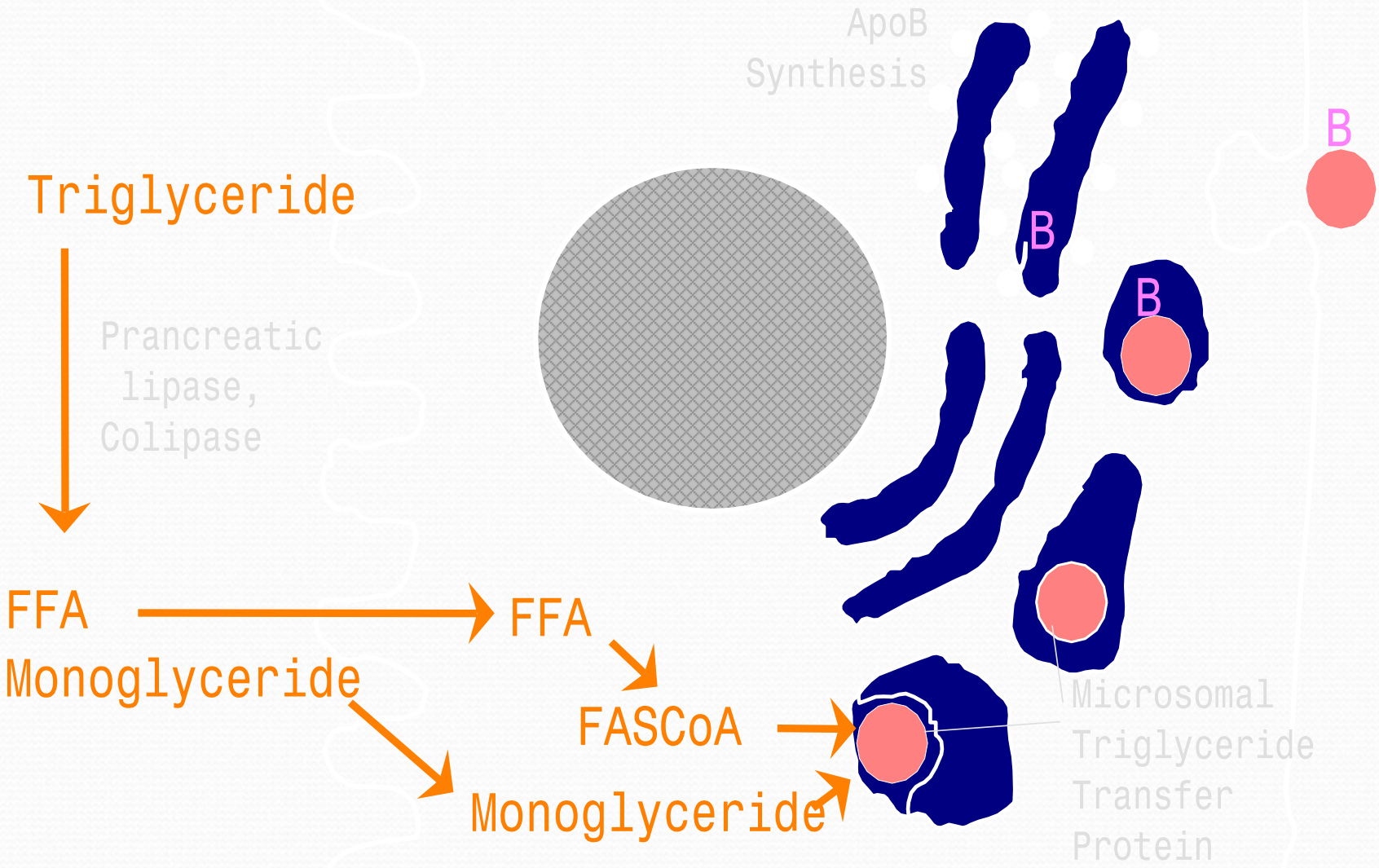
cis-18:1 ω-6 (oleic)

trans-18:1 ω-6 (elaidic)

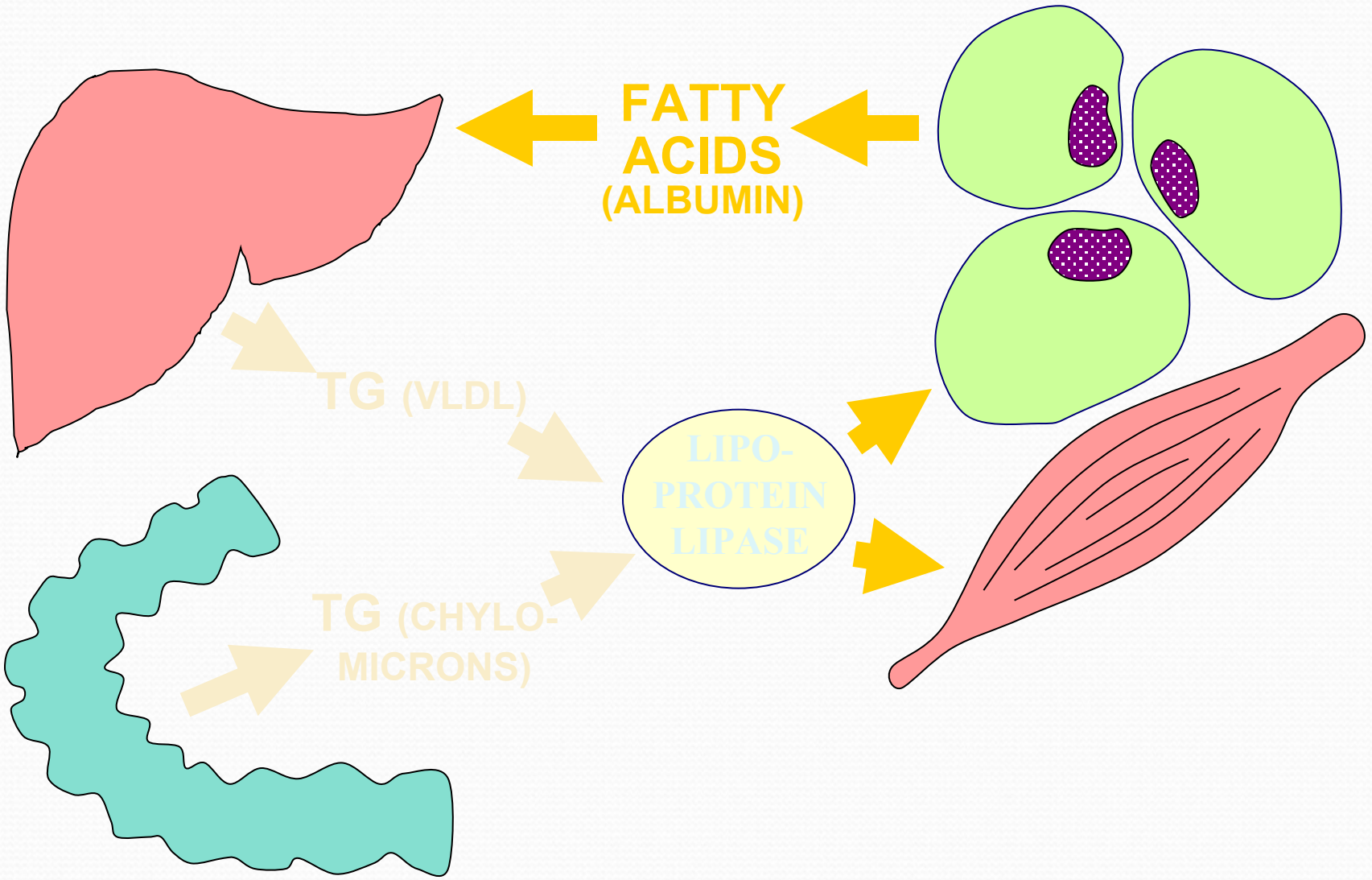
18:2 ω-6 (linoleic)

18:3 ω-3 (alpha linolenic)

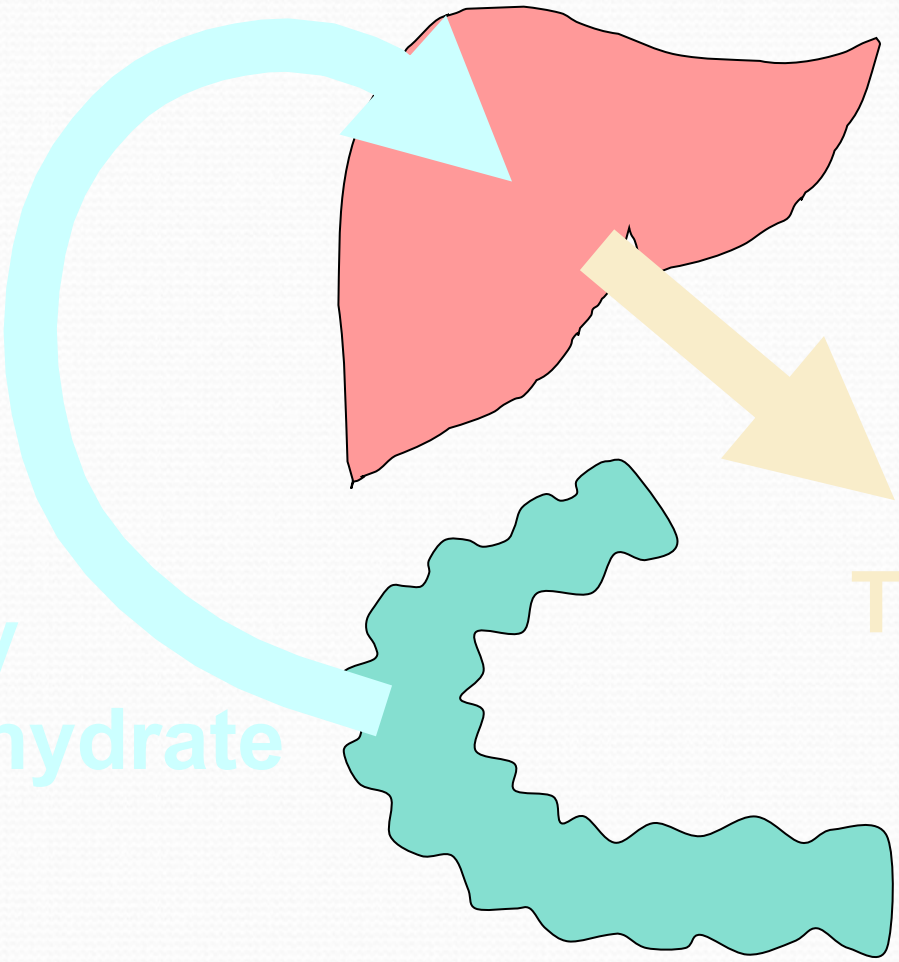
20:5 ω-3 (EPA)


ApoB
Synthesis
B
B
B
Triglyceride
Prancreatic
lipase,
Colipase
FFA
Monoglyceride
FFA
FASCoA
Monoglyceride
Microsomal
Triglyceride
Transfer
Protein

Fatty Acid and Triglyceride Flux

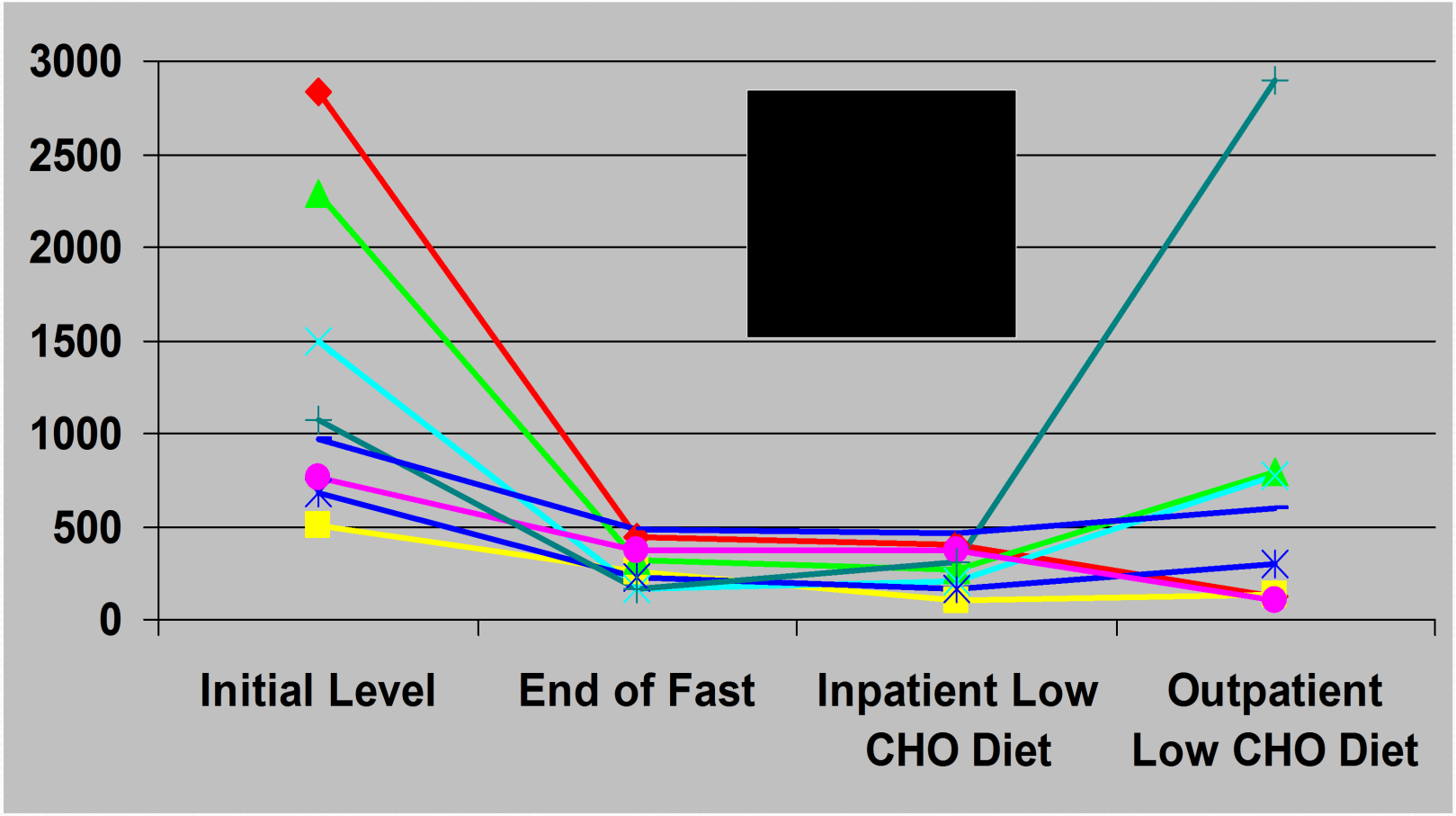


Dietary Carbohydrate Increases VLDL Production



ffect of Carbohydrate Restriction on Carbohydrate-nduced Hypertriglyceridemia

Treatment: Fast for average 5 days, then consume low CHO diet.

