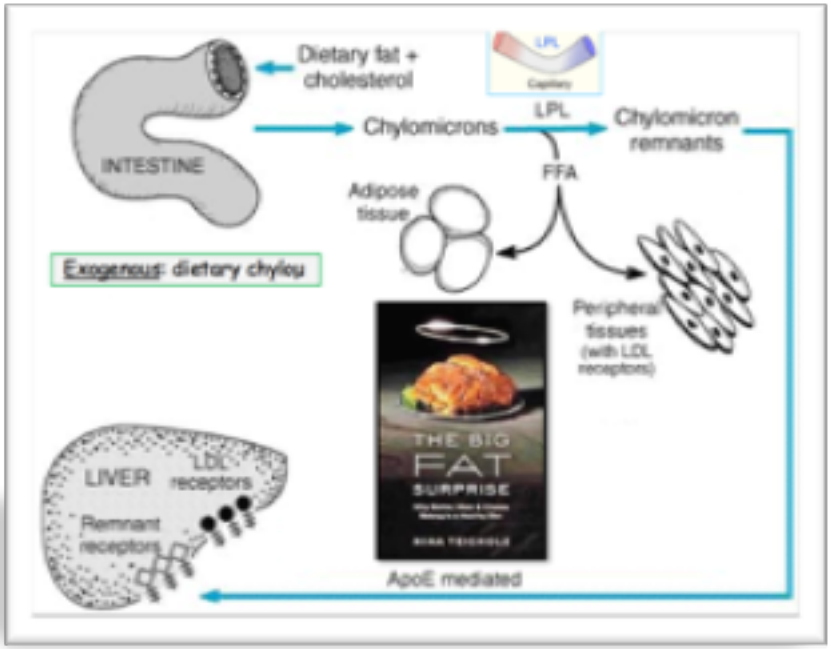
Podcast (Video Recorded Lecture Series):
Lipoprotein Metabolism and Lipid Therapy for the USMLE Step One Exam



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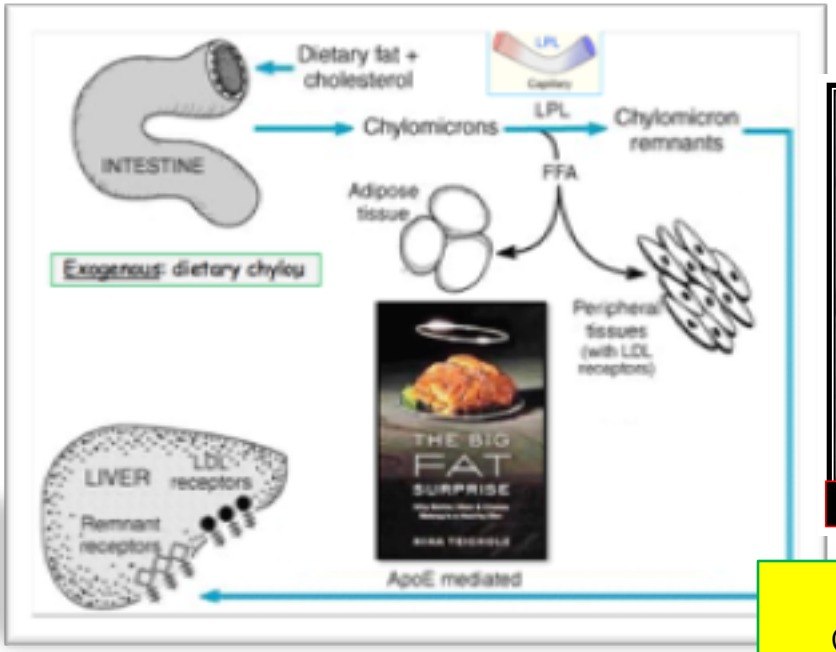

Tutorial Services
(check website for details)

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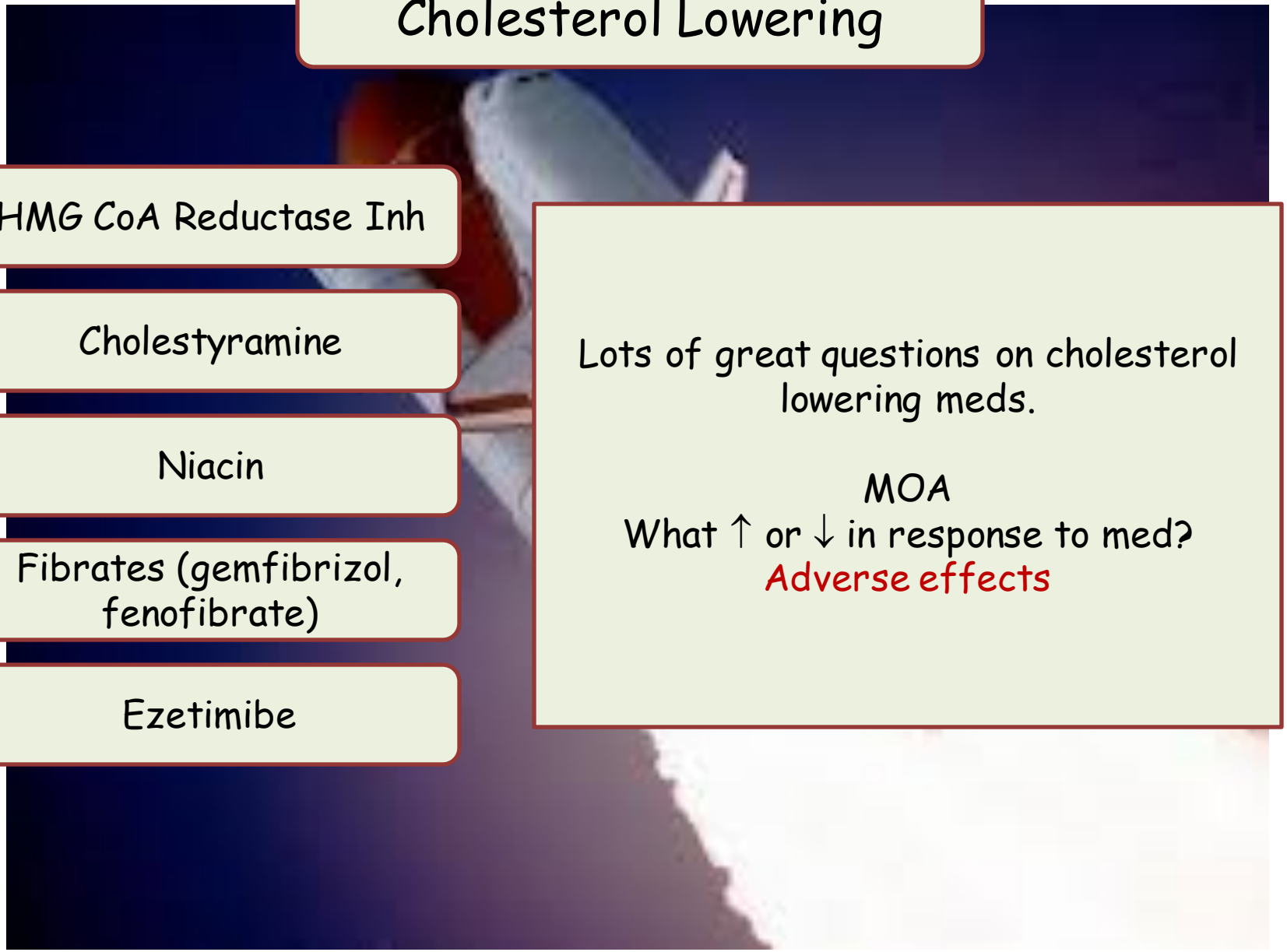
Meds:
Lipids
Antianginals

Cholesterol Lowering



- HMG CoA Reductase Inh
- Cholestyramine
- Niacin
- Fibrates (gemfibrizol, fenofibrate)
- Ezetimibe

Lots of great questions on cholesterol lowering meds.

MOA
What ↑ or ↓ in response to med?
Adverse effects

Cholesterol Lowering: MOA

HMG CoA Reductase Inh	
Cholestyramine	
Niacin	
Fibrates (gemfibrizol, fenofibrate)	
Ezetimibe	

Cholesterol Lowering: AE

HMG CoA Reductase Inh	
Cholestyramine	
Niacin	
Fibrates (gemfibrizol, fenofibrate)	
Ezetimibe	

Although we think about lipids in a pathologic sense, their role is fairly innocent by design:

- Chylomicrons and VLDL are designed to provide energy to the tissues (FFA); thus, the role of LPL.
- The metabolism of VLDL generates LDL, which is designed to provide cholesterol to the periphery for membrane and steroid hormone synthesis
- Some cells (including hepatocytes) have the ability to synthesize cholesterol through formation of mevalonic acid by HMG CoA Reductase

These simple principles provide targets for pharmacorx:

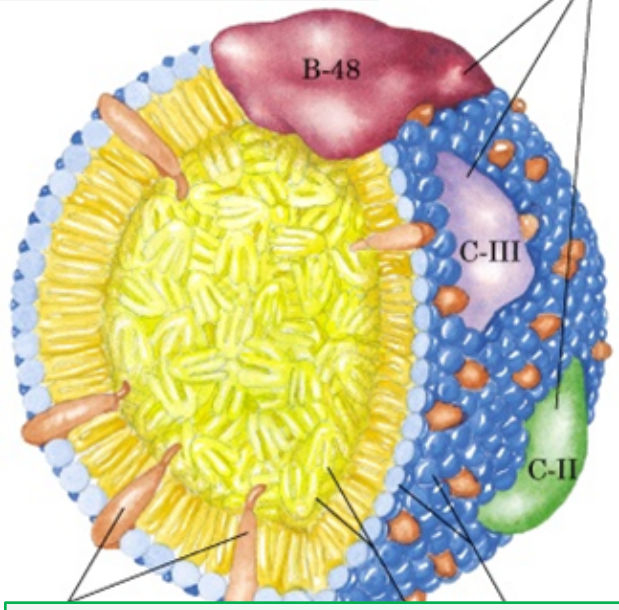
- ↓ Cholesterol Synthesis
- Upregulation of LDL Receptor (for hepatic clearance)
- Upregulation of Lipoprotein Lipase