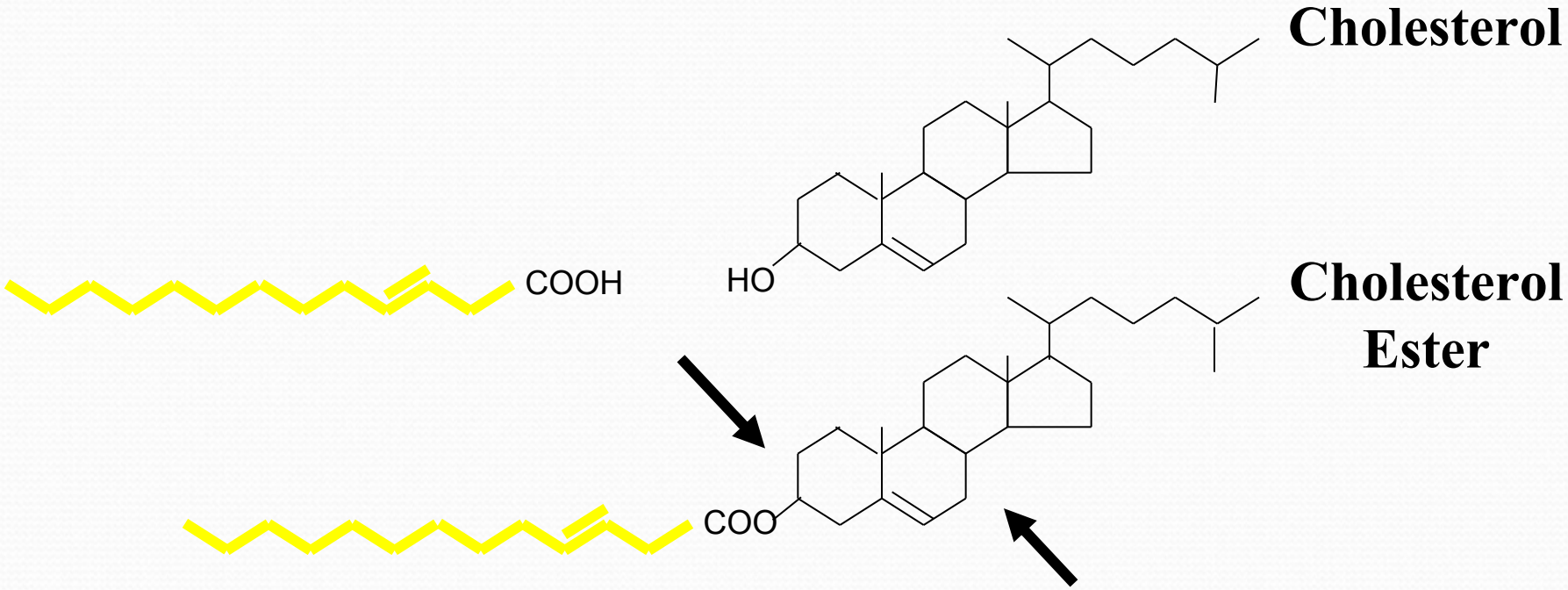


Reisell et al., Am J Clin Nutr 1966;19:84

Lipoprotein Metabolism

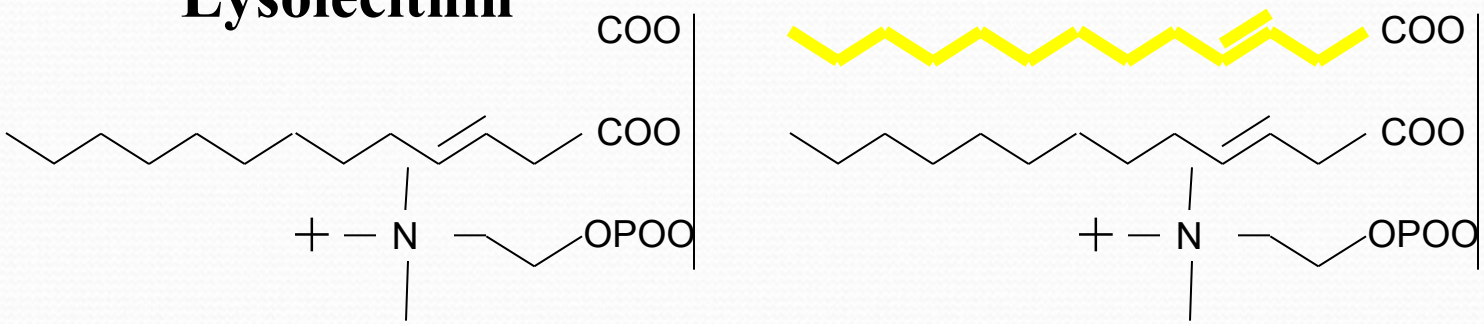
Cholesterol Ester Synthesis

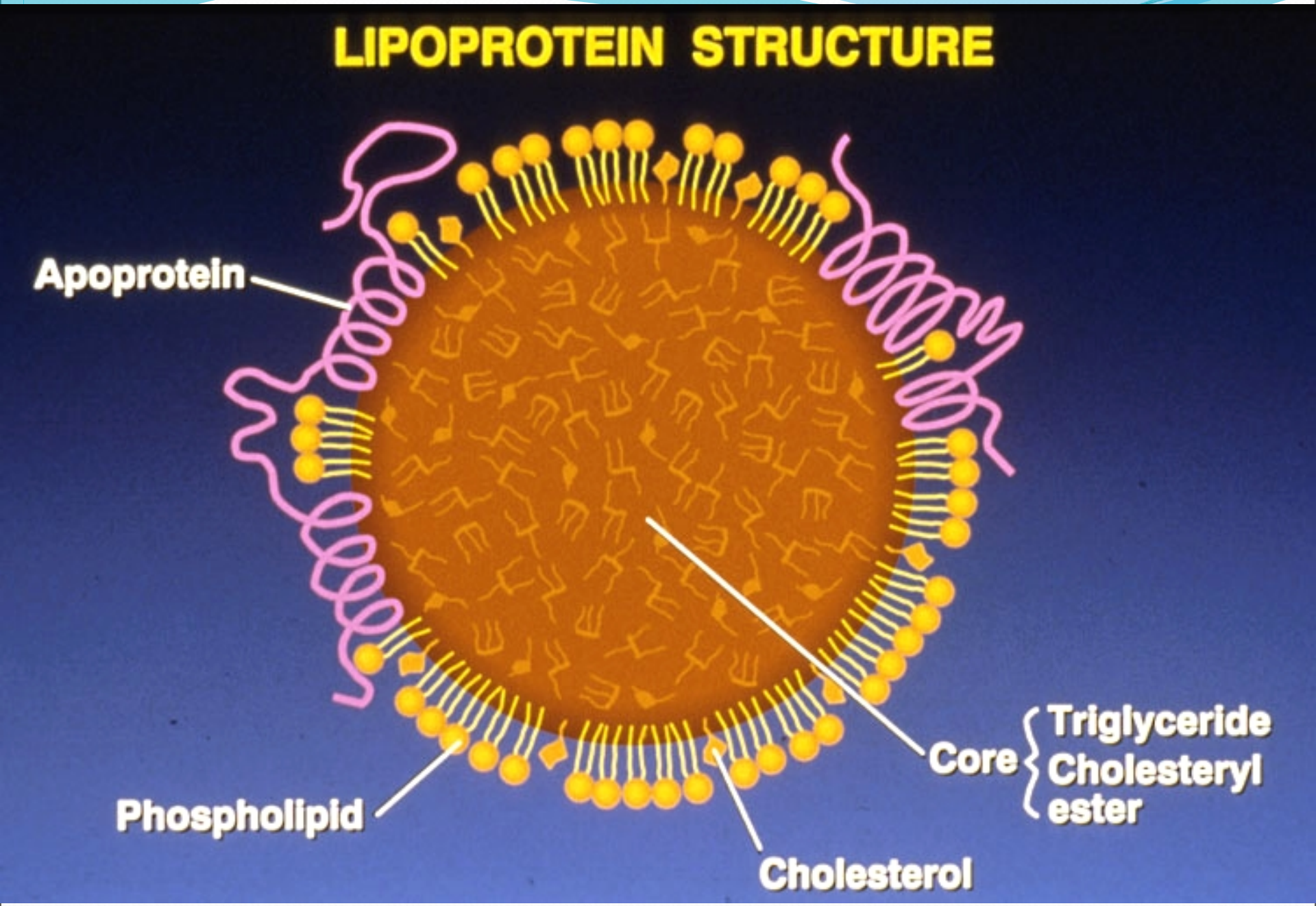
Acyl-Cholesterol Acyl Transferase (ACAT)

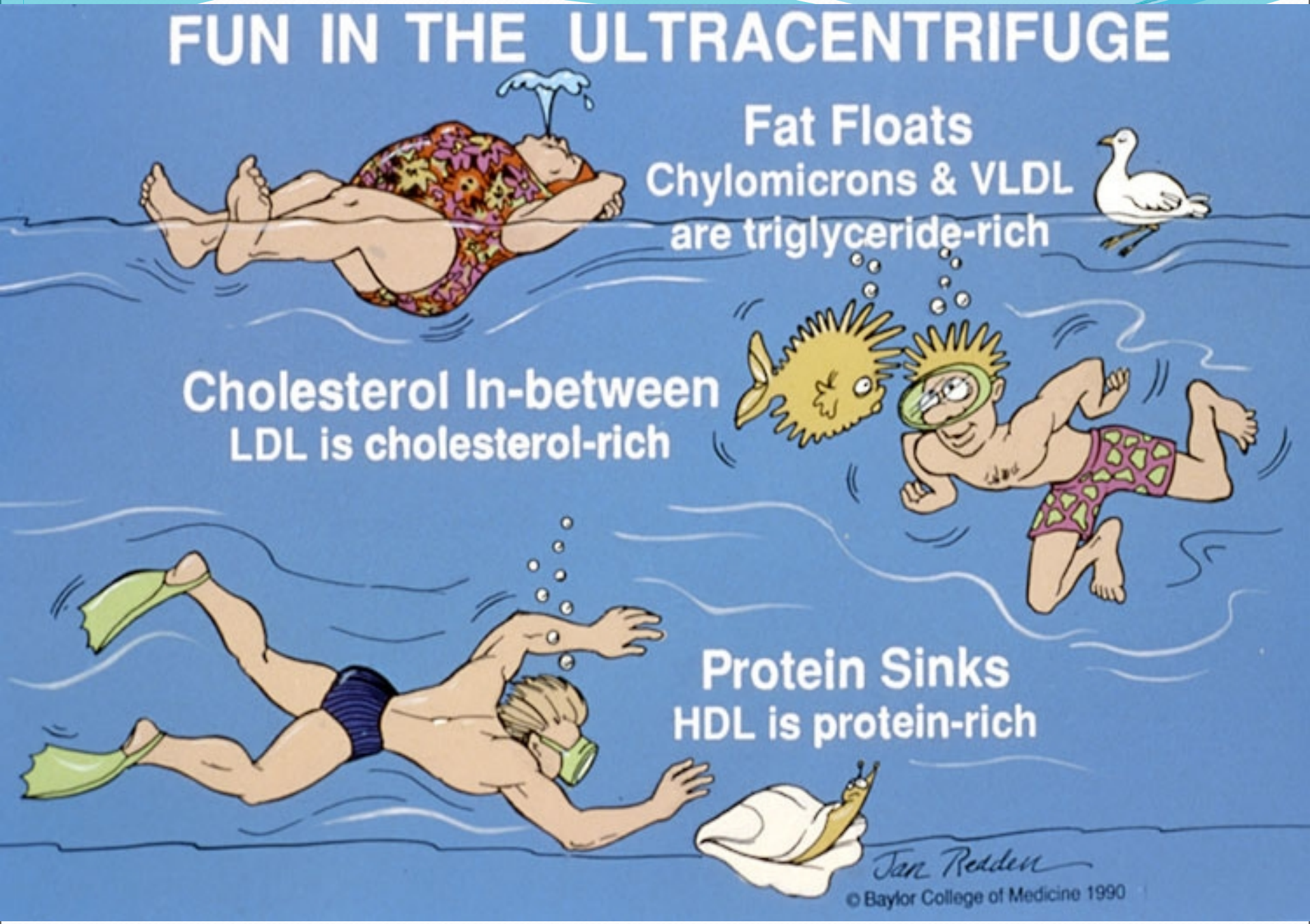


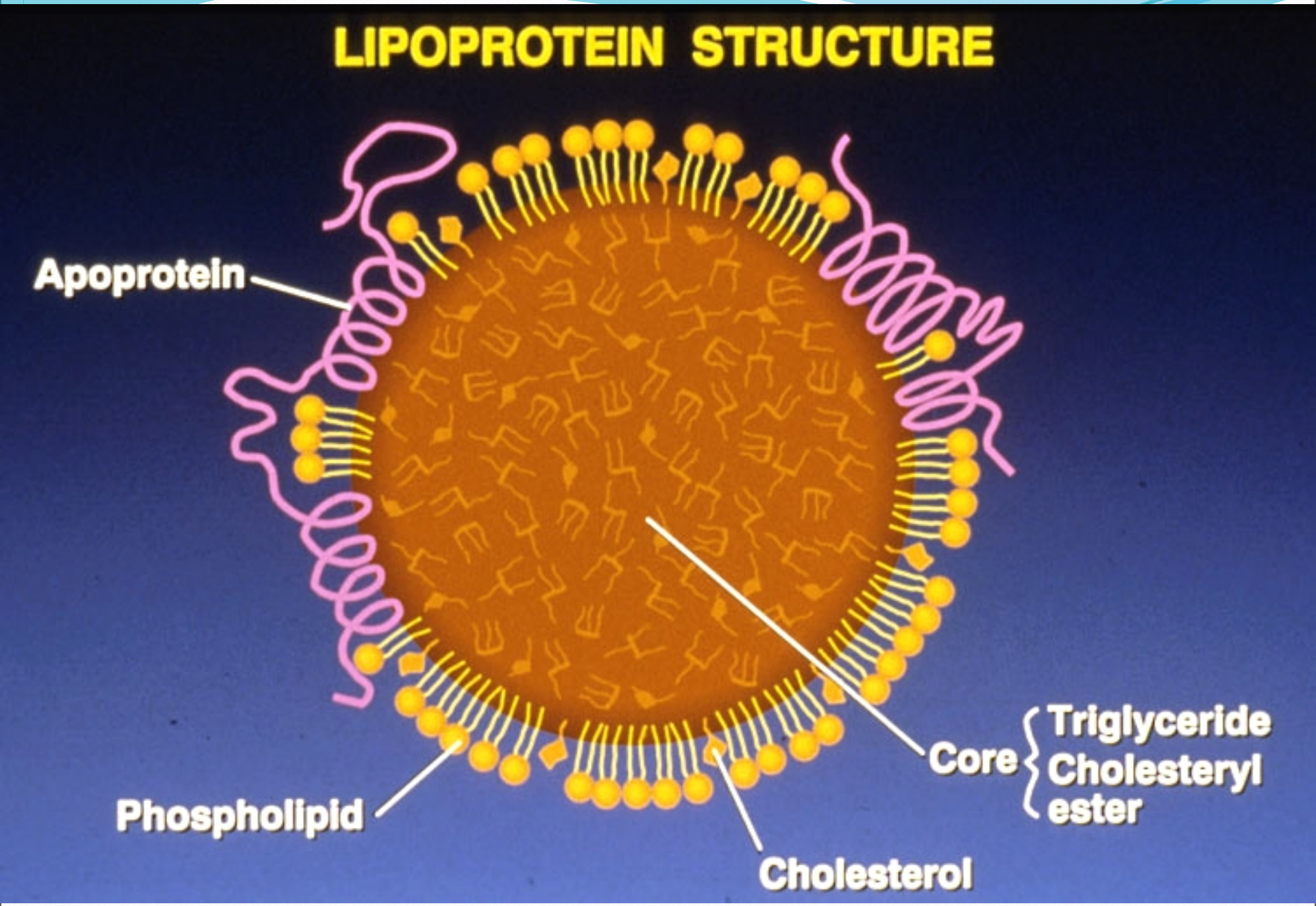
Lecithin-Cholesterol Acyl Transferase (LCAT)

Lysolecithin



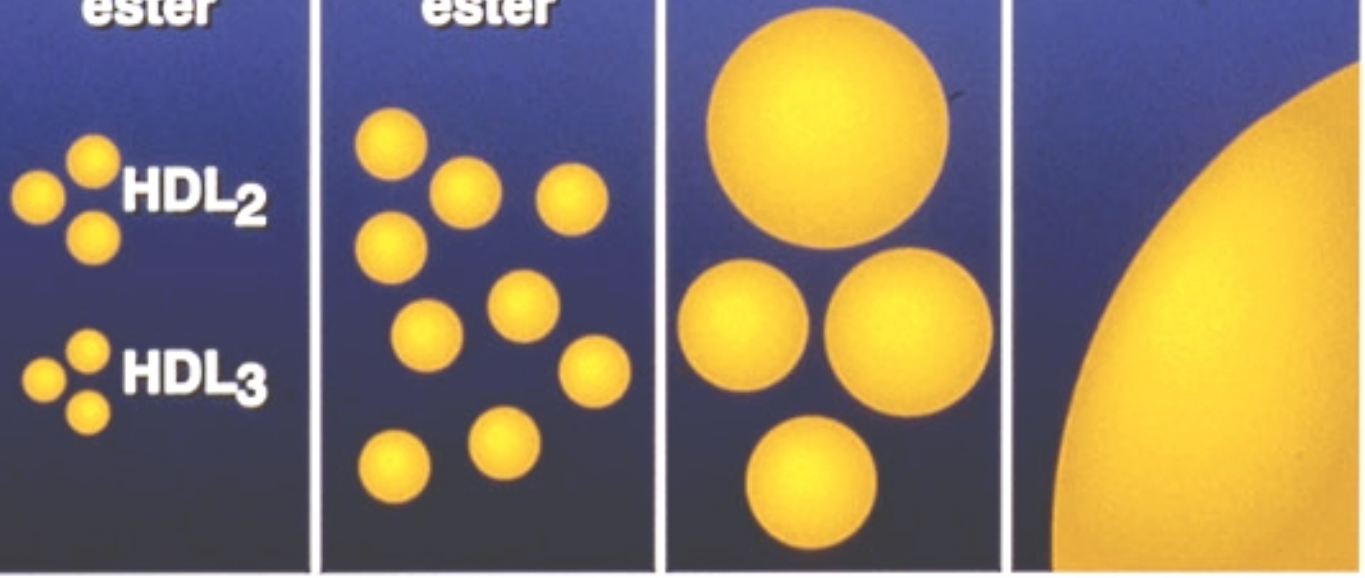

LIPOPROTEIN STRUCTURE
Apoprotein
Phospholipid
Cholesterol
Core
Triglyceride
Cholesteryl ester


FUN IN THE ULTRACENTRIFUGE
Fat Floats
Chylomicrons & VLDL
are triglyceride-rich
Cholesterol In-between
LDL is cholesterol-rich
Protein Sinks
HDL is protein-rich
Jan Redden
© Baylor College of Medicine 1990


LIPOPROTEIN STRUCTURE
Apoprotein
Phospholipid
Cholesterol
Core
Triglyceride
Cholesteryl ester

FOUR MAJOR LIPOPROTEIN CLASSES

	High Density	Low Density	Very Low Density	Chylo-microns
Apolipo-proteins	A-I, A-II E, Cs	B-100	B-100, Cs, E	B-48, Cs, E, A-I, A-II
Major core lipids	Cholesteryl ester	Cholesteryl ester	Triglyceride	Triglyceride
Relative sizes	HDL_2 HDL_3			