Emulsified into Simple Micelles:
Bile Salts plus fat droplets

Fat Globule

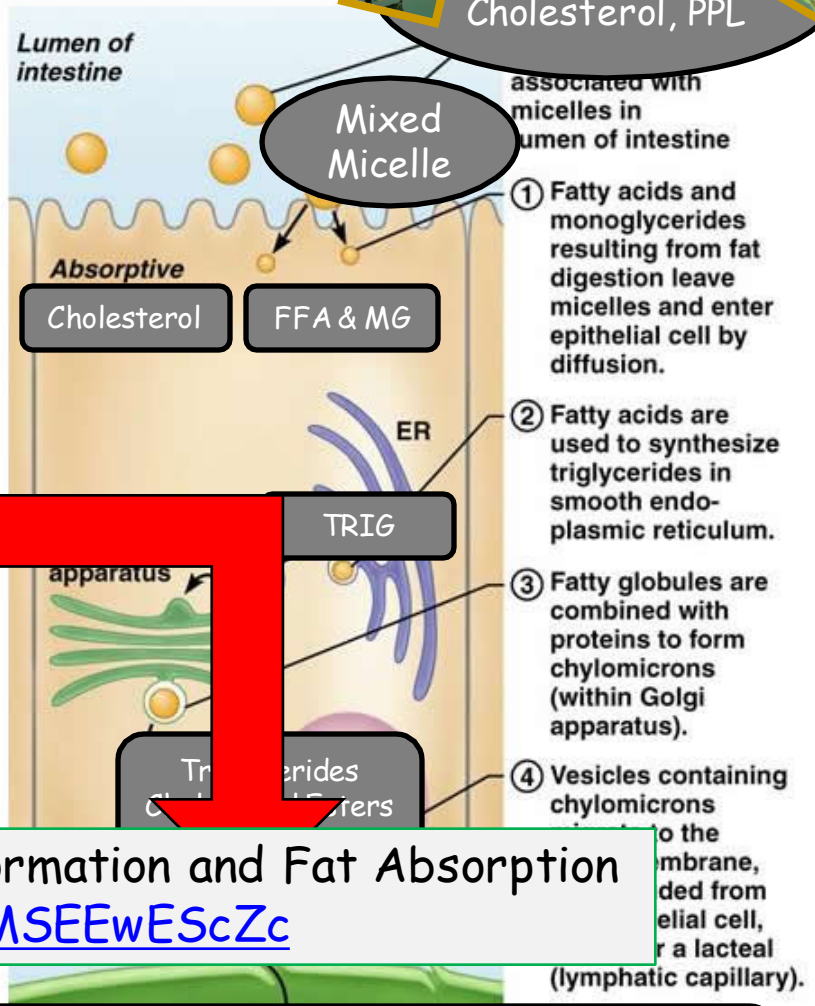
Chylomicron

Apolipoproteins



Cho

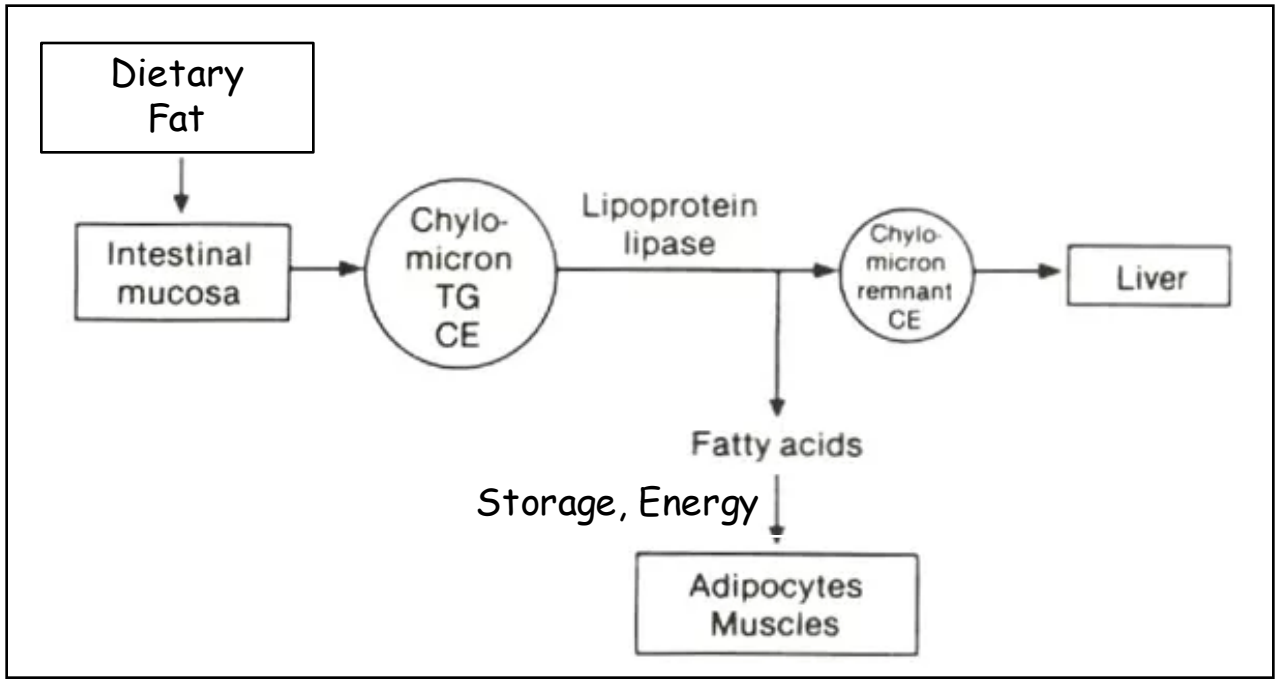
FFA, MG,
Cholesterol, PPL



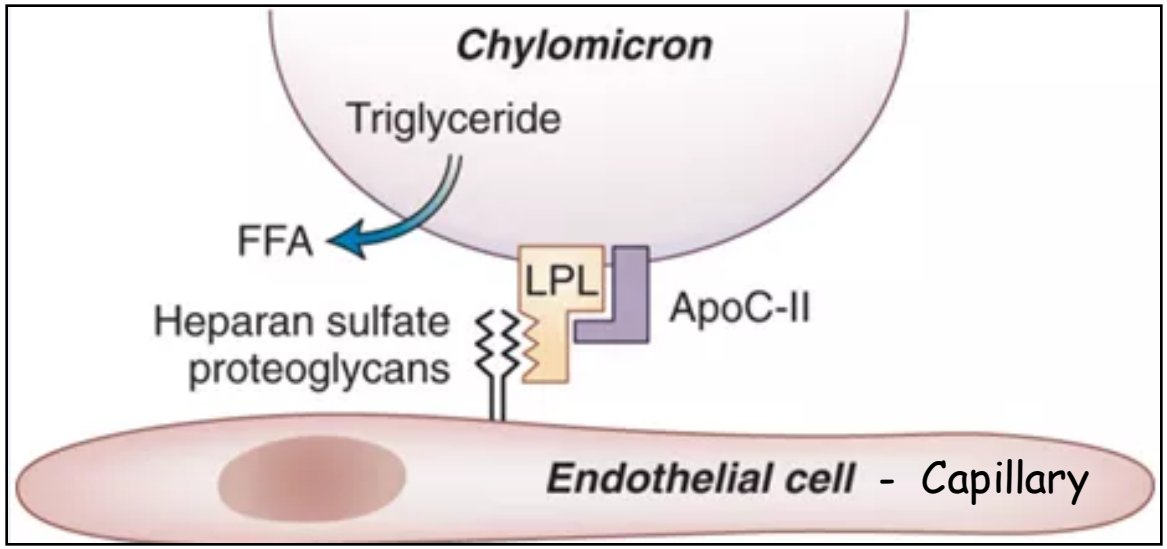
Discussed in video: Chylomicron Formation and Fat Absorption
https://youtu.be/KMSEEwEScZc

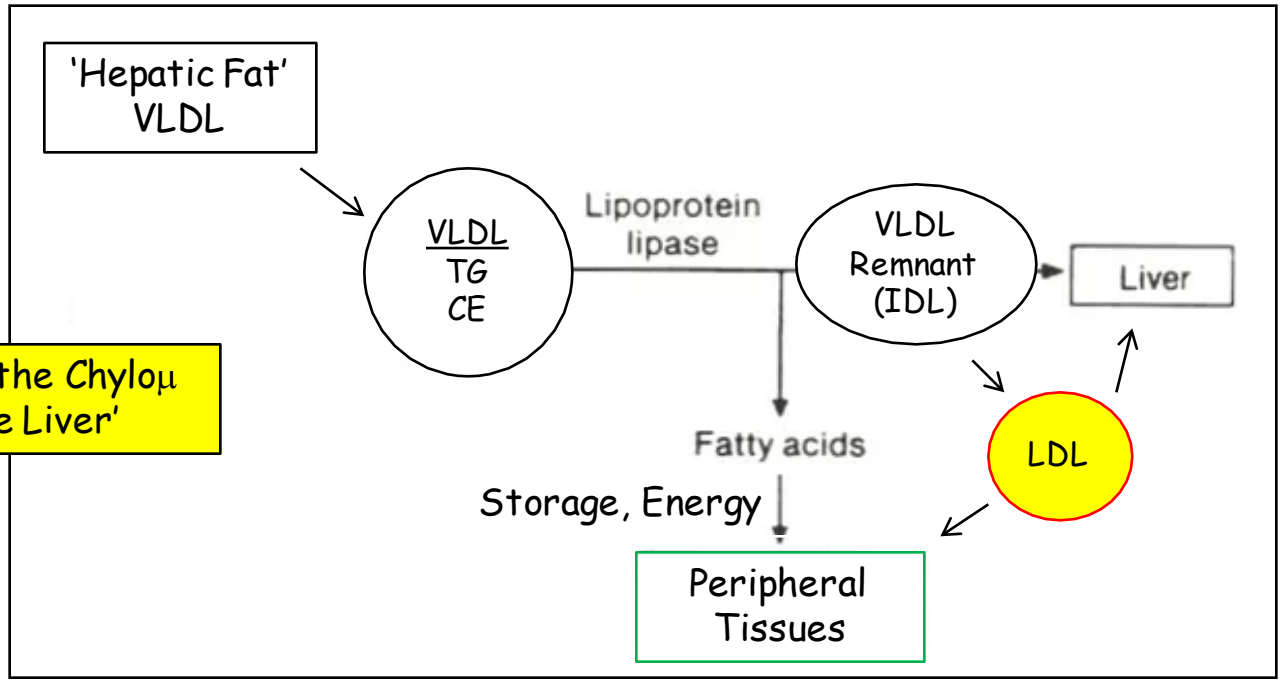
In setting of pancreatic insufficiency: colipase/lipase, PLA2, cholesterol esterase

Lacteals → Thoracic Duct→ Subclavian Vein
(not the portal vein)

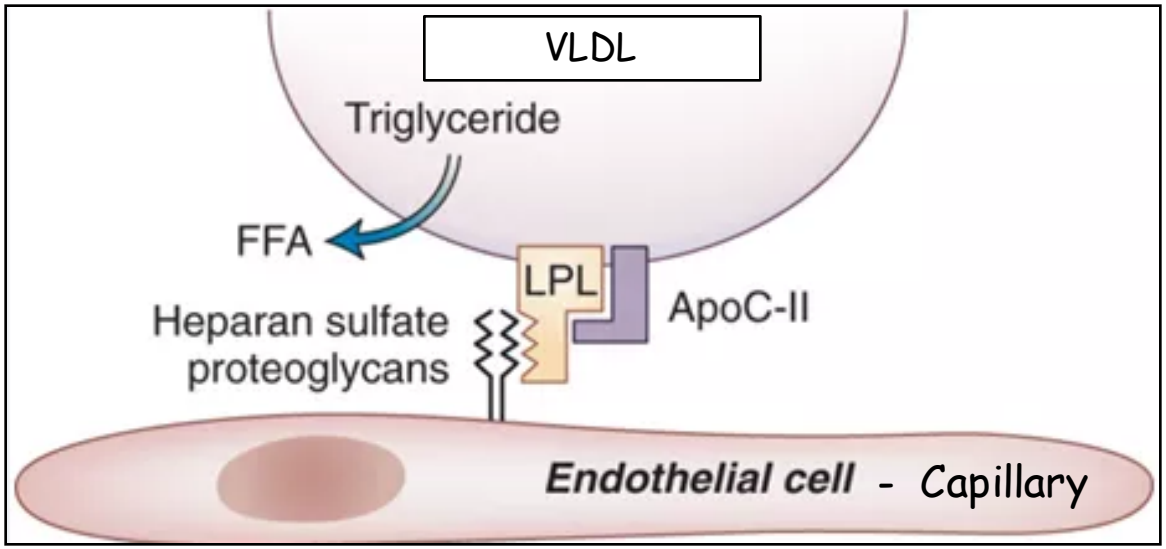


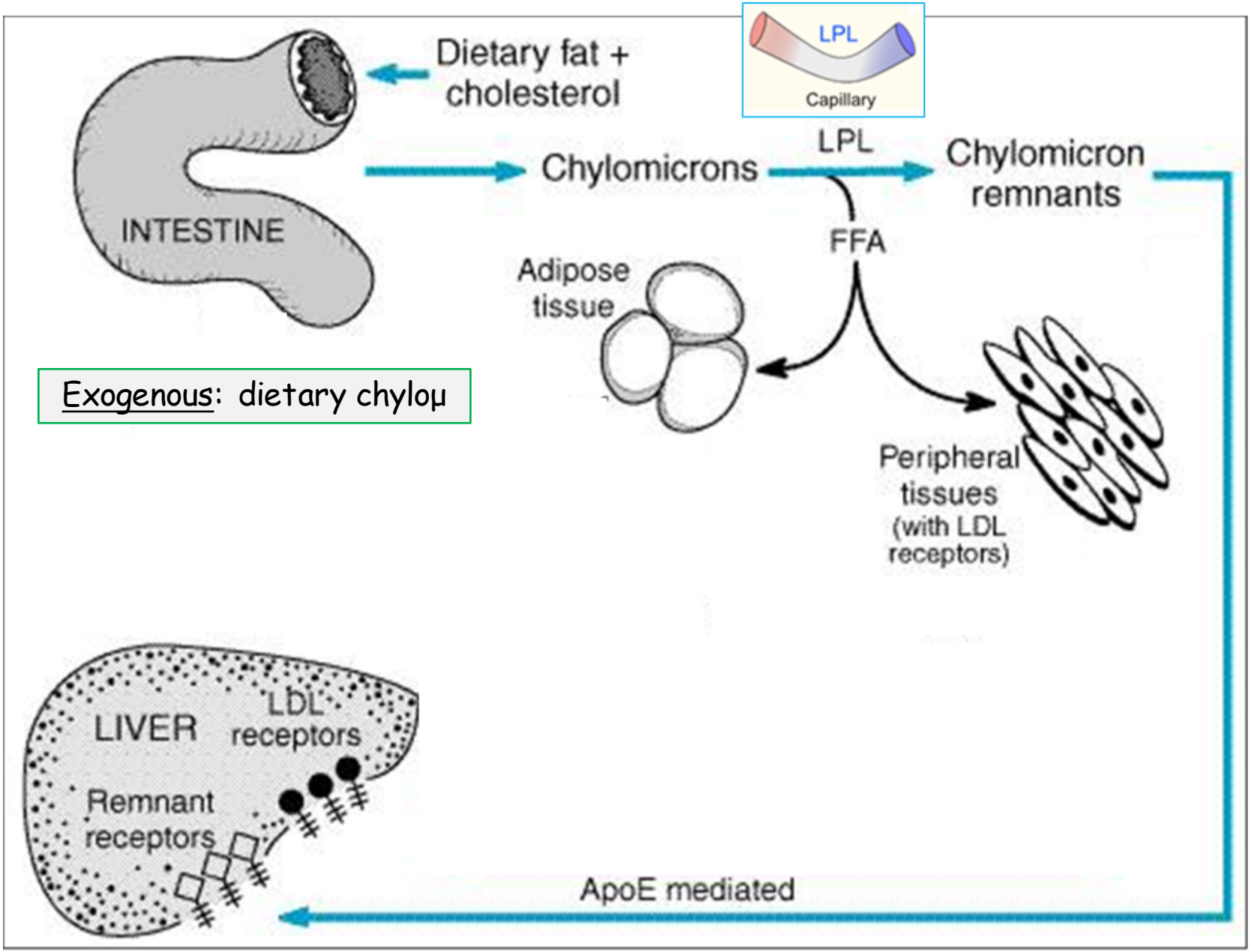
Exogenous (dietary) Pathway

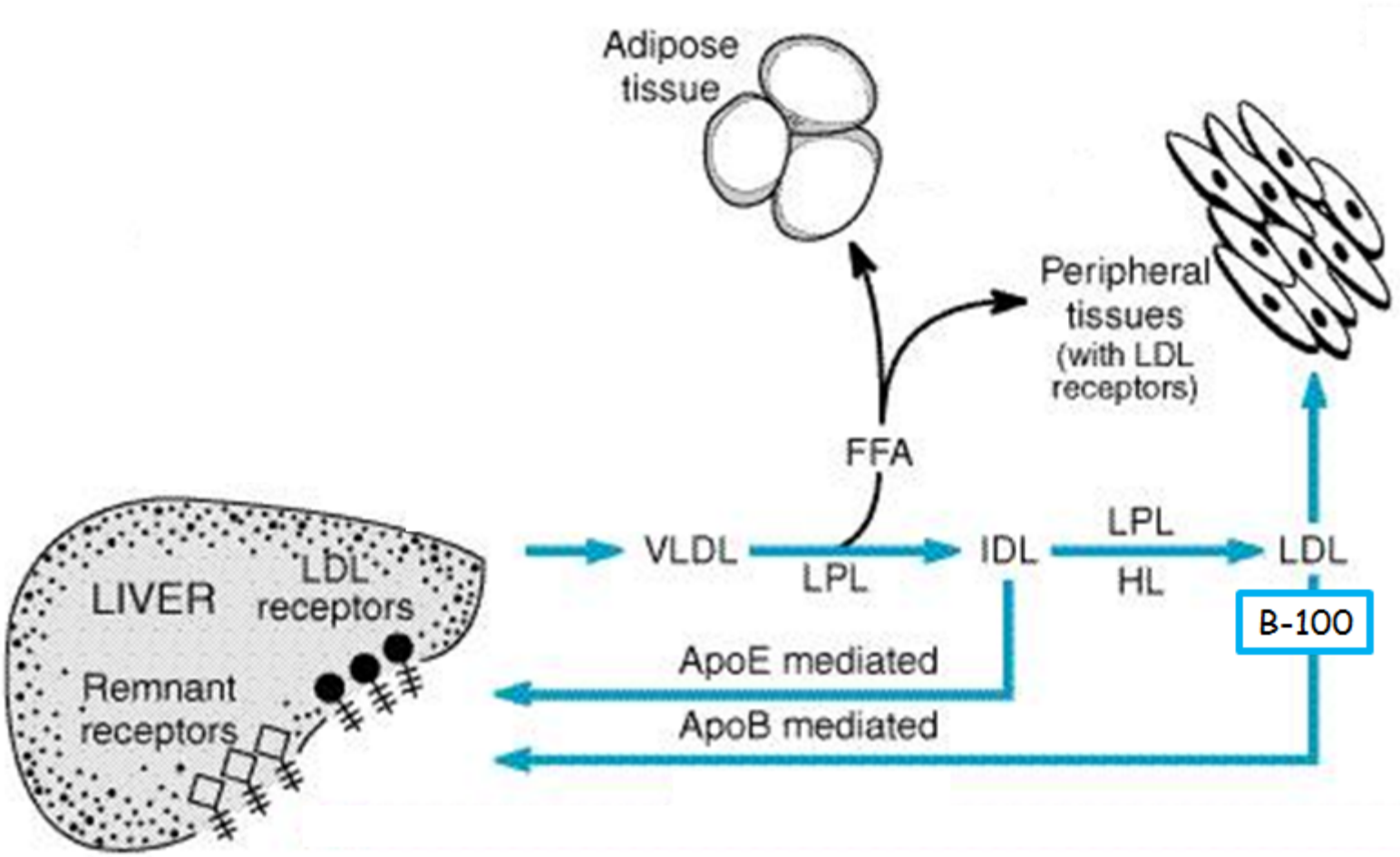




Endogenous (hepatic) Pathway

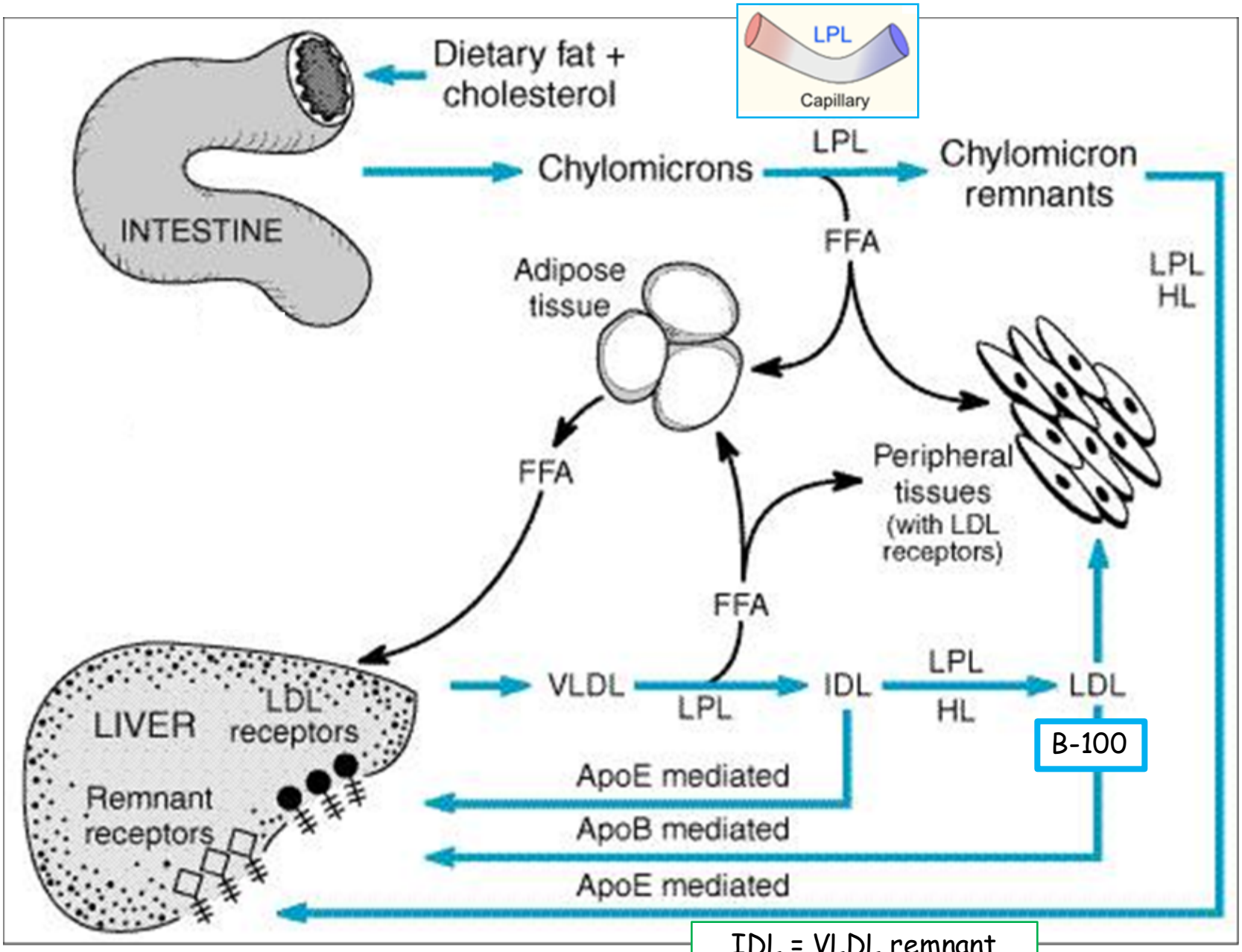


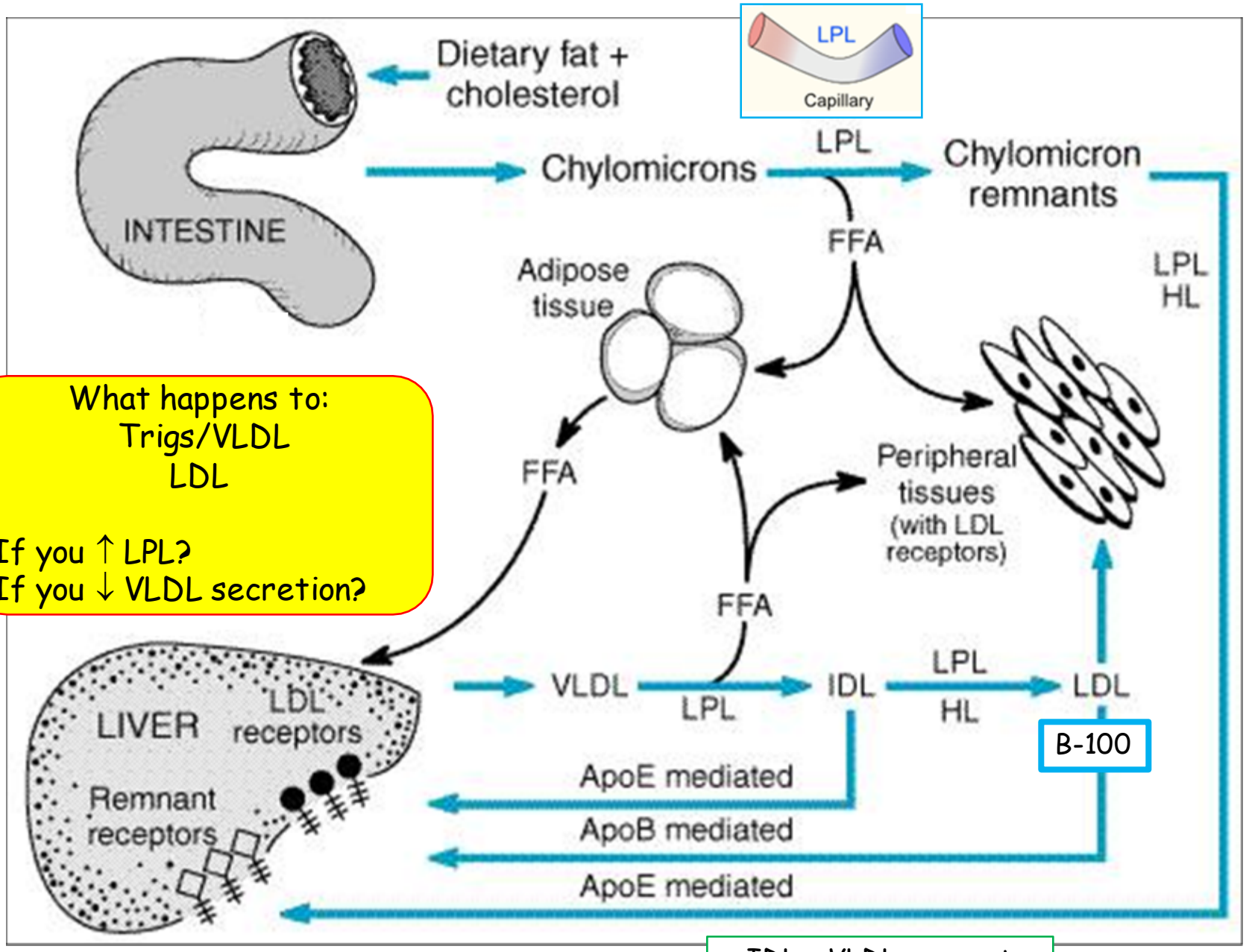

Dietary fat +
cholesterol
LPL
Capillary
INTESTINE
Chylomicrons
LPL
Chylomicron
remnants
FFA
Adipose
tissue
Exogenous: dietary chylom
Peripheral
tissues
(with LDL
receptors)
LIVER
LDL
receptors
Remnant
receptors
ApoE mediated



Endogenous: Hepatic VLDL

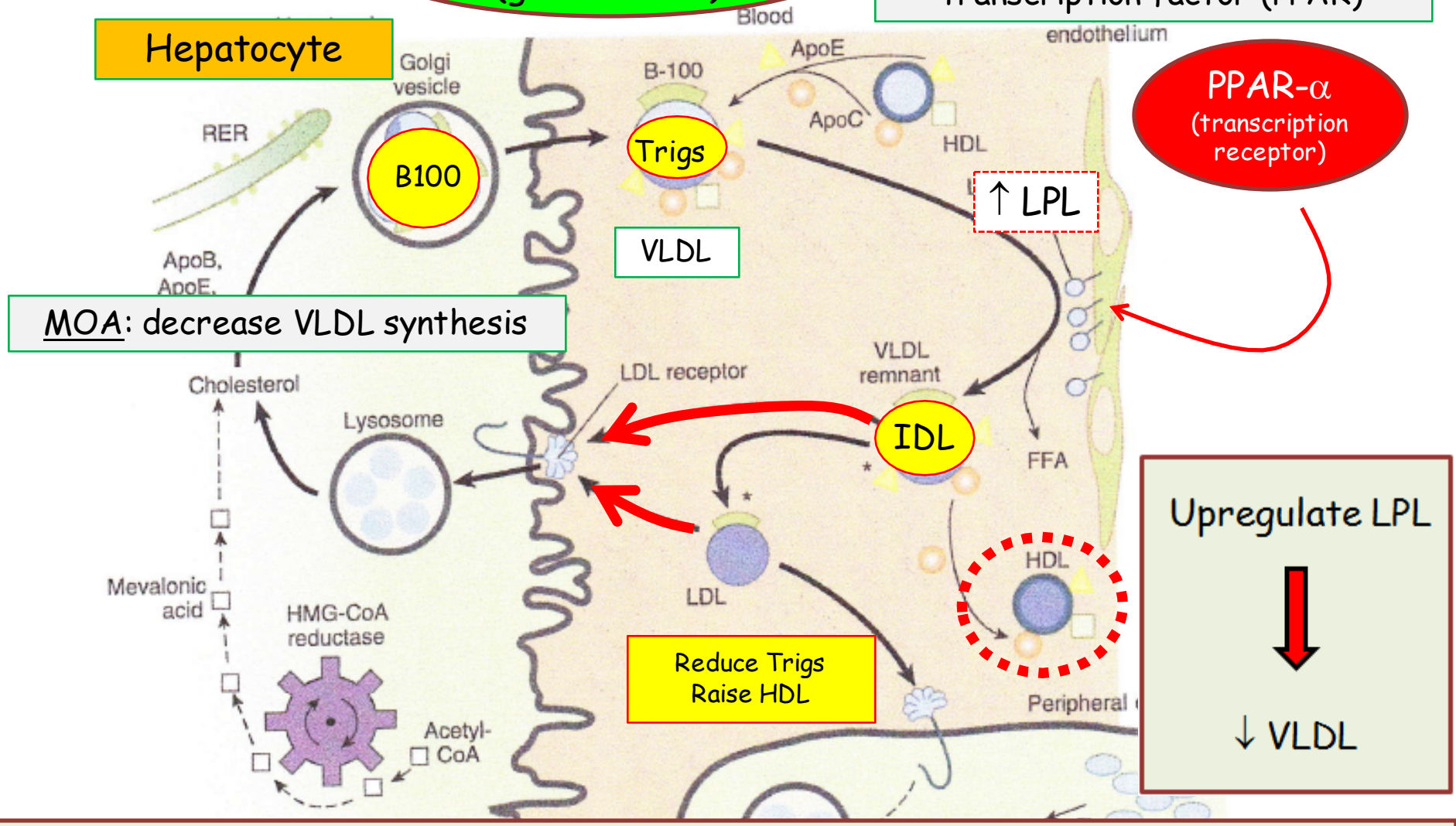
IDL = VLDL remnant


LPL
Capillary
Dietary fat +
cholesterol
INTESTINE
Chylomicrons
LPL
Chylomicron
remnants
FFA
LPL
HL
Adipose
tissue
FFA
Peripheral
tissues
(with LDL
receptors)
FFA
LIVER
LDL
receptors
Remnant
receptors
VLDL
LPL
IDL
LPL
HL
LDL
B-100
ApoE mediated
ApoB mediated
ApoE mediated
IDL = VLDL remnant


LPL
Capillary
Dietary fat + cholesterol
INTESTINE
Chylomicrons
LPL
Chylomicron remnants
FFA
LPL
HL
Adipose tissue
FFA