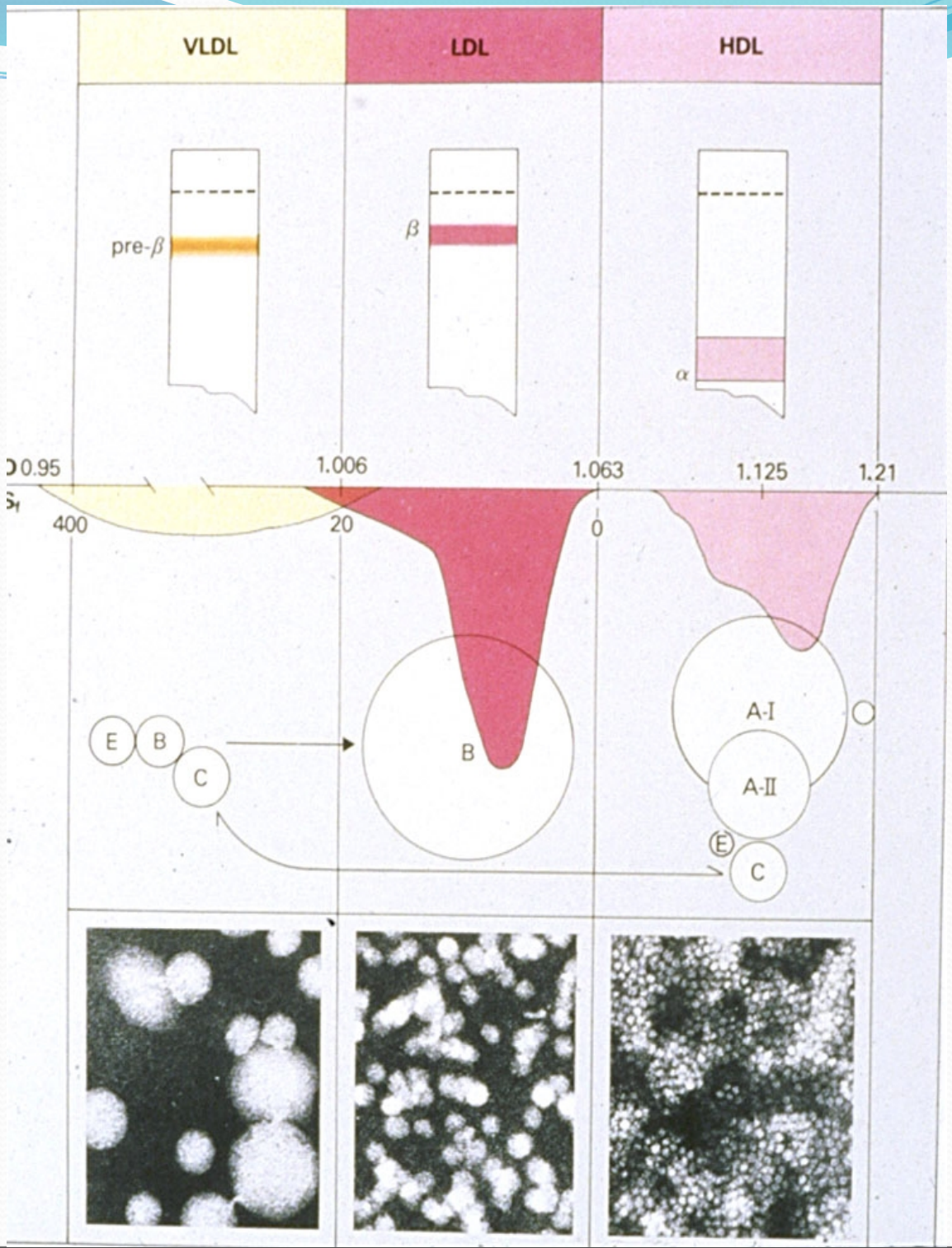


Lipoproteins:
Separation by –

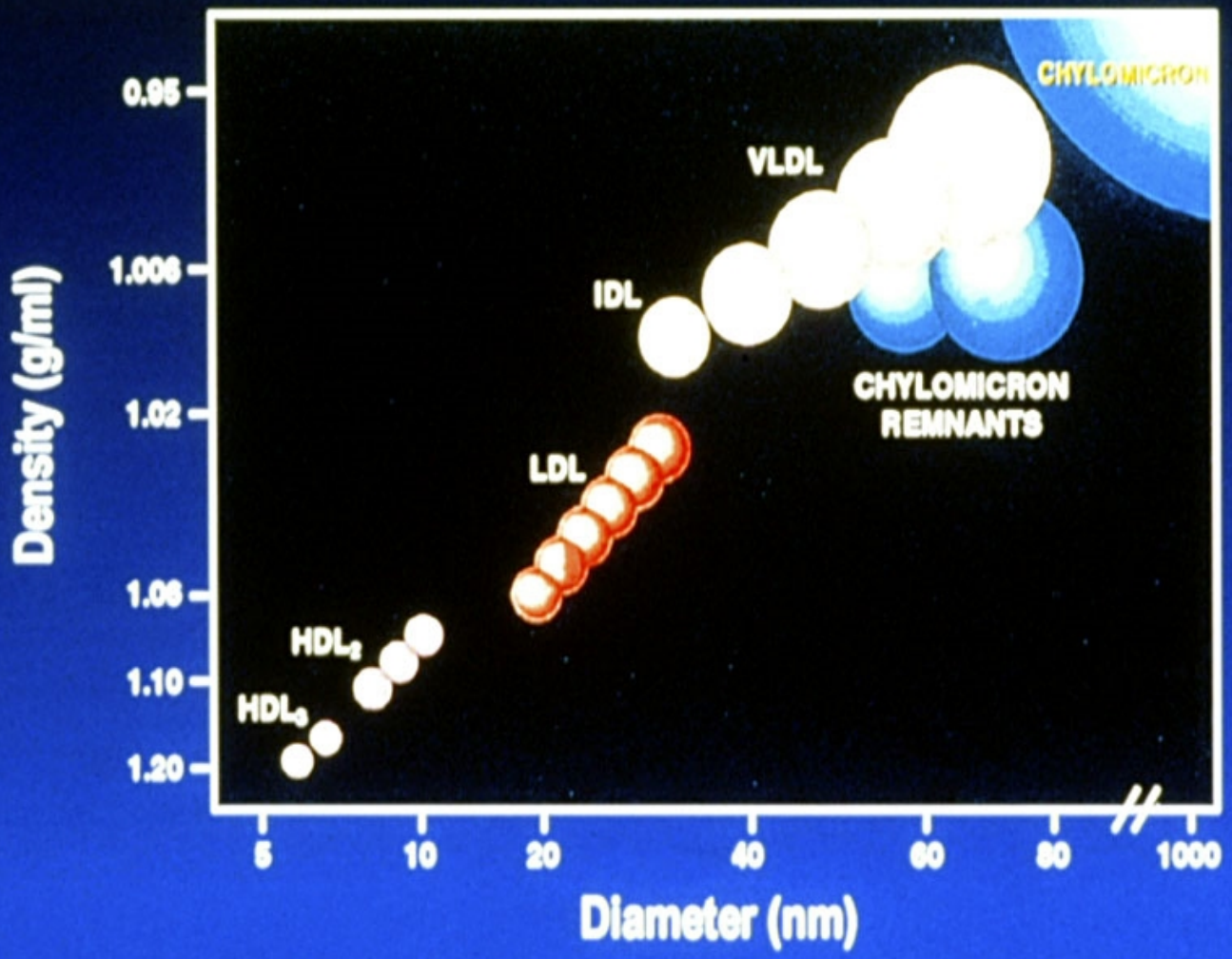
Electrophoresis

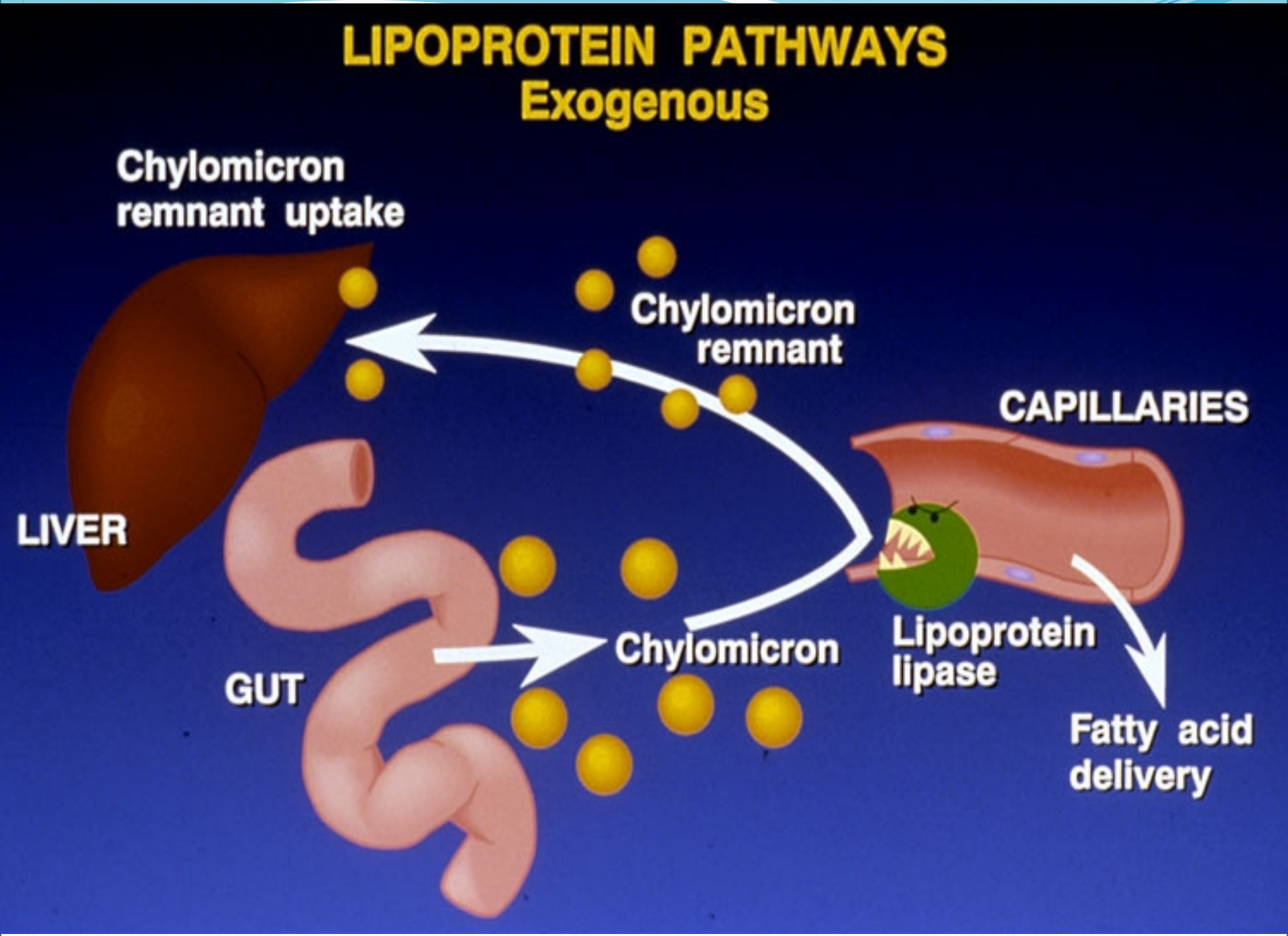
Density

Size by
Electron Microscopy

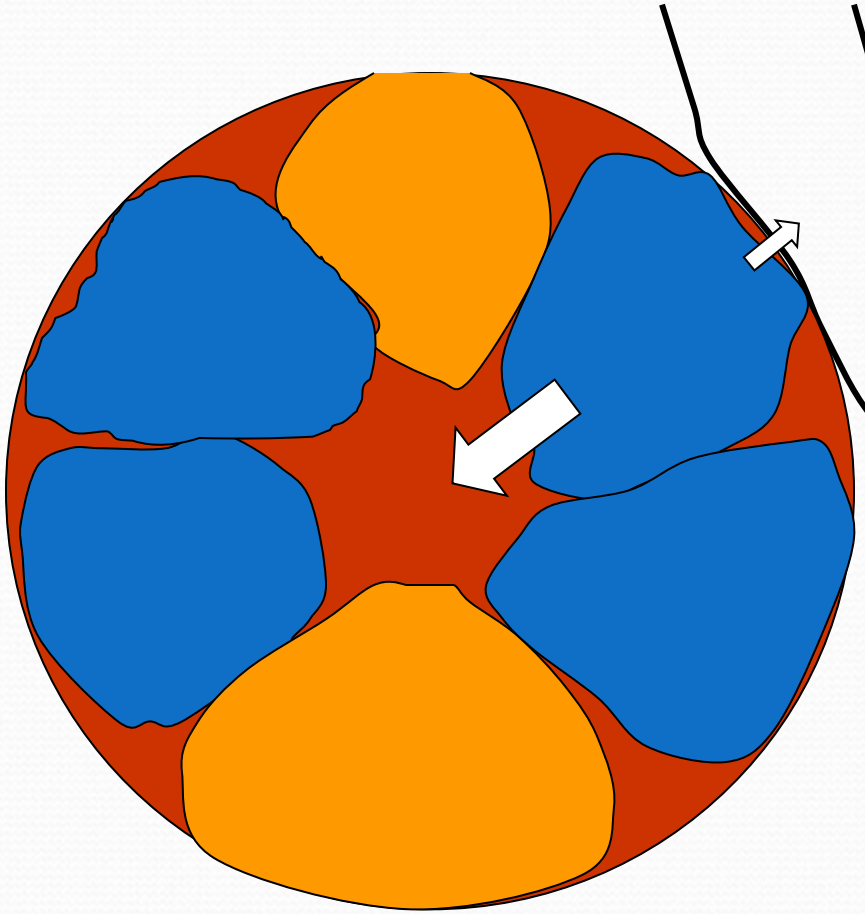


Distribution of Lipoproteins along a Density Continuum



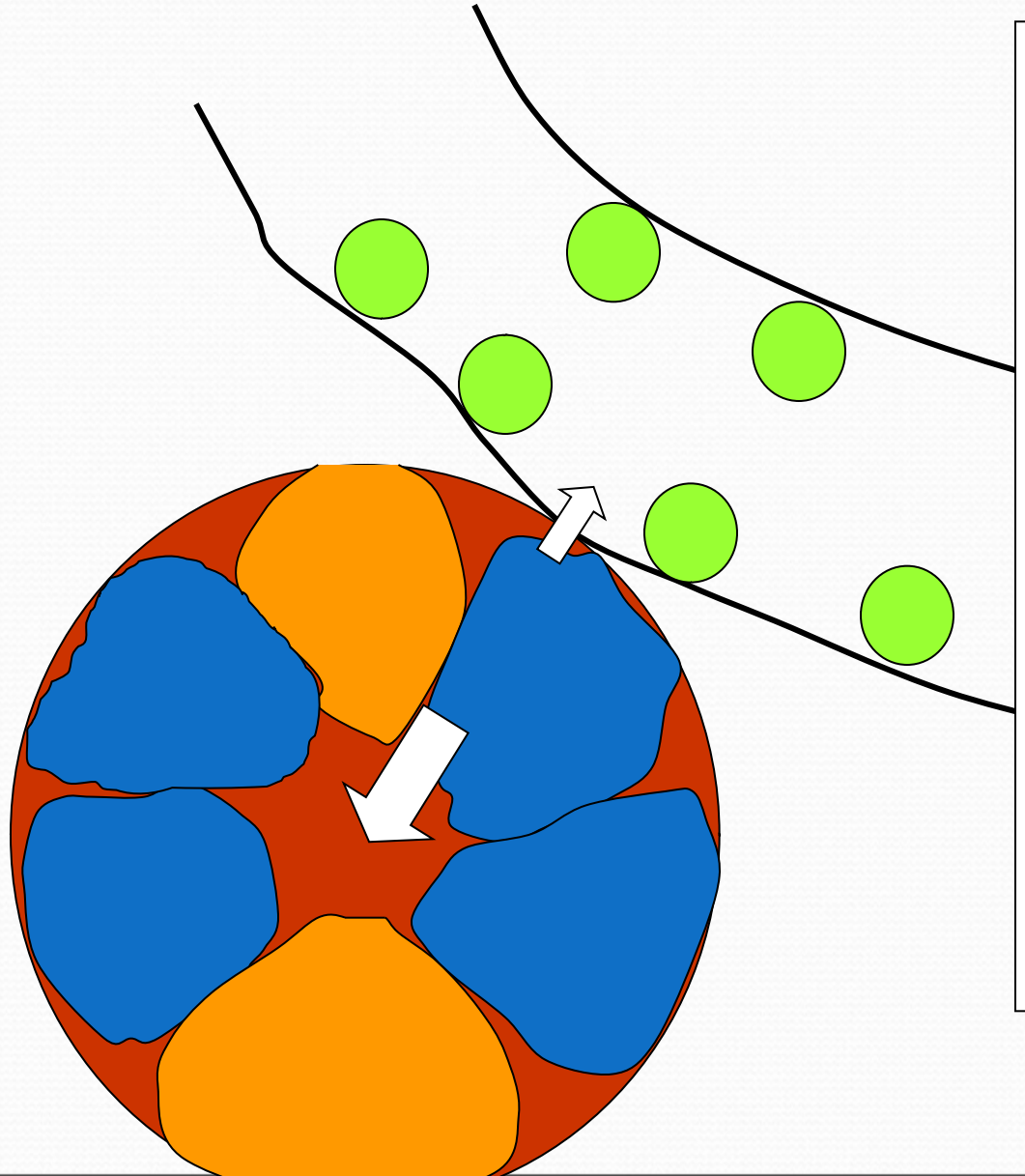

LIPOPROTEIN PATHWAYS
Exogenous
Chylomicron remnant uptake
Chylomicron remnant
CAPILLARIES
LIVER
GUT
Chylomicron
Lipoprotein lipase
Fatty acid delivery

Pancreatic Lipase Movement



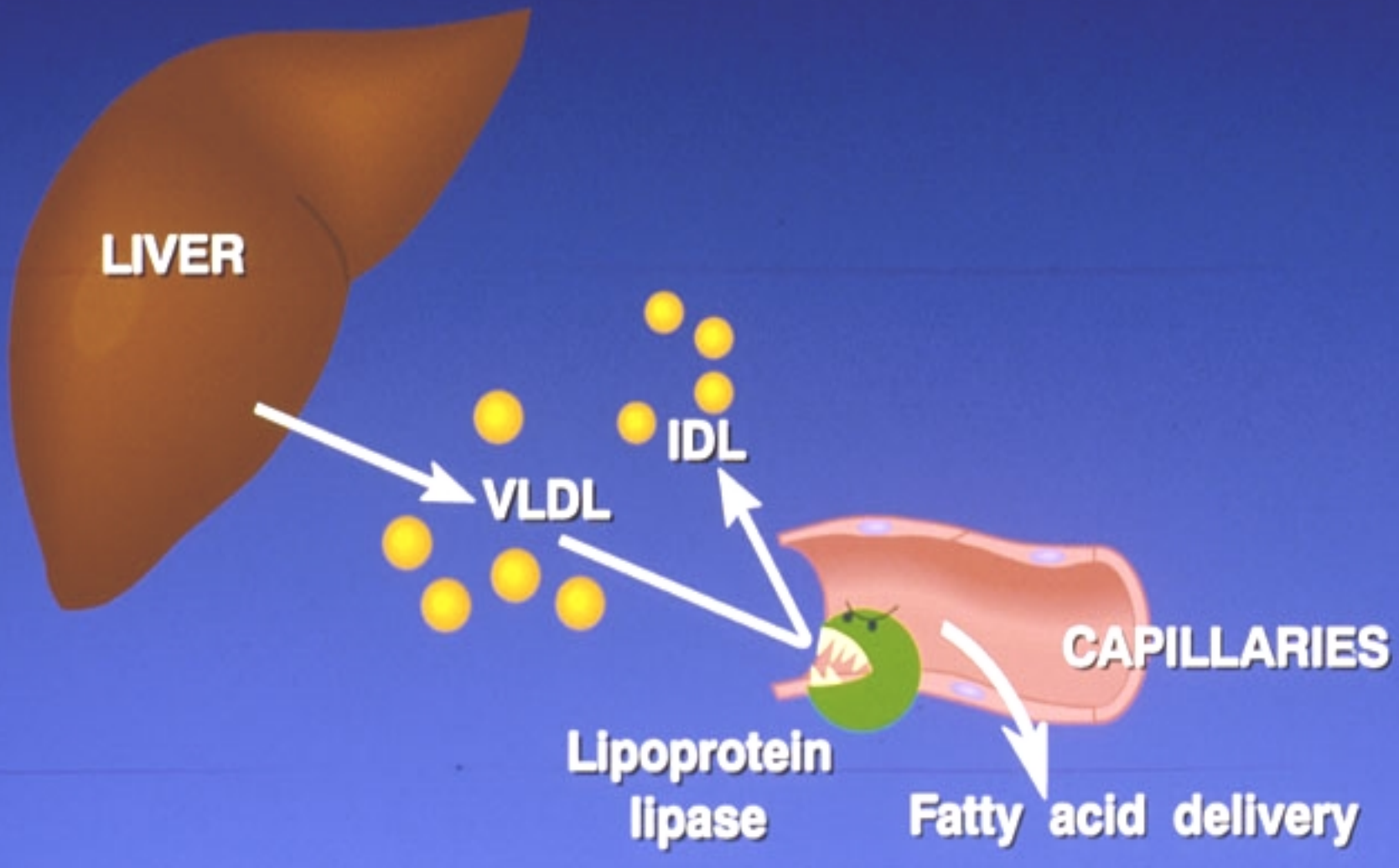
Most pancreatic lipase is secreted into the pancreatic duct, but some moves back into capillaries.

Chylomicron Role in Pancreatitis

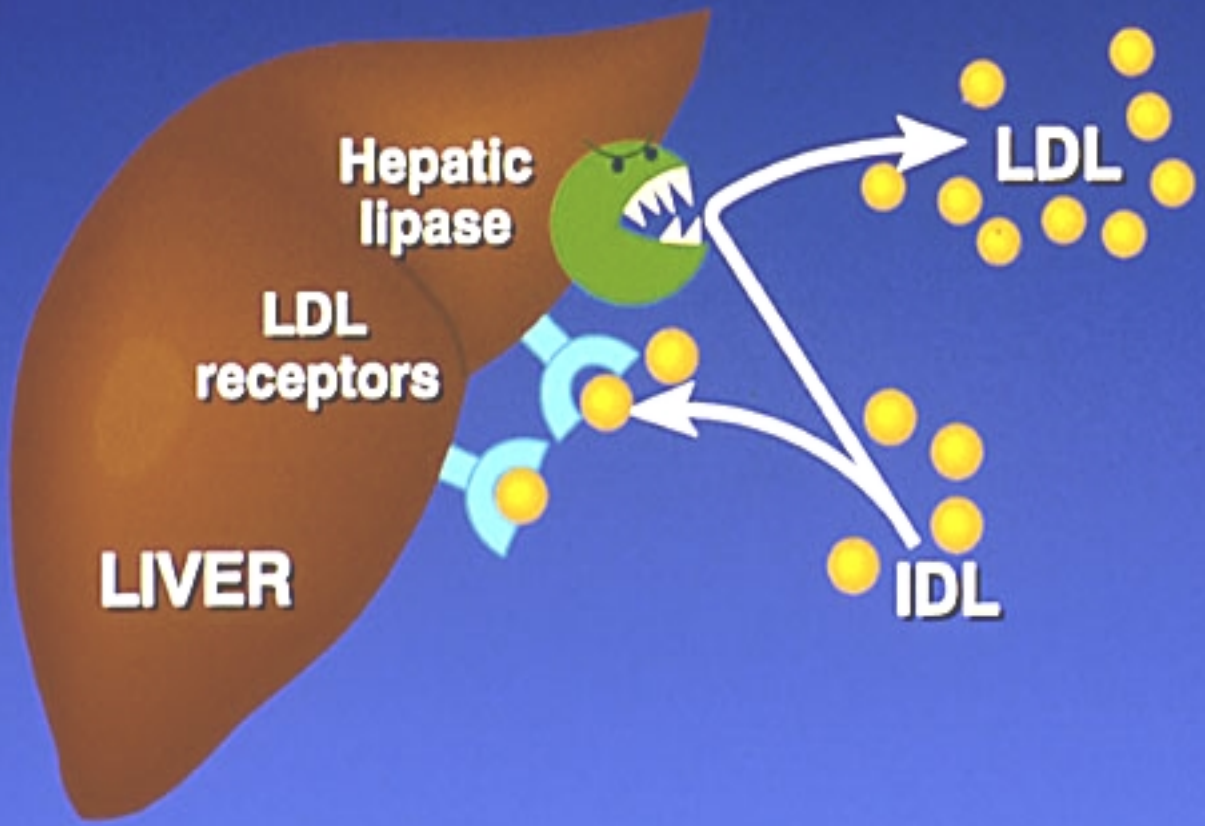


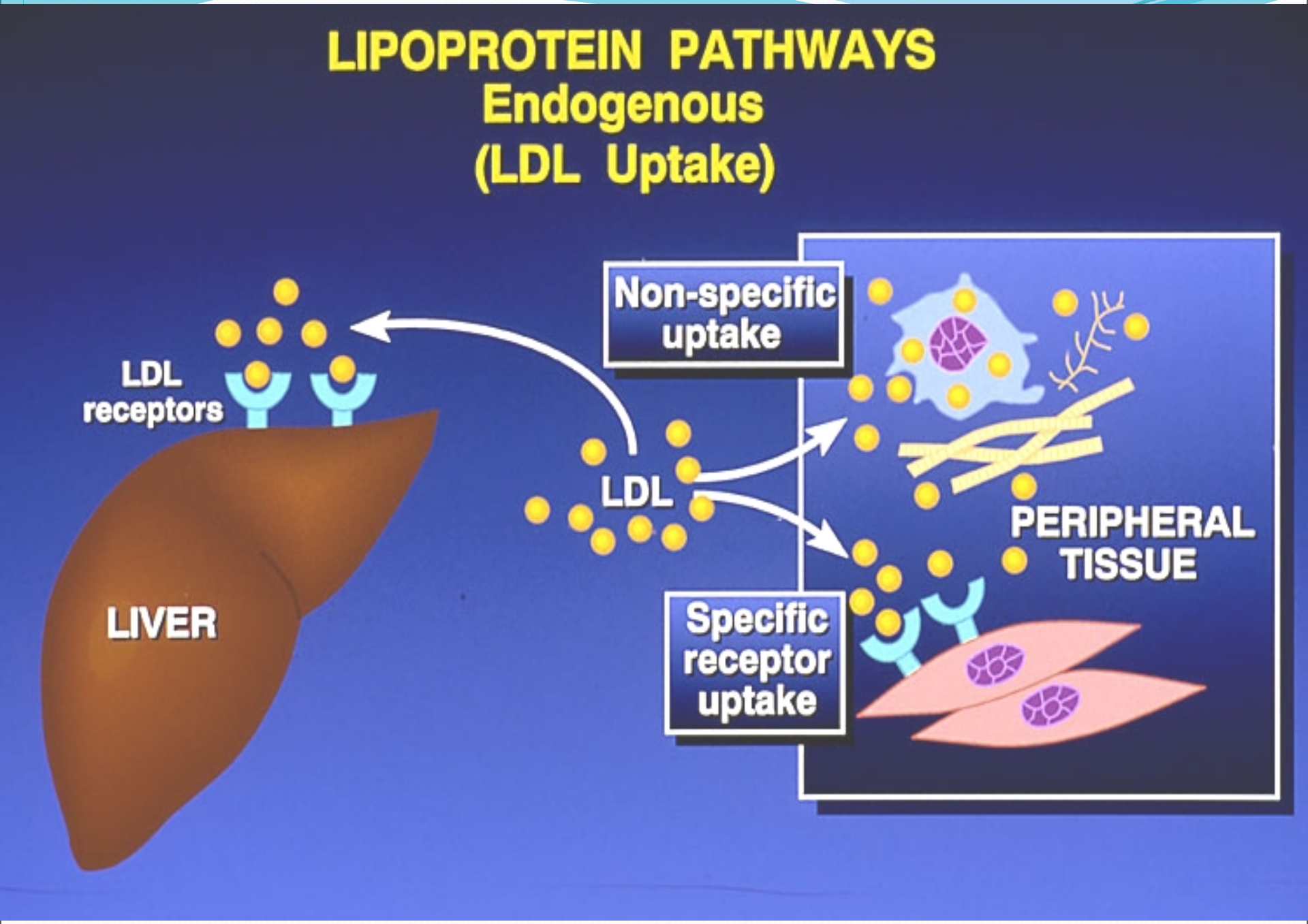
Pancreatic lipase acts on chylomicrons adherent to capillary endothelium, producing fatty acid anions, or soaps. By detergent action, cell membranes are disrupted, releasing more lipase, and additional fatty acid anions are produced in a vicious cycle.