Peripheral tissues (with LDL receptors)
FFA
LIVER
LDL receptors
Remnant receptors
VLDL
LPL
IDL
LPL
HL
LDL
B-100
ApoE mediated
ApoB mediated
ApoE mediated
What happens to:
Trigs/VLDL
LDL
If you ↑ LPL?
If you ↓ VLDL secretion?
IDL = VLDL remnant

Fibrate (gemfibrozil)

MOA: increased expression of transcription factor (PPAR)



Because fibrates upregulate LPL via PPAR, they should be considered 'specialists' in Triglyceride/VLDL metabolism.
As such, fibrate questions will always address the high triglyceride patient

Discussed in Bile Metabolism AND Lithogenesis Videos:

https://youtu.be/TF1ADSDHbSg
(Bile metabolism)

https://youtu.be/vc9TCZMDofA
(Cholelithiasis)

(1) Interaction w/ statin → rhabdomyolysis

(inhibit CYP3A4 → ↑ statin)

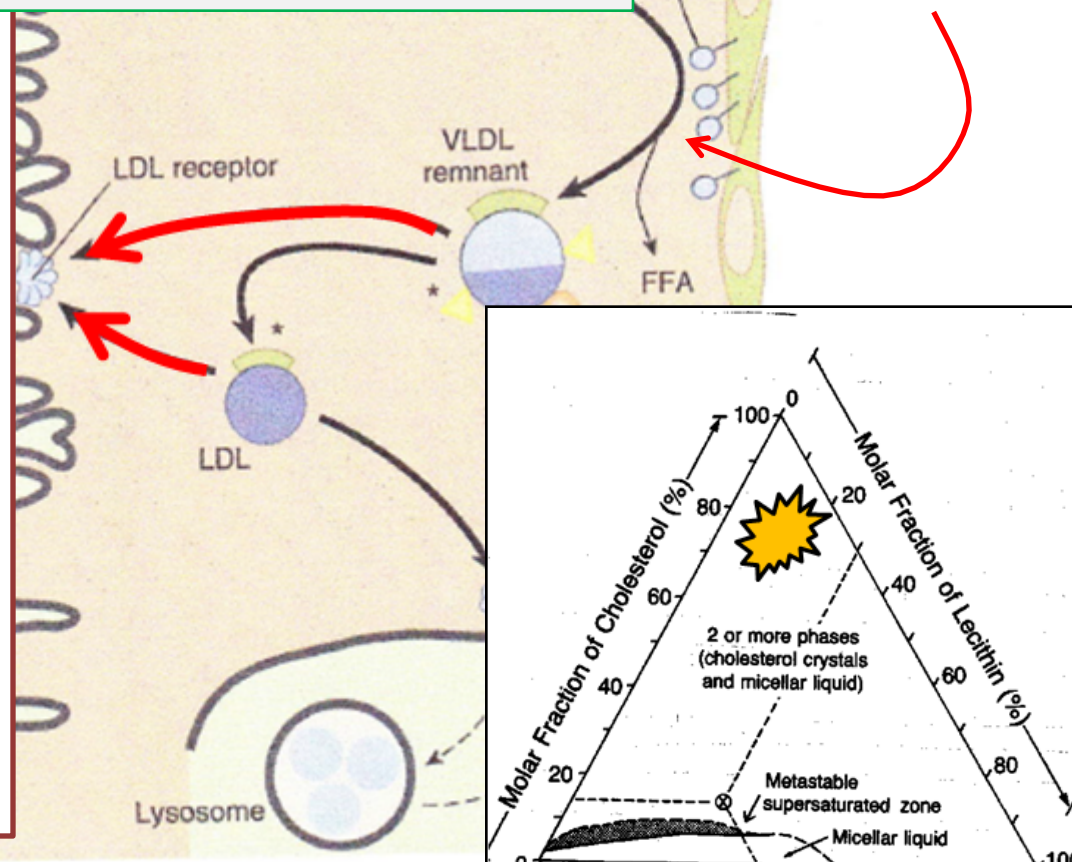
(2) Cholelithiasis

(IDL/LDL returned to liver & ↓ 7-a-OHase activity → ↑ cholesterol saturation of bile)

Fibrates

Fibrate
mfibrozil)

PPAR-α



They will ask about AE (2):

(1) Interaction w/ statin → rhabdomyolysis

(inhibit CYP3A4 → ↑ statin)