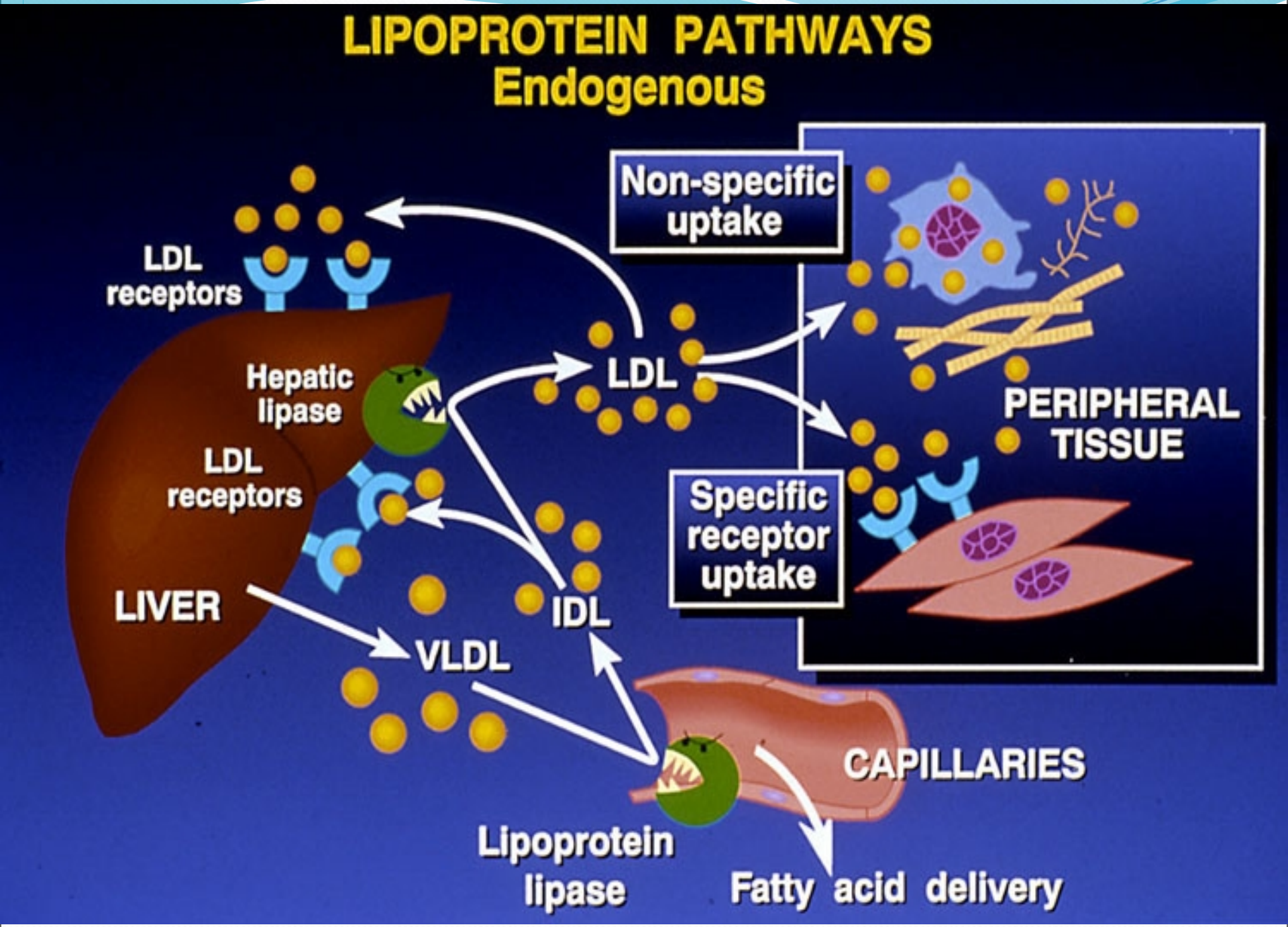
LIPOPROTEIN PATHWAYS
Endogenous
(VLDL-IDL)



LIPOPROTEIN PATHWAYS
Endogenous
(IDL-LDL)




LIPOPROTEIN PATHWAYS
Endogenous
(LDL Uptake)
Non-specific uptake
LDL receptors
LDL
PERIPHERAL TISSUE
LIVER
Specific receptor uptake

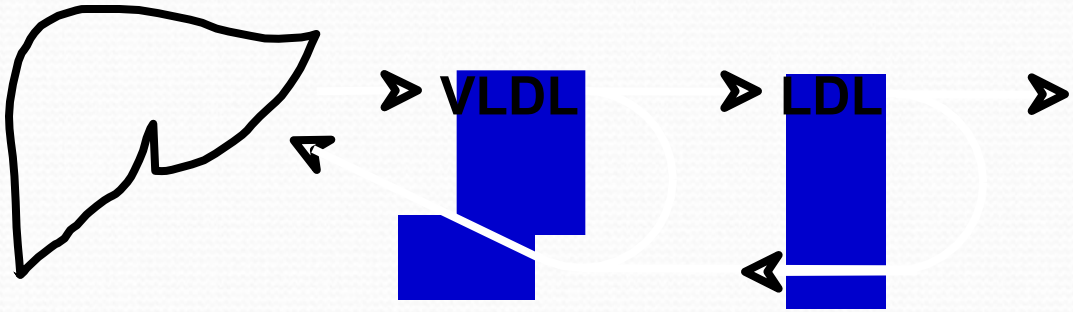

LIPOPROTEIN PATHWAYS
Endogenous
Non-specific uptake
LDL receptors
Hepatic lipase
LDL
PERIPHERAL TISSUE
LDL receptors
Specific receptor uptake
LIVER
IDL
VLDL
CAPILLARIES
Lipoprotein lipase
Fatty acid delivery

Apolipoproteins

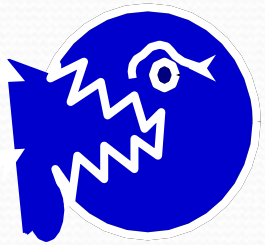
apoA-I	HDL structural protein; LCAT activator;RCT
apoA-II	HL activation
apoA-IV	Tg metabolism; LCAT activator; diet response
apoB-100	Structural protein of all LP except HDL
apoB-48	Binding to LDL receptor
apoC-I	Inhibit Lp binding to LDL R; LCAT activator
apoC-II	LpL activator
apoC-III	LpL inhibitor; antagonizes apoE
apoE	B/E receptor ligand *E2:IDL; *E4: Diet Responsivity

Metabolic Relationships Among Lipoproteins

1.

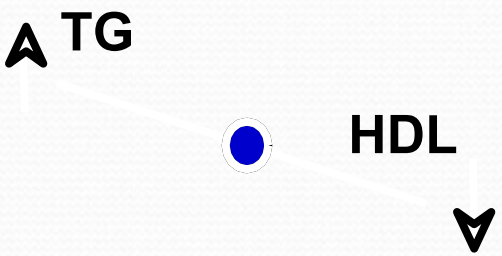


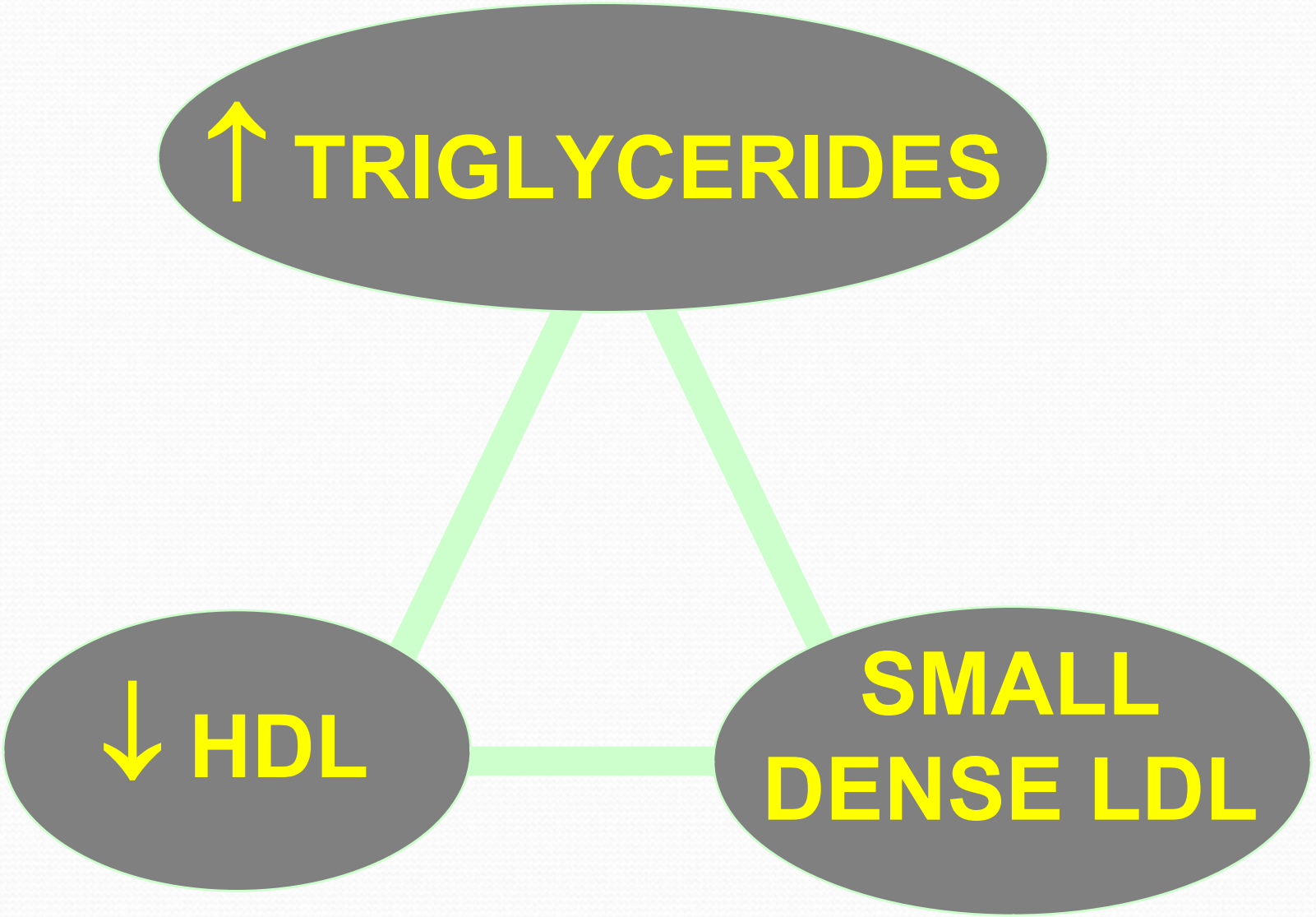
2.



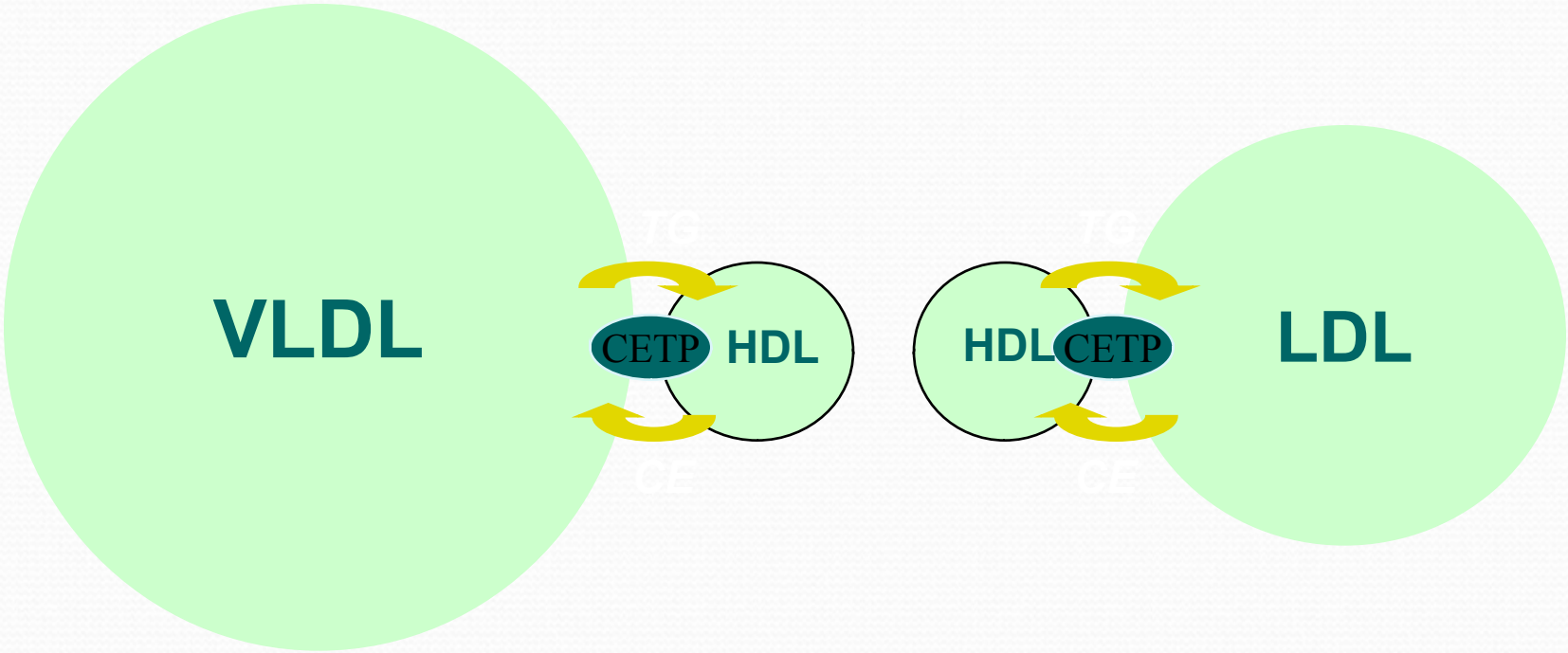
Lipoprotein Lipase`

3.

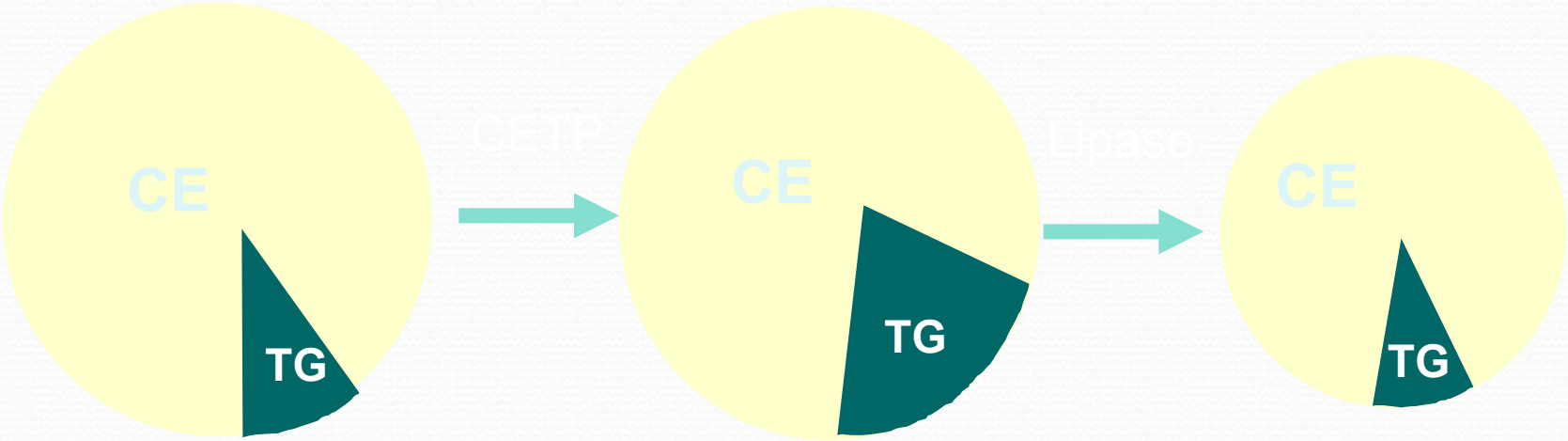



↑ TRIGLYCERIDES
↓ HDL
SMALL DENSE LDL

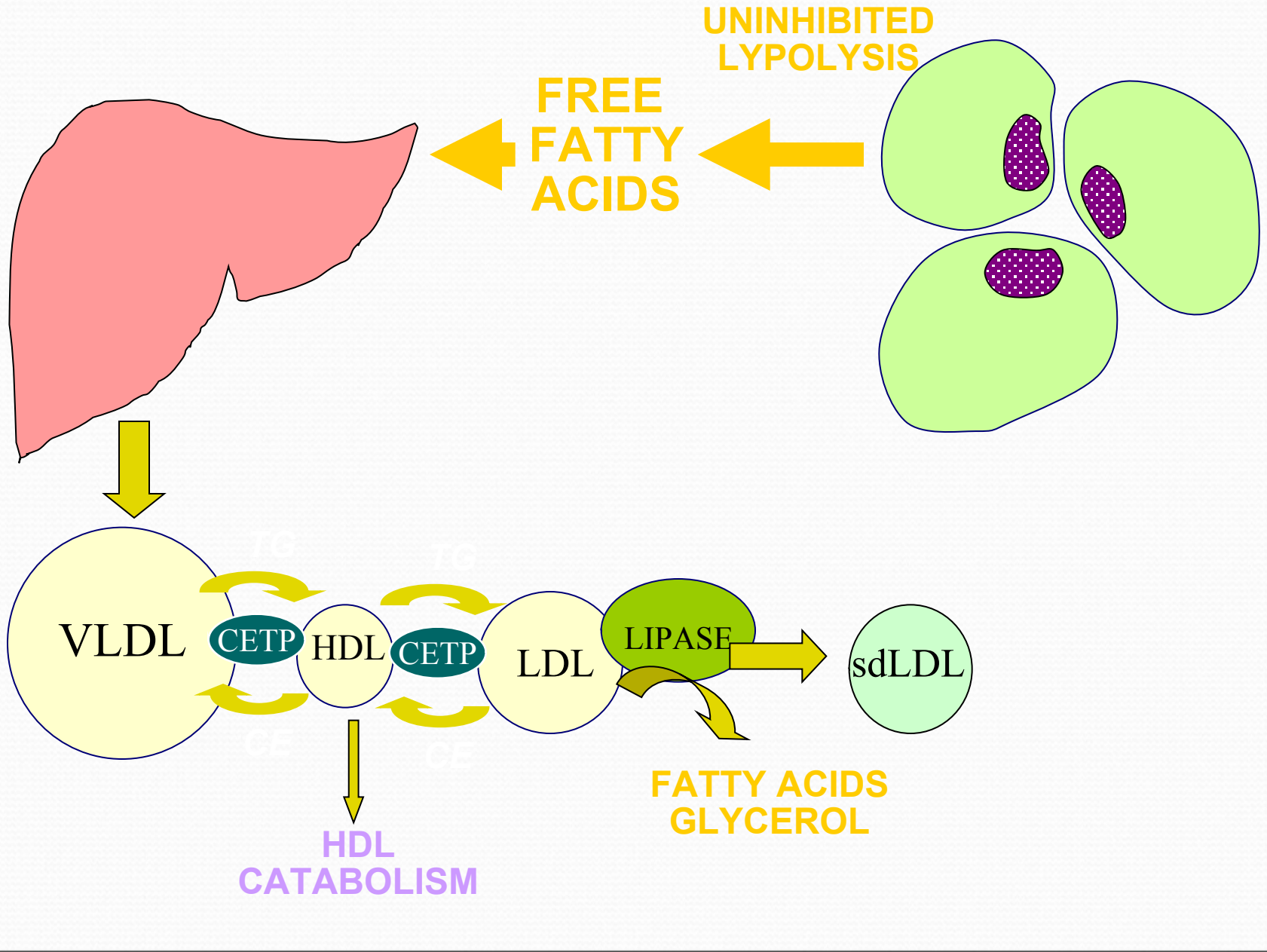
Role of CETP in Triglyceride/ Cholesteryl Ester Exchange



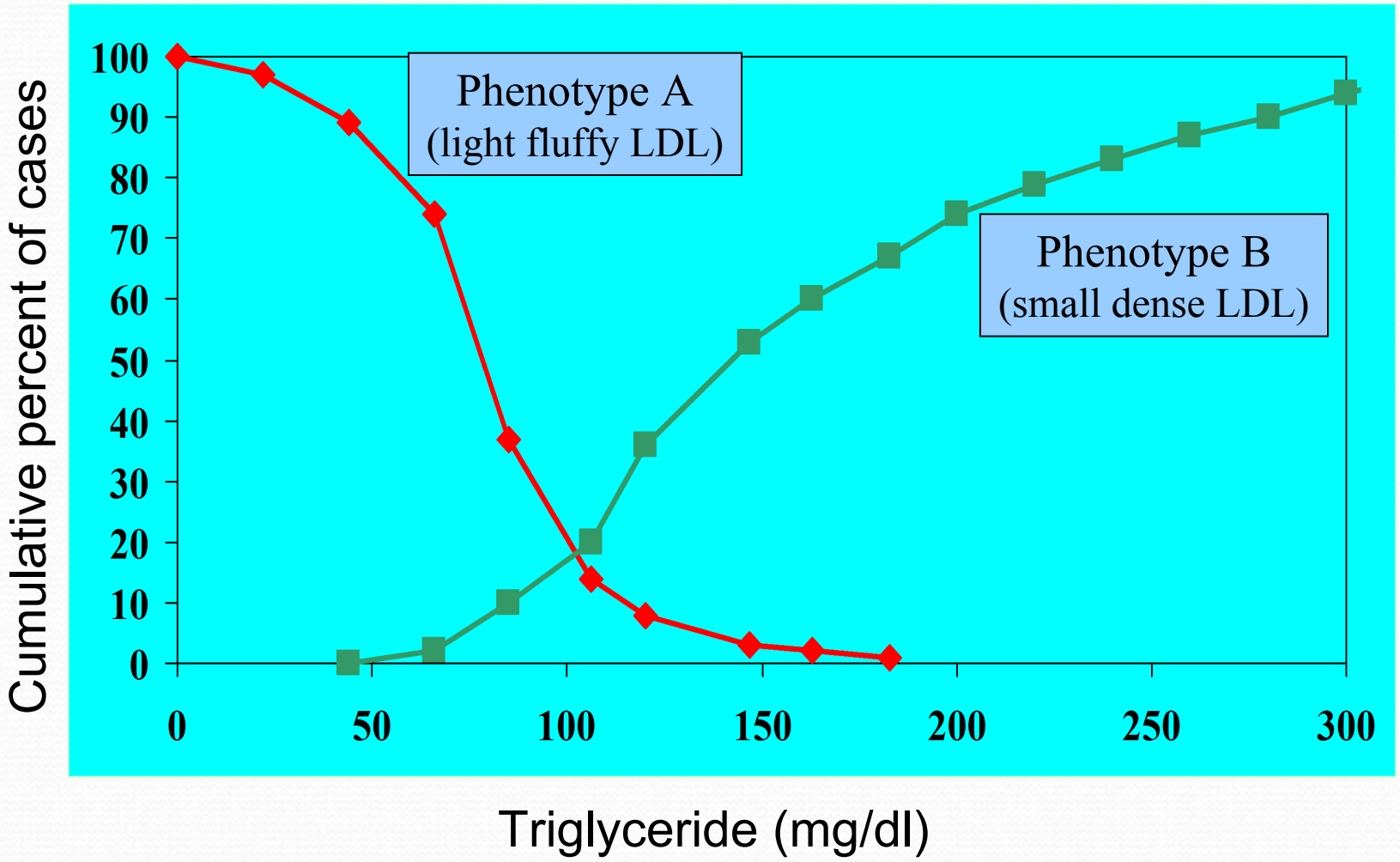
Role of Triglycerides in Producing Small Dense LDL or HDL



Dyslipidemia of Metabolic Syndrome

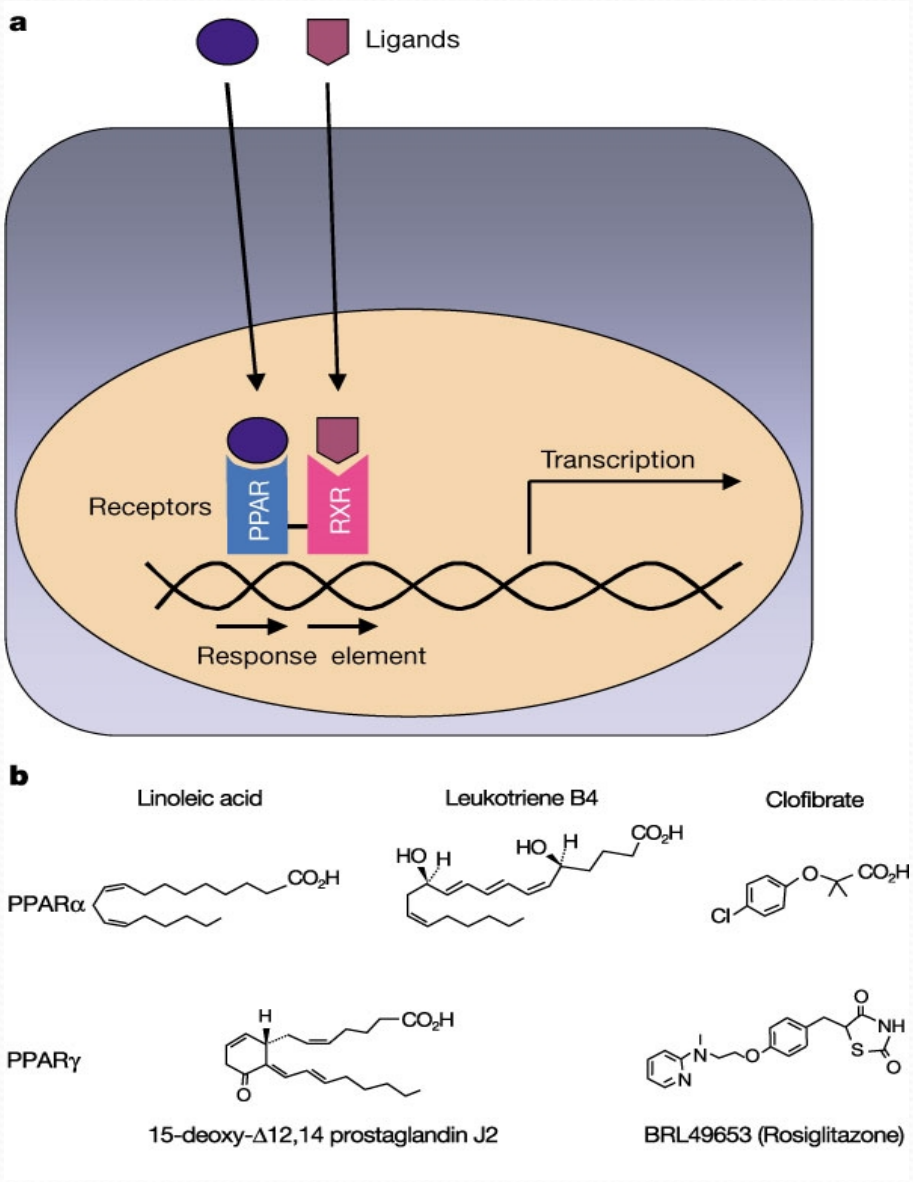


Distribution of LDL Size Phenotypes According to Triglyceride Levels



Austin et al, Circulation 1990; 82:495

Peroxisome Proliferator-Activated Receptor: A Nuclear Receptor for Metabolic Genes