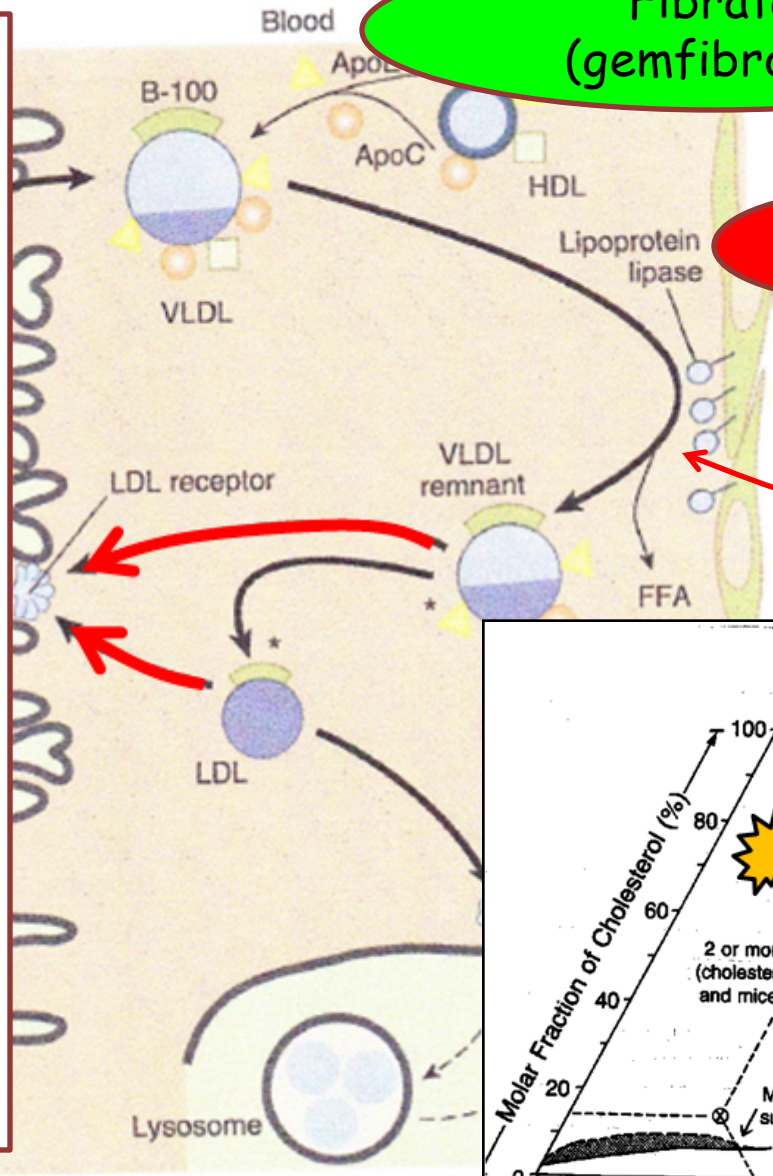
(2) Cholelithiasis

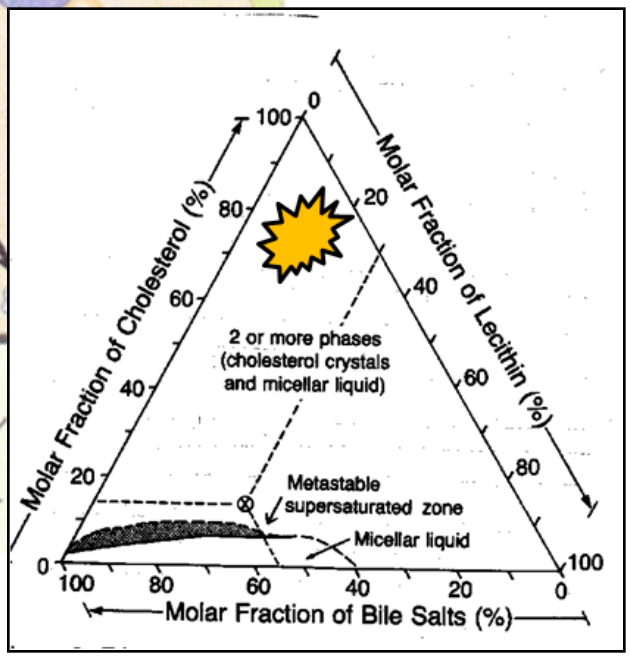
(IDL/LDL returned to liver & ↓ 7-a-OHase activity → ↑ cholesterol saturation of bile)

Fibrates

Fibrate (gemfibrozil)

PPAR-α



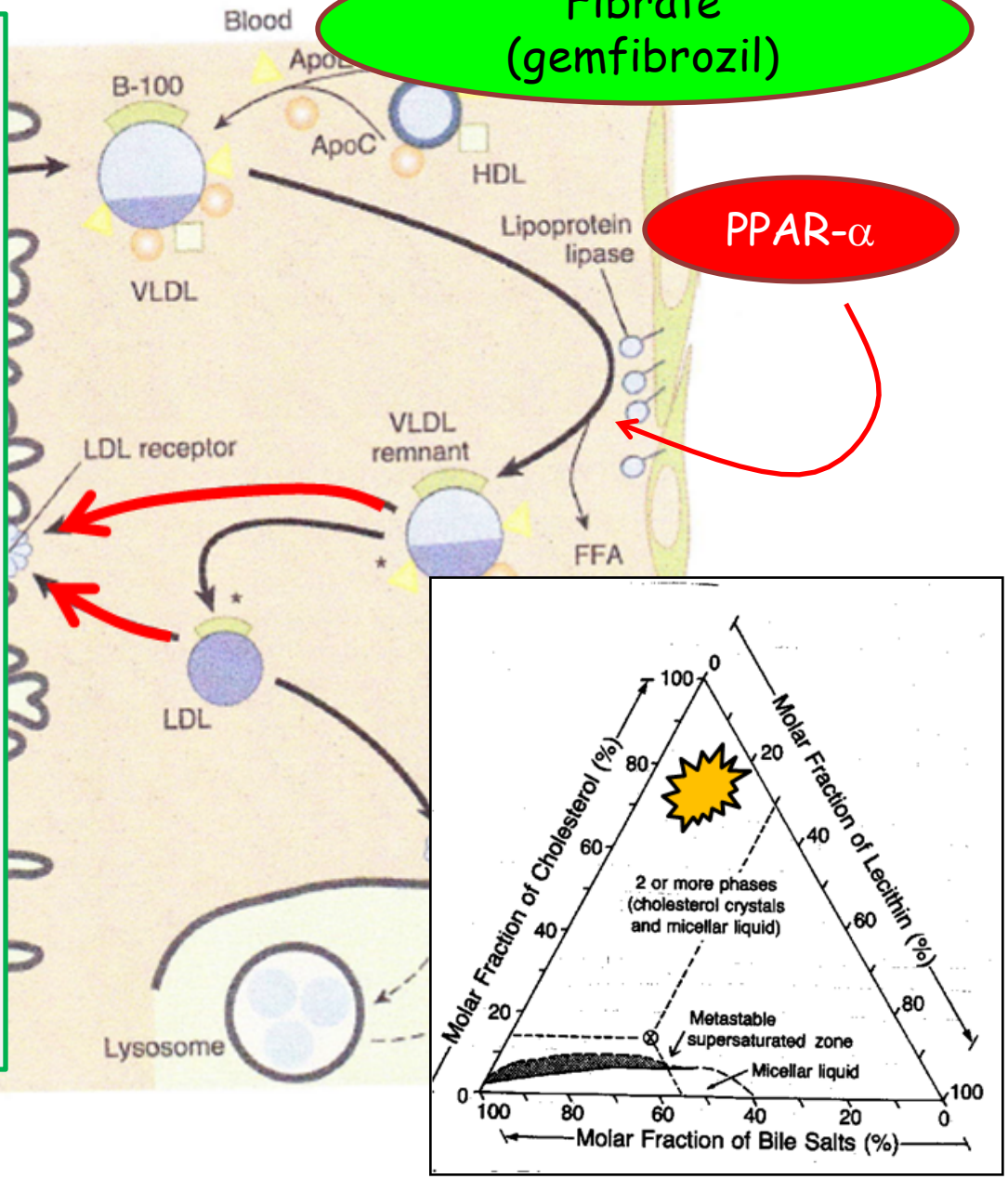


Fibrate (gemfibrozil)

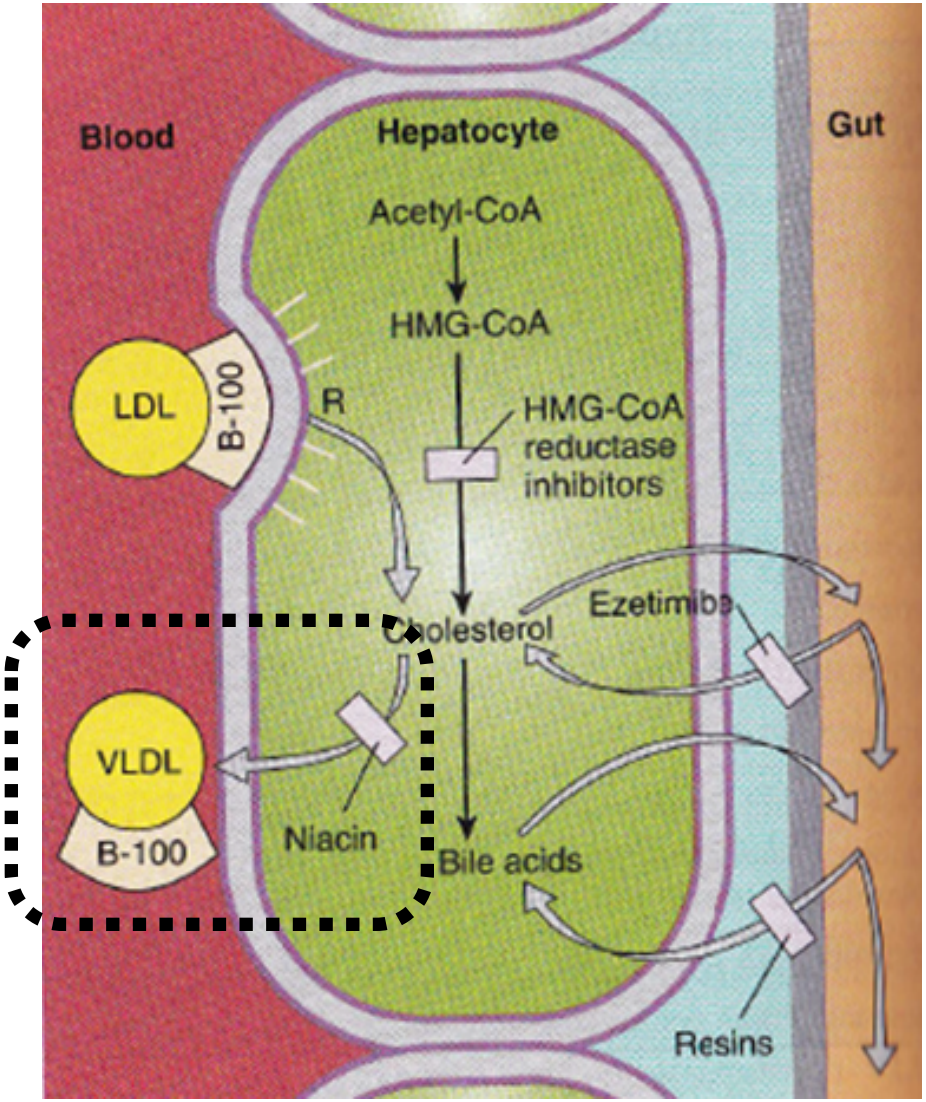
PPAR-α

<u>That's it</u>:

MOA (2): PPAR → ↑ LPL, ↓ VLDL synthesis
Result: ↓ Triglyceride
AE: Stones
AE: ↓ metabolism of statin → rhabdomyolysis



Fibrates

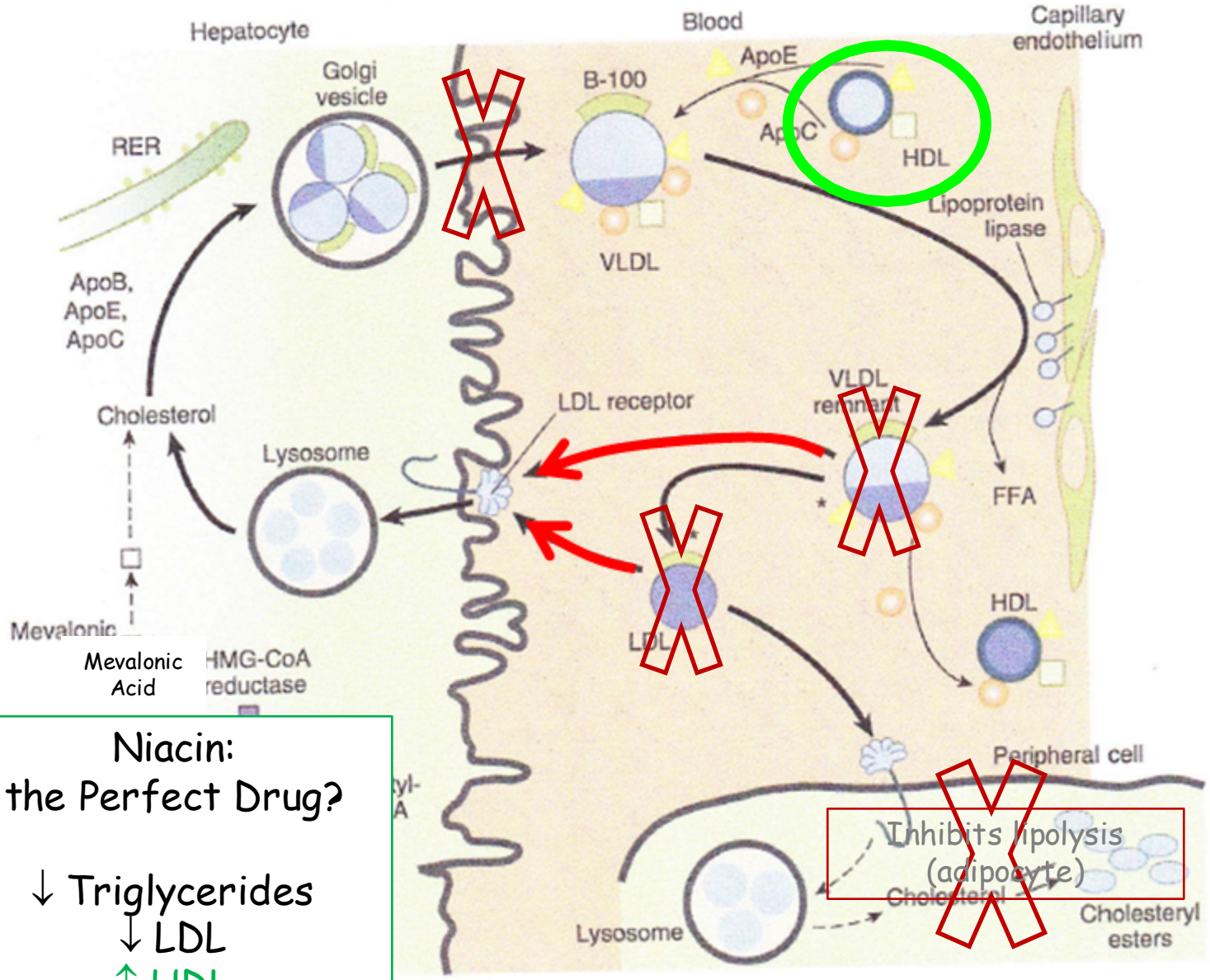


Niacin

MOA: Inhibits VLDL secretion
(inhibits intrahepatic TG synthesis)

(lesser effect: inhibition of lipolysis in adipocyte; FYI)

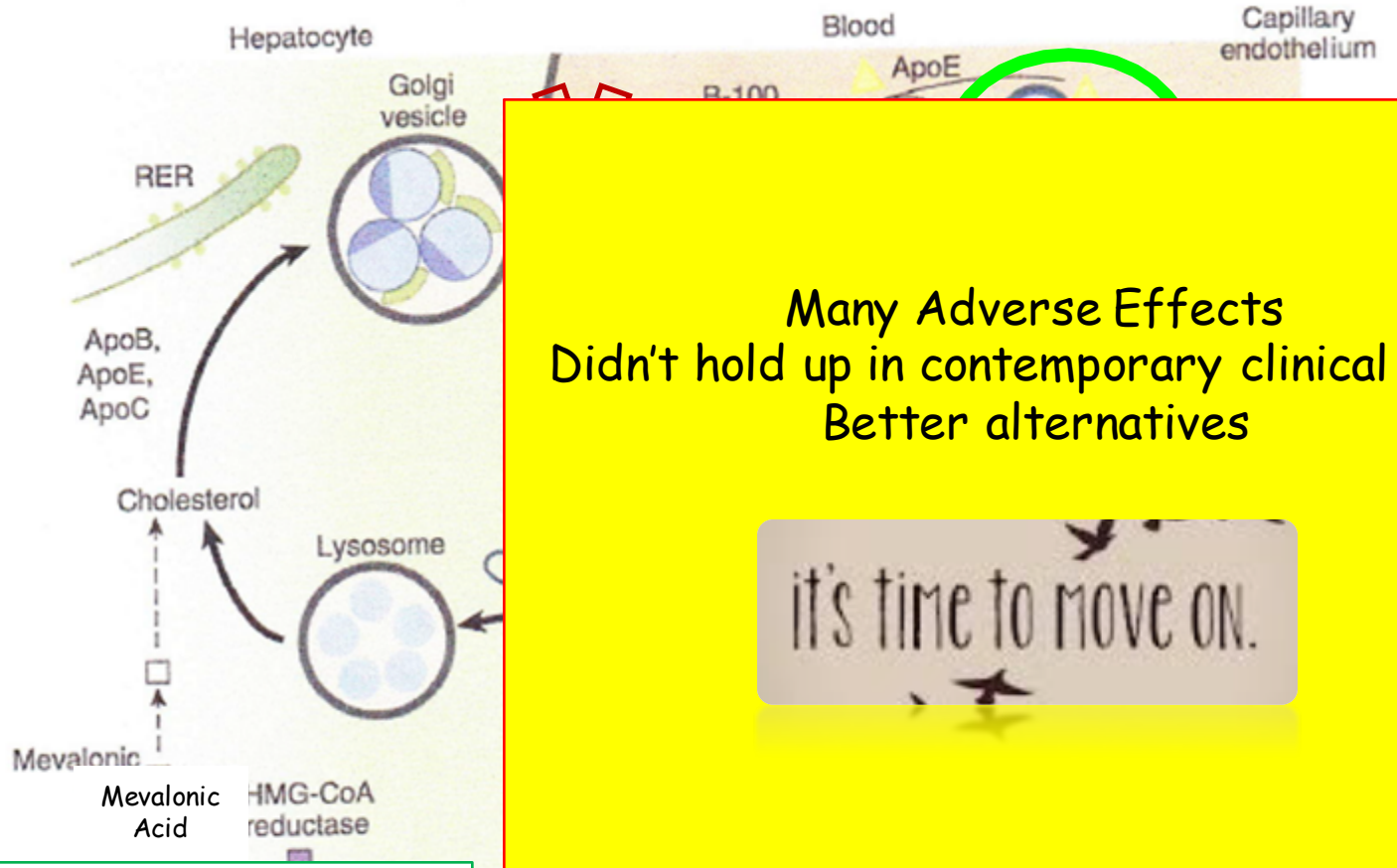
Niacin pathways: effects of decreasing VLDL synthesis



Niacin:
the Perfect Drug?

↓ Triglycerides
↓ LDL
↑ HDL

Niacin pathways: effects of decreasing VLDL synthesis

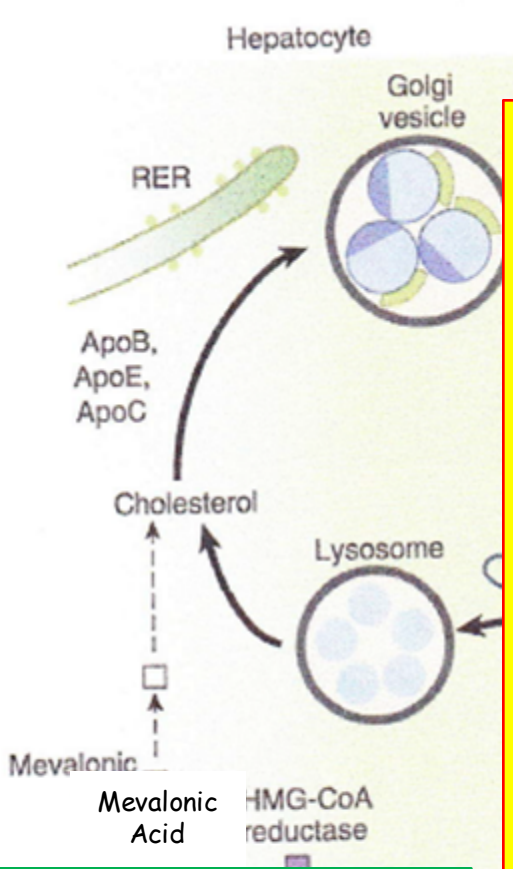


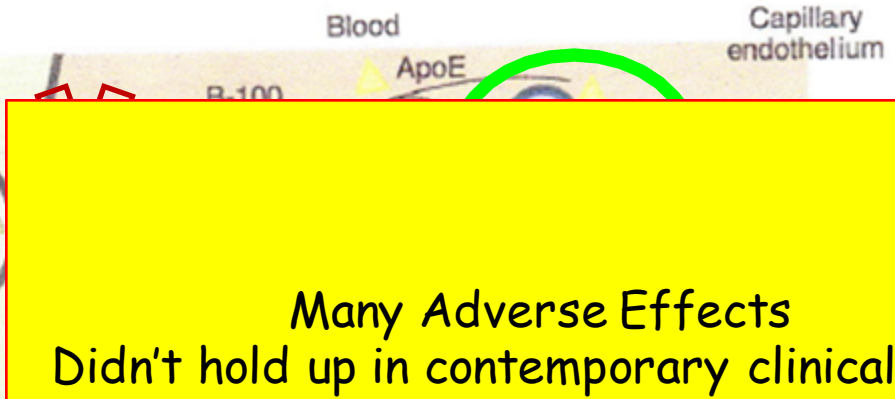
Many Adverse Effects
Didn't hold up in contemporary clinical trials
Better alternatives

Niacin:
the ~~Perfect~~ Drug?

↓ Triglycerides
↓ LDL
↑ HDL

Niacin pathways: effects of decreasing VLDL synthesis



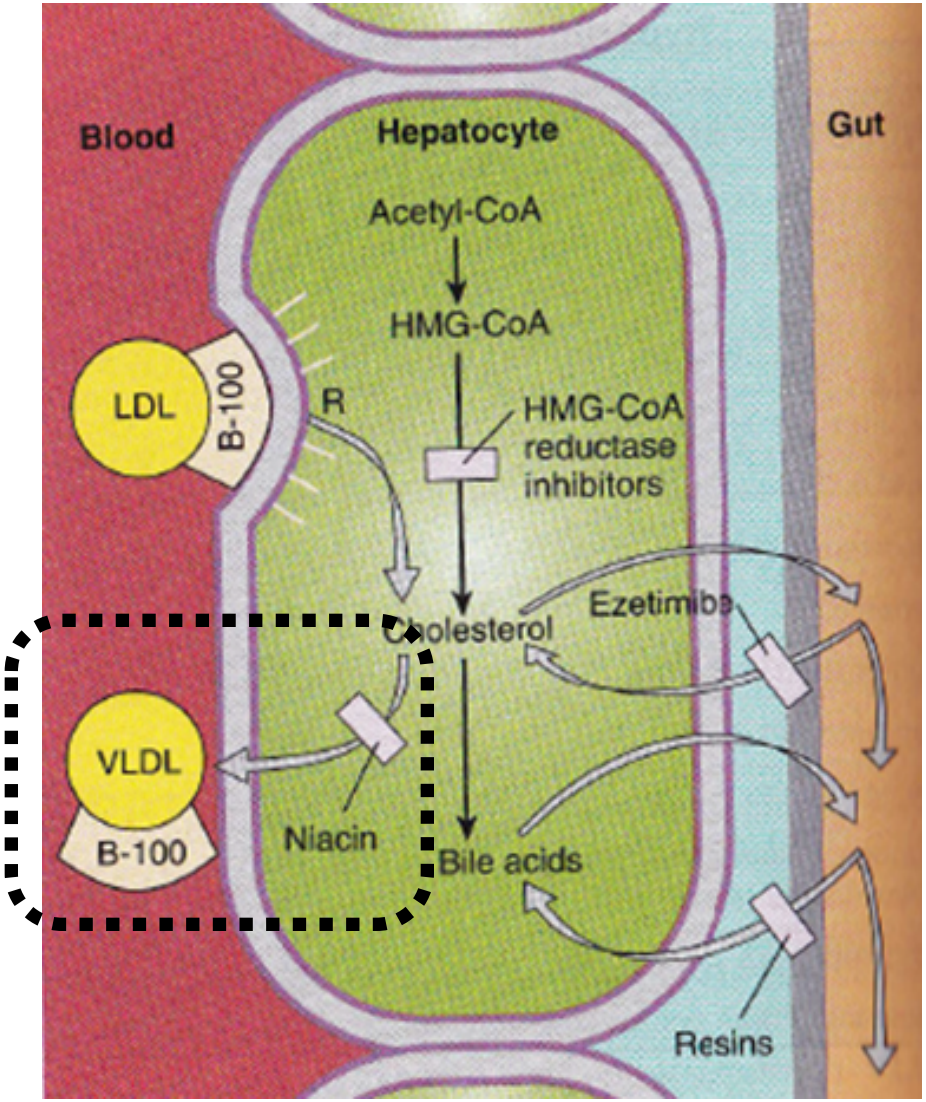


Niacin:
the ~~Perfect~~ Drug?