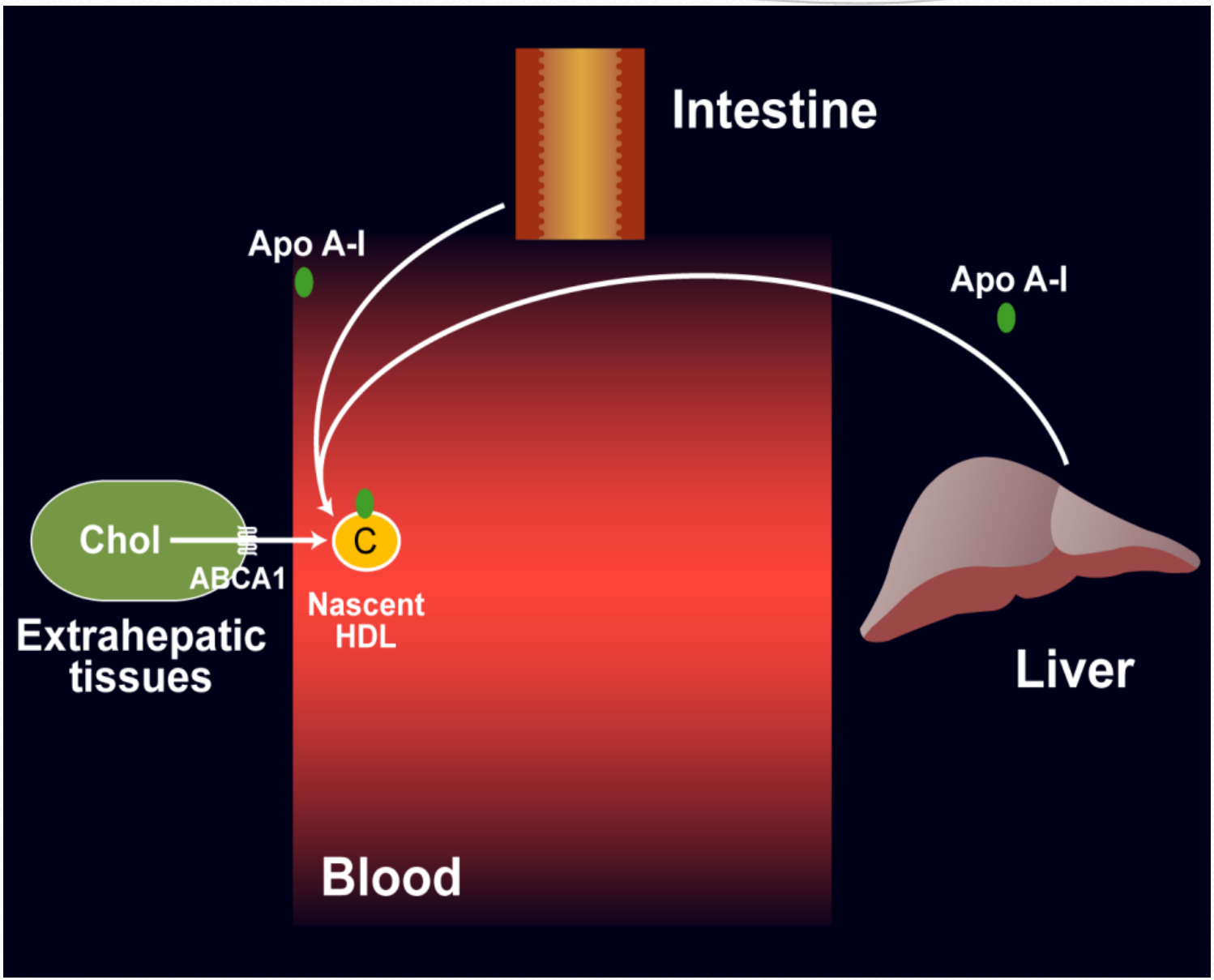


Role of PPAR* ✂ and ☎ in VLDL, LDL and HDL metabolism

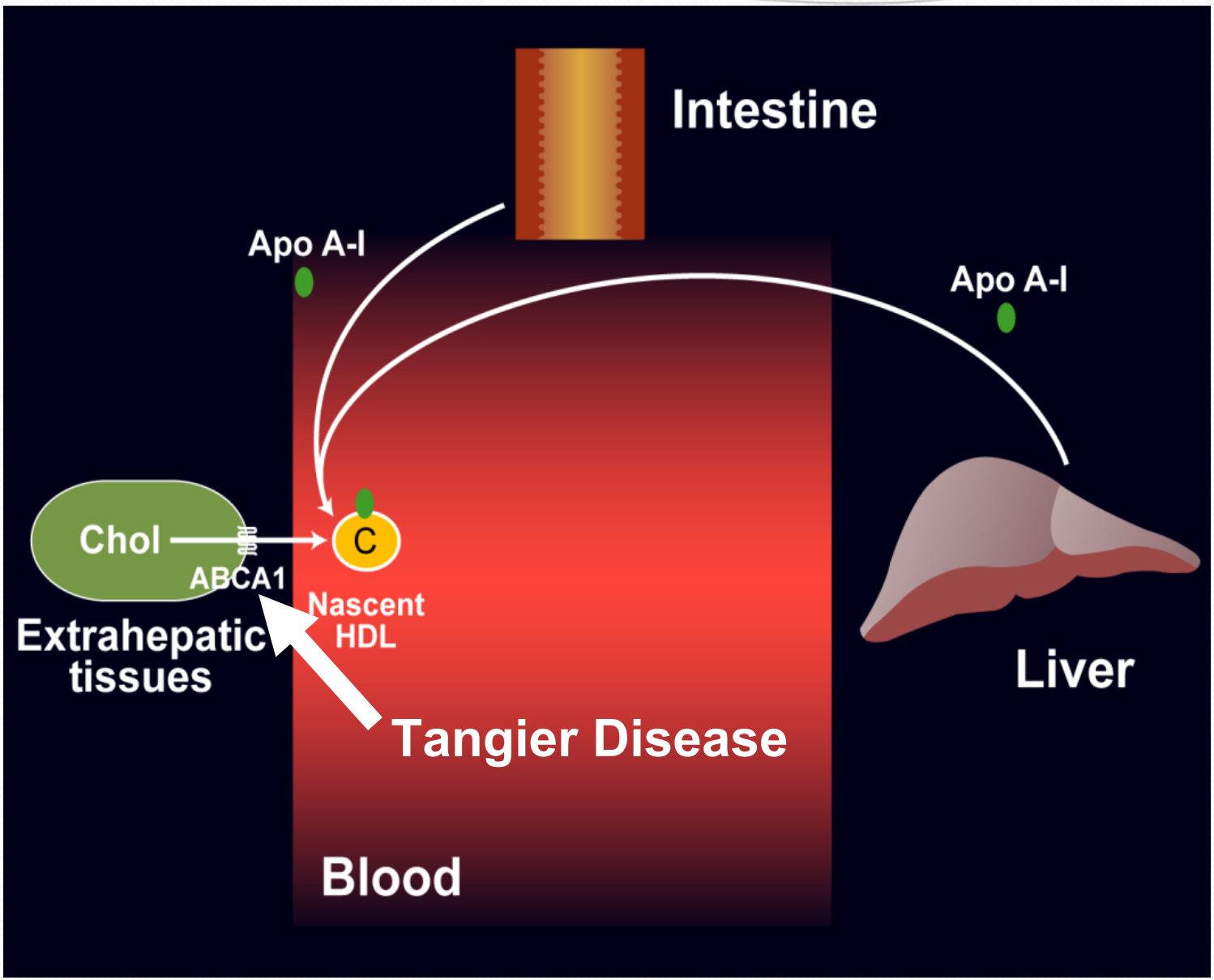
PPAR ✂	PPAR ☎
Tissues: Liver, kidney, heart, muscle. Ligands: fatty acids, fibrates Actions: Stimulate production of apo A I, lipoprotein lipase, increase expression of ABC A-1, increase FFA uptake and catabolism, decrease FFA and VLDL synthesis.	Tissues: Adipose tissue and intestine. Ligands: arachidonic acid, Glitazones Actions: increase expression of ABC A-1, increase FFA synthesis and uptake by adipocytes, increase insulin sensitivity (?)