↓ Triglycerides
↓ LDL
↑ HDL

Many Adverse Effects
Didn't hold up in contemporary clinical trials
Better alternatives

Q-bank Cautionary Tales:
Best agent for RR → statins
Best agent to ↑ HDL → niacin



Niacin:

MOA: Inhibits VLDL secretion ∴
↓ LDL as well
Inhibits lipolysis in adipose

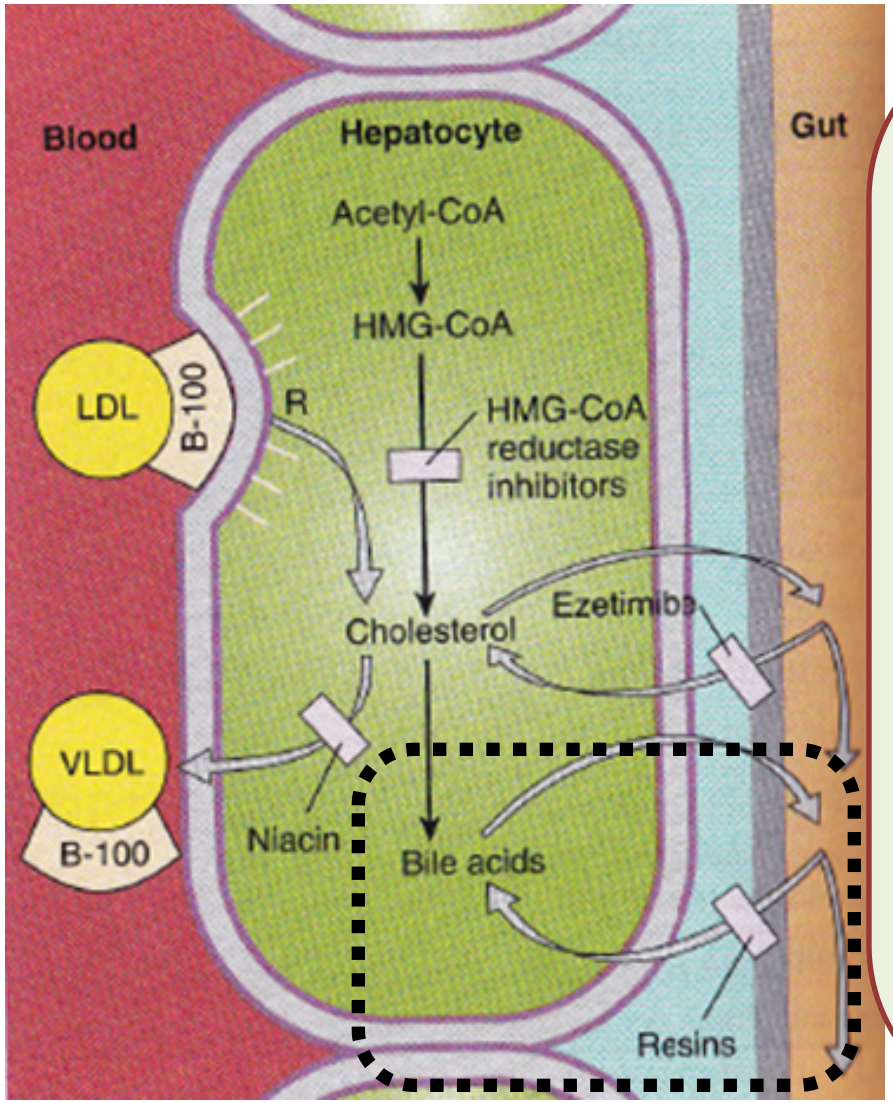
Patient profile: high triglycerides

Distinguish from fibrate by MOA and AE

Focus AE (3):

Flushing (PG ↔ ASA)
Hyperuricemia ('podagra on rx')
Hyperglycemia (diabetic w/ high trigs; which agent to avoid?)

Hepatotoxic



Binding Resins
(cholestyramine)

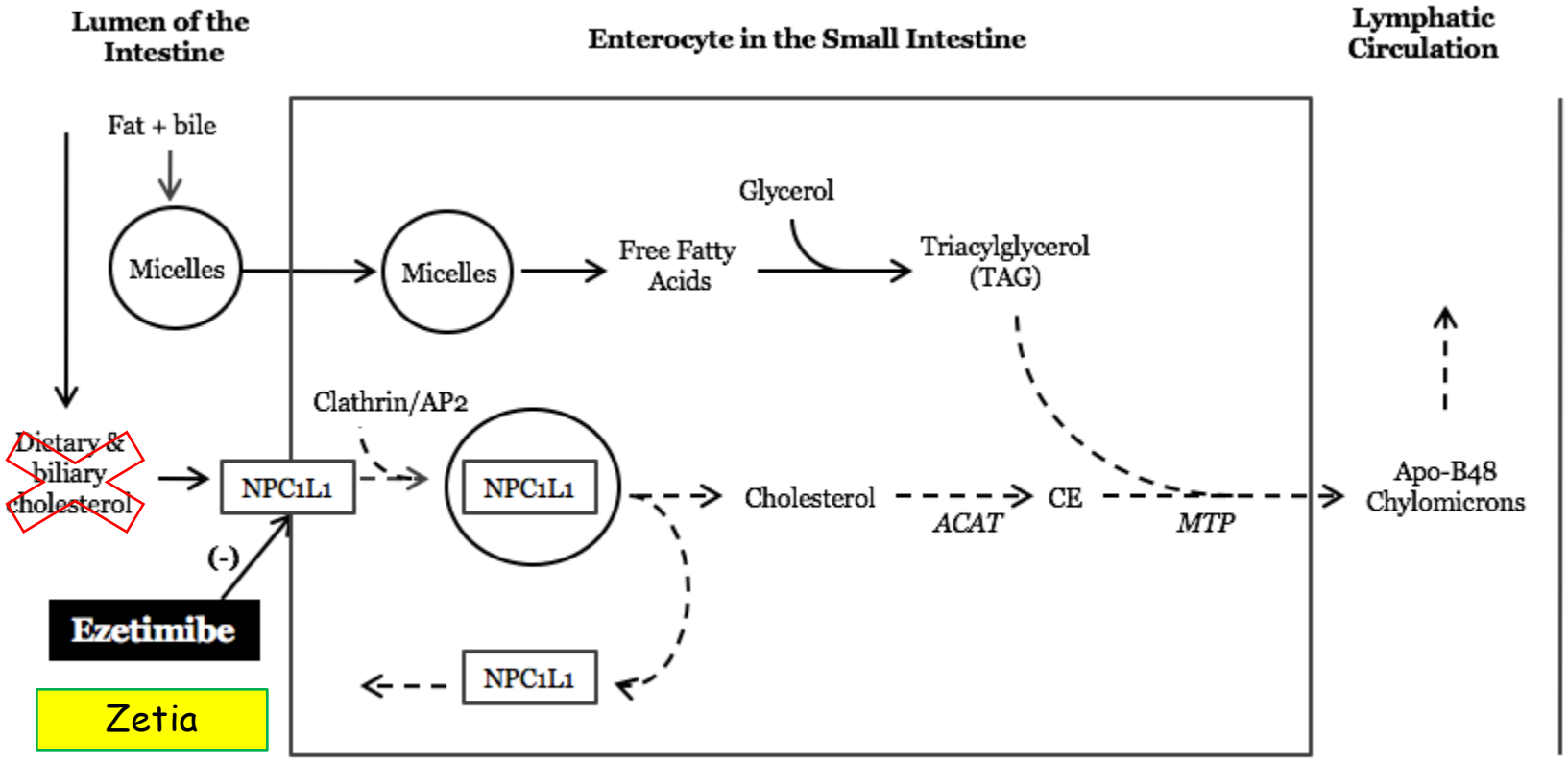
Decrease enterohepatic circulation of bile salts

10-fold increase in bile salt production
(leading to cholesterol excretion)

Upregulation of LDL receptor
(need cholesterol)

Increased production of VLDL →
hypertriglyceridemia

Used to rx bile-salt induced diarrhea (s/p CCY – 10%)



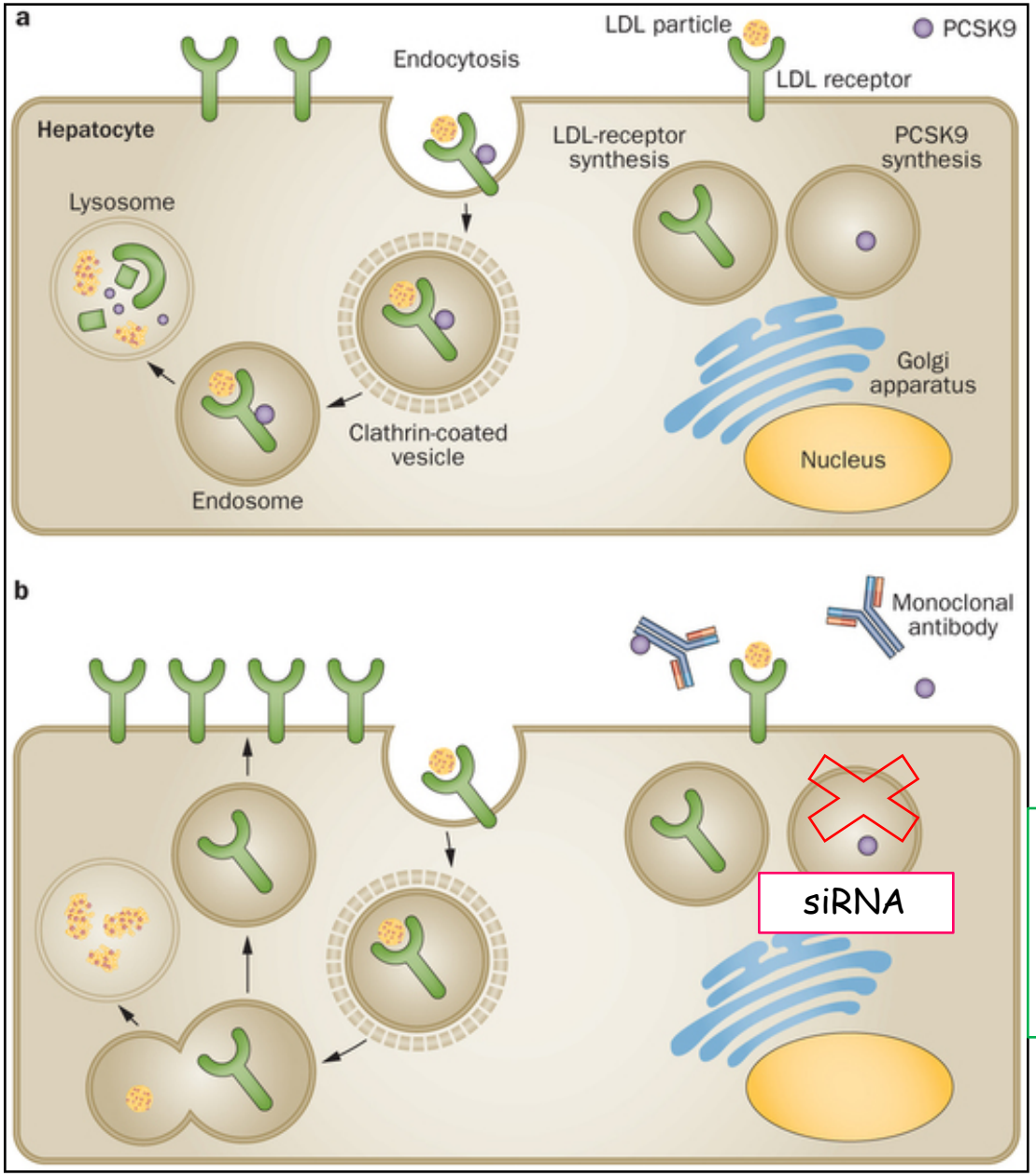
MOA:

Inhibits Niemann-Pick C1-like-1 protein located on luminal side of the small intestine.