* Peroxisome Proliferator Activated Receptor

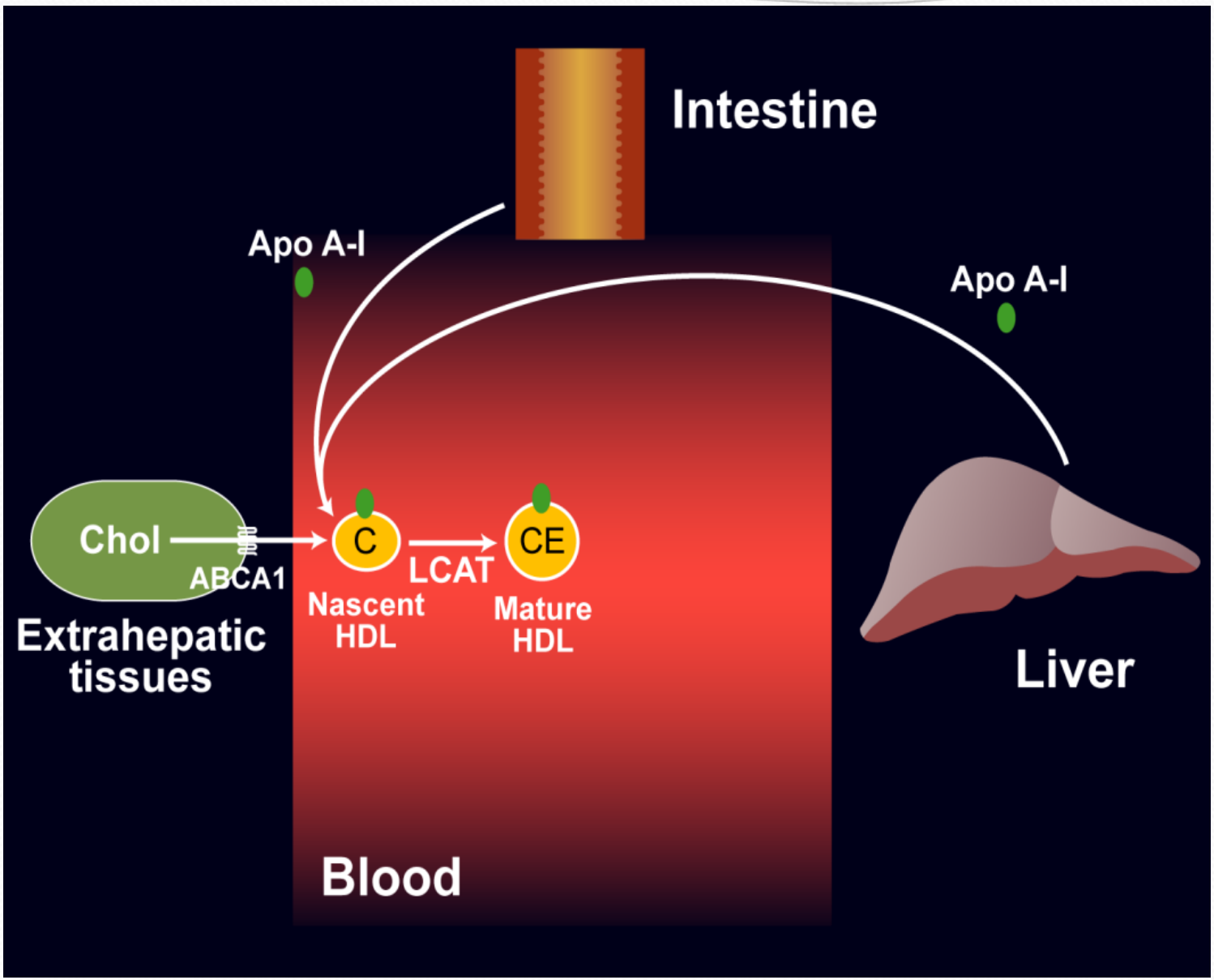
HDL and Reverse Cholesterol Transport



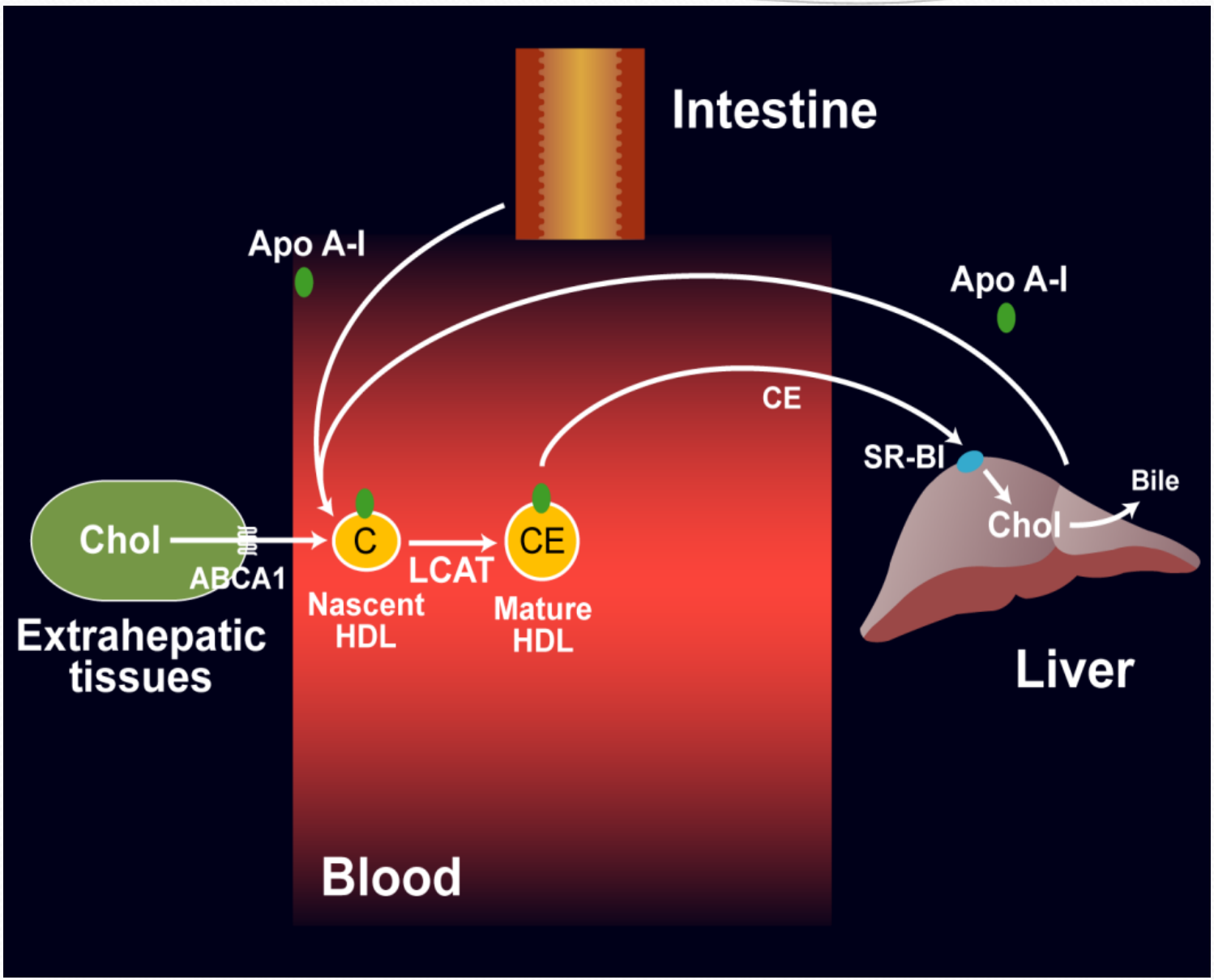
HDL and Reverse Cholesterol Transport



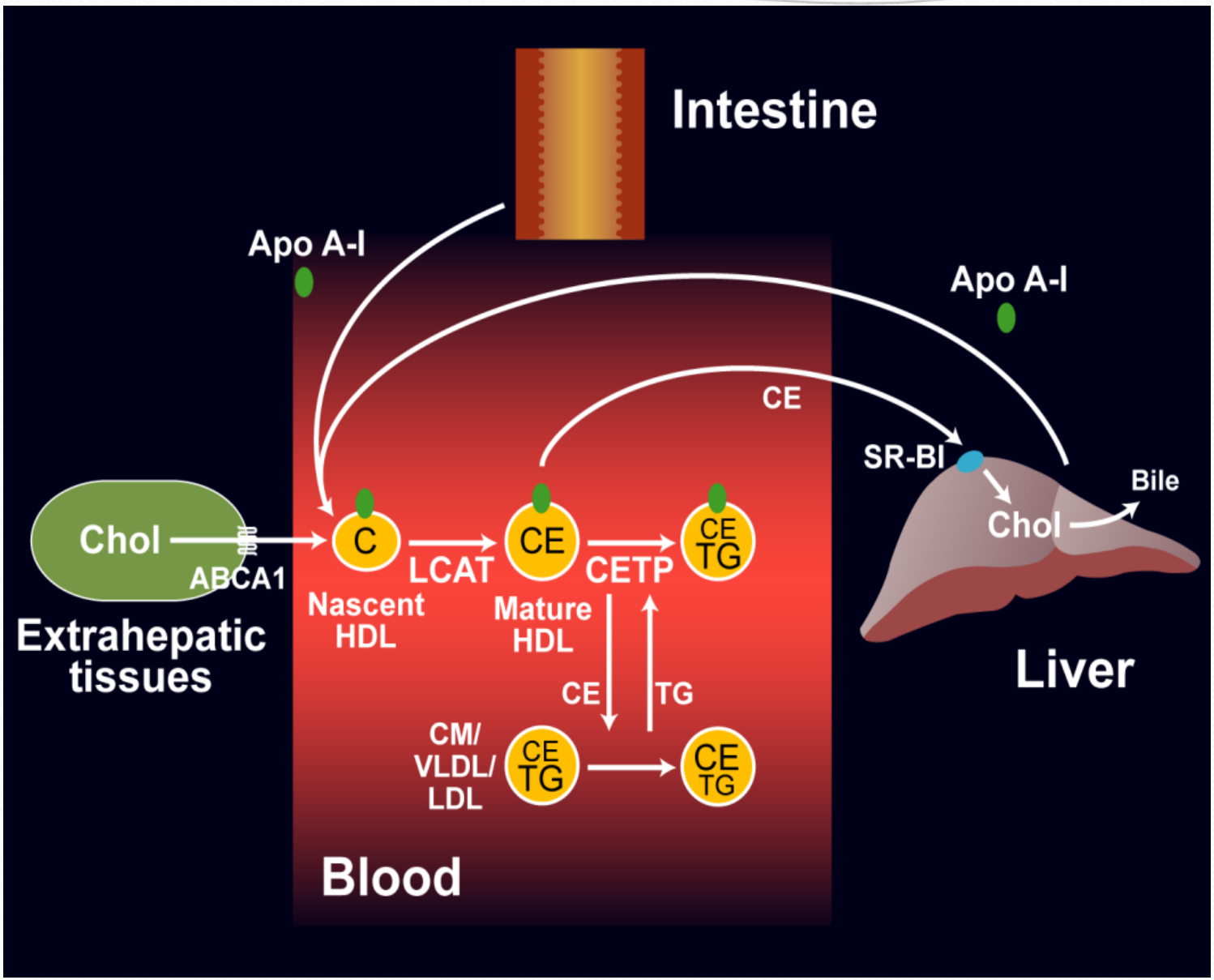
HDL and Reverse Cholesterol Transport



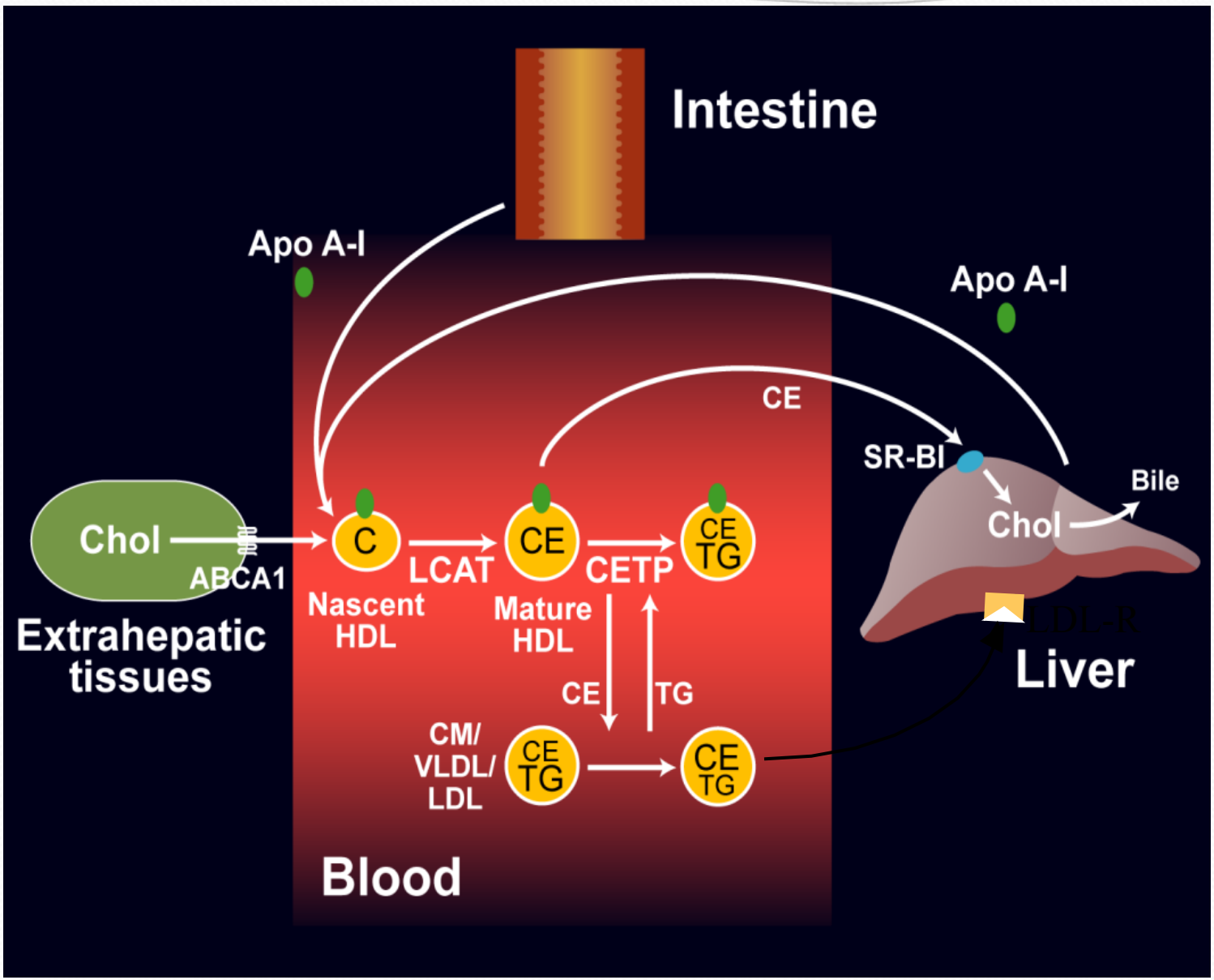
HDL and Reverse Cholesterol Transport



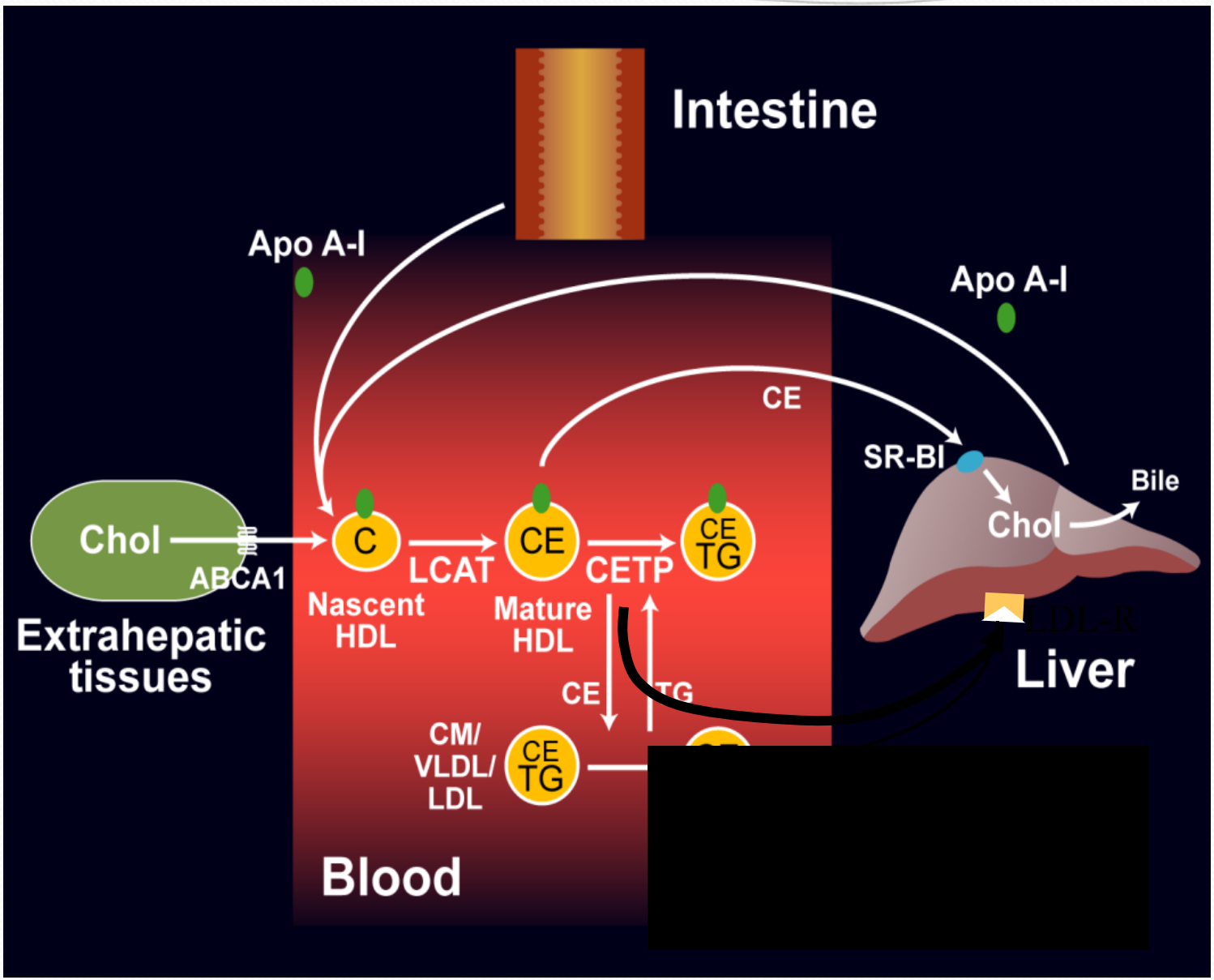
HDL and Reverse Cholesterol Transport



HDL and Reverse Cholesterol Transport

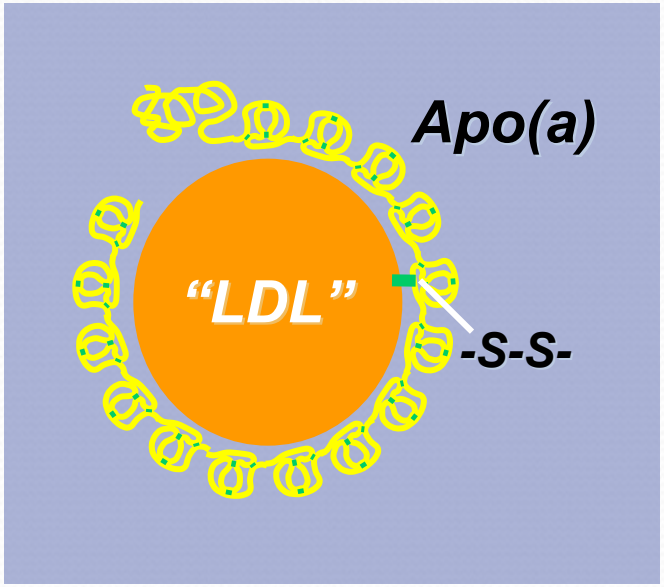


HDL and Reverse Cholesterol Transport

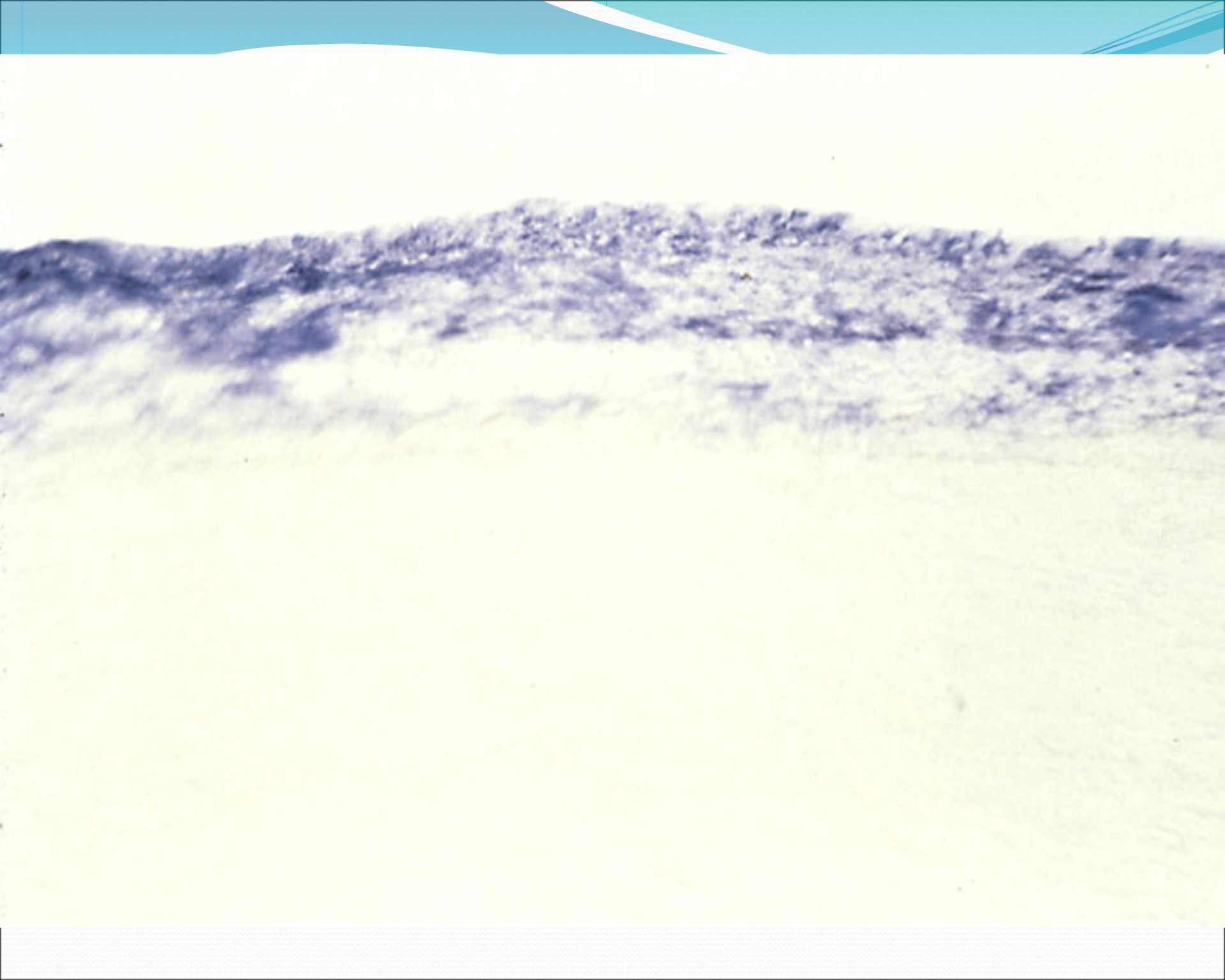


Lipoprotein(a), or Lp(a)

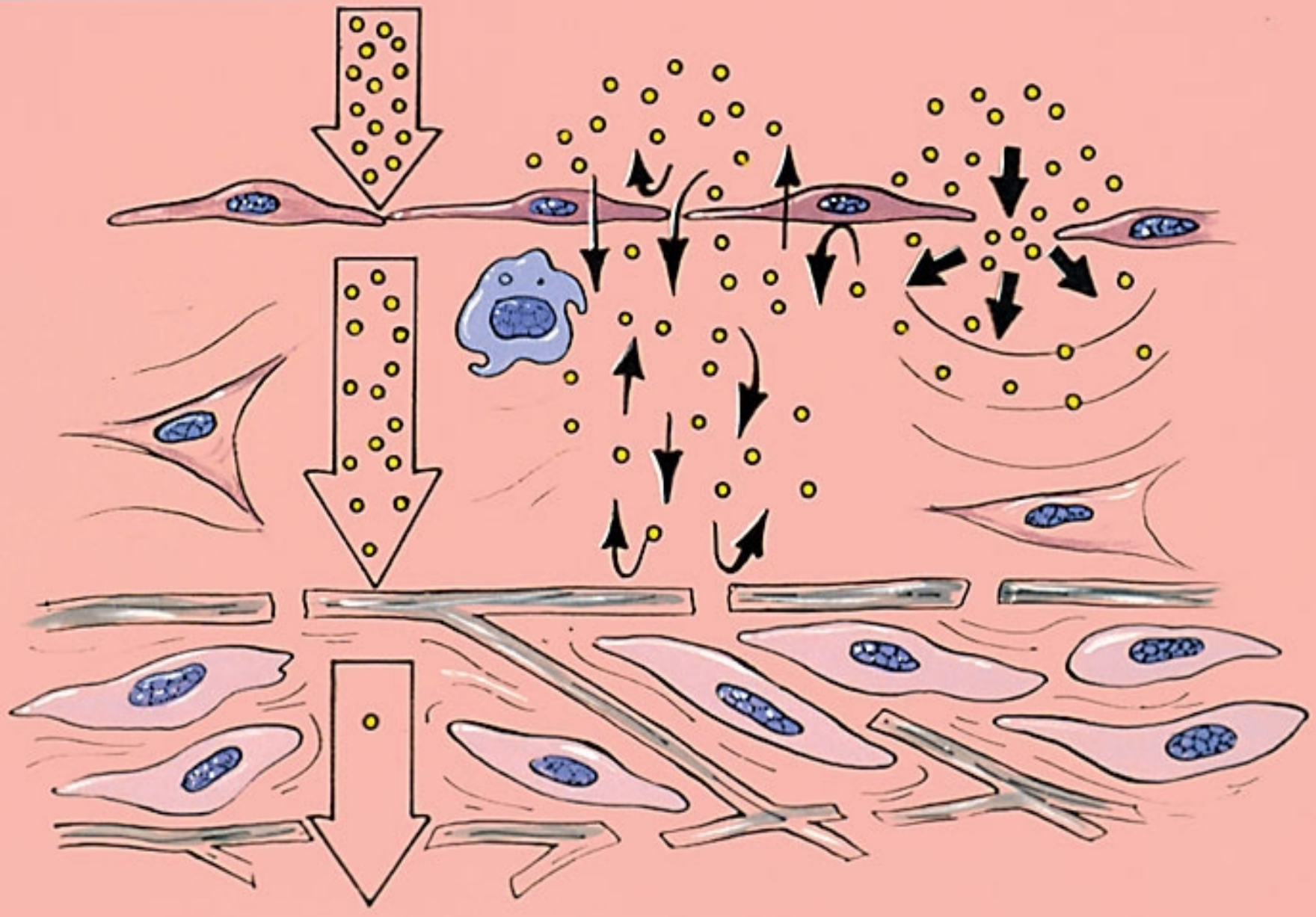
- An atherogenic lipoprotein containing apo(a) and apoB.
- 20-30% of people have levels suggesting C-V risk.
- Black subjects have Lp(a) normal range twice as high as white and Asiatic subjects.



- Apo(a) sequence similar to plasminogen, and Lp(a) interferes with spontaneous thrombolysis.
- Lp(a) levels highly genetic, resistant to diet and drug therapy, although niacin may help.



Arterial Lipoprotein Dynamics



Summary – Lipid and Lipoprotein Metabolism

- Cholesterol absorption, synthesis, and disposition
- Triglyceride/fatty acid transformations and energy metabolism
- Lipoprotein core and surface components
- Lipoprotein origins and destinations governed by apo's
- Derangement in the metabolic syndrome
- Reverse cholesterol transport – the dominant direction
- Lipoprotein(a)
- Lipoproteins in the arterial wall