It binds to the transmembrane loop of NPC1L1 inhibiting internalization/endocytosis

AE: nothing important

PCSK9 → Target the LDL receptor for degradation



PCSK9 Inhibitors:

PCSK9 agents interfere with recycling of the LDL receptor.

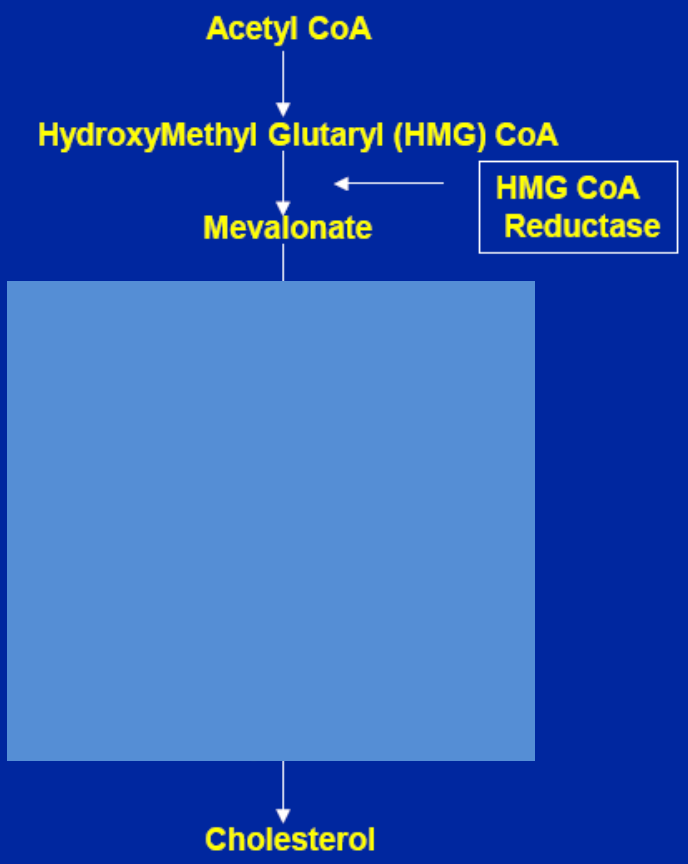
Patients with genetic deficiency of PCSK9 have low LDL cholesterol and low rates of CAD

Monoclonal antibodies against PCSK9 increase LDL receptor and lower cholesterol values.

Clinical trials pending on CAD reduction.
Cost is an issue.
siRNA oligonucleotides are in study.
Oral inhibitors are in development.
Stay tuned!

Statins: 1st agent was Mevacor. Pay attention to the Meva in Mevacor

Cholesterol Biosynthesis

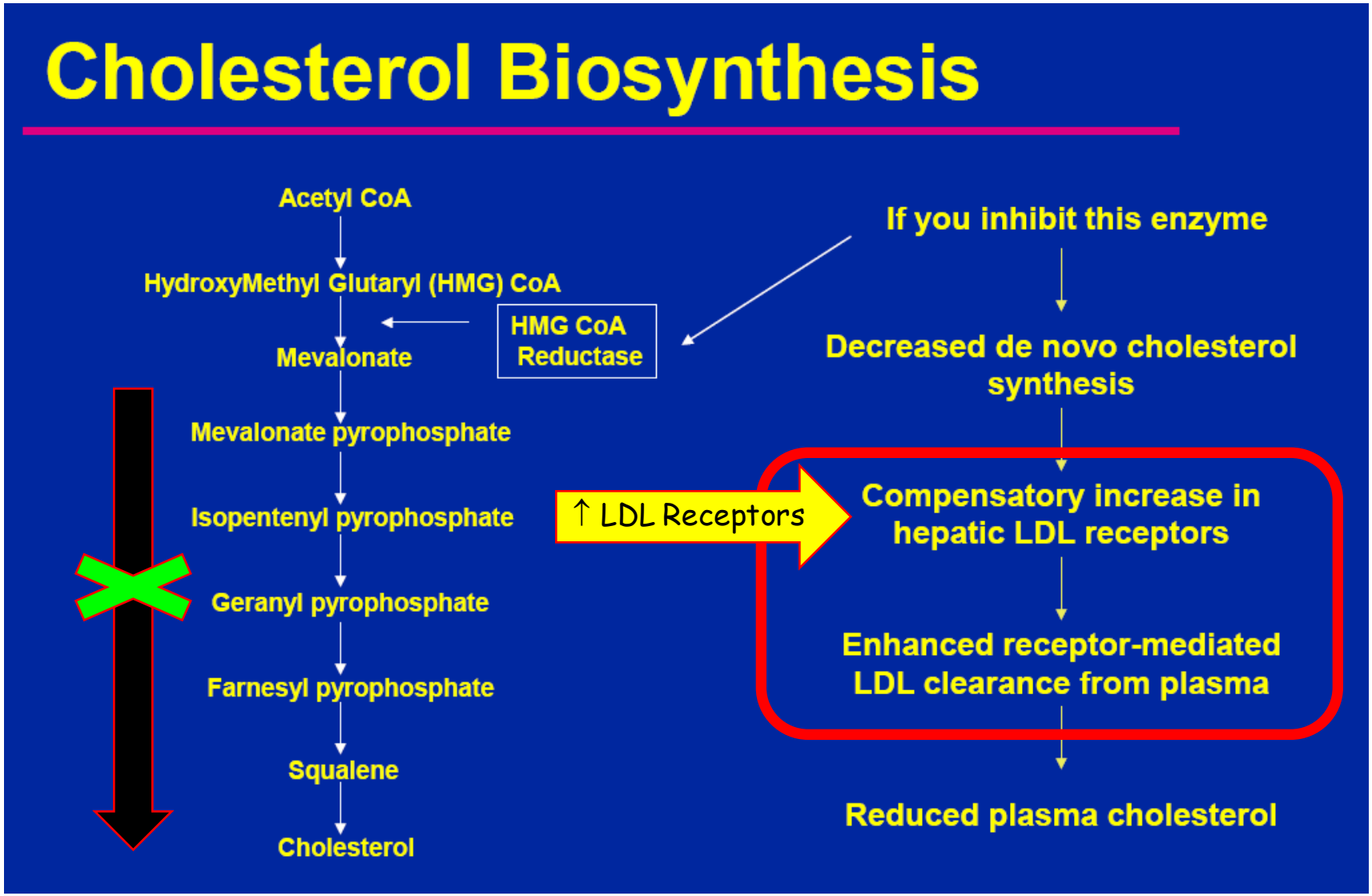


If you inhibit this enzyme

If you inhibit this enzyme:

What happens to Mevalonate level?
What happens to LDL receptor?

Statins: 1st agent was Mevacor. Pay attention to the Meva in Mevacor



Cholesterol Biosynthesis

AE (2): Myalgia PLUS Drug Intax

Be familiar with the inhibitors of statin metabolism (i.e. they increase drug level and risk for rhabdo)

E-mycin & ketoconazole most likely to be seen.

Fibrates increase risk as well…

Cholesterol Lowering: MOA

HMG CoA Reductase Inh	Upregulates LDL receptor
Cholestyramine	Bile Acid Sequestrant/LDL- R ↑
Niacin	↓ VLDL and lipolysis
Fibrates (gemfibrizol, fenofibrate)	Activate PPAR-α/↑ LPL
Ezetimibe	Inhibits cholesterol absorption via NPC1L1 transmembrane protein

PCSK9 Inhibitors → ↑ LDL receptor (protect against degradation)

Cholesterol Lowering: AE

HMG CoA Reductase Inh	Myalgia+
Cholestyramine	Triglyceride elevation
Niacin	Hyperuricemia (Gout)/IGT Flushing (PG mediated)
Fibrates (gemfibrizol, fenofibrate)	Cholelithiasis/Rhabdo
Ezetimibe	Pretty Damn Safe

Your patient is diagnosed with metabolic syndrome. You start a medication to manage his dyslipidemia. He calls the clinic complaining about acute onset of severe pain, redness and swelling of his foot. Physical exam confirms swelling and redness of the first metatarsal joint. Which medication was most likely to precipitate this condition?

A. Simvastatin
B. Niacin
C. Fenofibrate
D. Cholestyramine
E. Ezetimibe

Your patient is diagnosed with HTN. You start a medication to manage his HTN. He calls the clinic complaining about acute onset of severe pain, redness and swelling of his foot. Physical exam confirms swelling and redness of the first metatarsal joint. Which medication was most likely to precipitate this condition?

A. Simvastatin
B. HCTZ
C. Fenofibrate
D. Cholestyramine
E. Ezetimibe

The patient is a 65 y.o. male who develops classic anginal symptoms. He refuses angiogram. He does agree to maximize his medical management. You decide to start him on pravastatin. The treatment is most likely to result in which of the following adaptive responses at the cellular level?

A. Decreased transcription of HMG-CoA reductase
B. Increased mevalonic acid degradation
C. Increased mevalonic acid synthesis
D. Increased hepatic expression of LDL cholesterol receptors

The patient is a 65 y.o. male who develops classic anginal symptoms. He refuses angiogram. He does agree to maximize his medical management. You decide to start him on pravastatin. The treatment is most likely to result in which of the following adaptive responses at the cellular level?

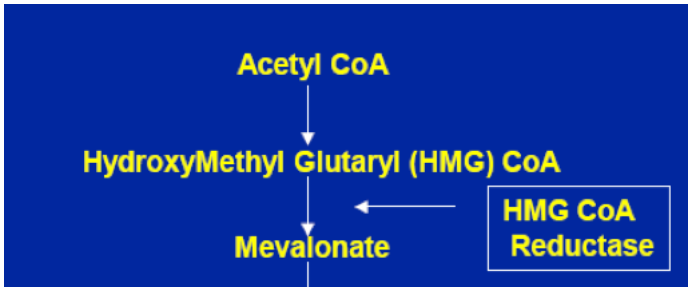
Increased

A. ~~Decreased~~ transcription of HMG-CoA reductase

B. Increased mevalonic acid degradation

C. Increased mevalonic acid synthesis

D. Increased hepatic expression of LDL cholesterol receptors



Given the patient's CAD, lipid lowering drug therapy is initiated. Upon repeat testing, his triglycerides are noted to be elevated. Which of the following drugs, when used as monotherapy, would be most likely to increase the triglyceride level?

A. Atorvastatin
B. Niacin
C. Gemfibrozil
D. Cholestyramine
E. Ezetimbe

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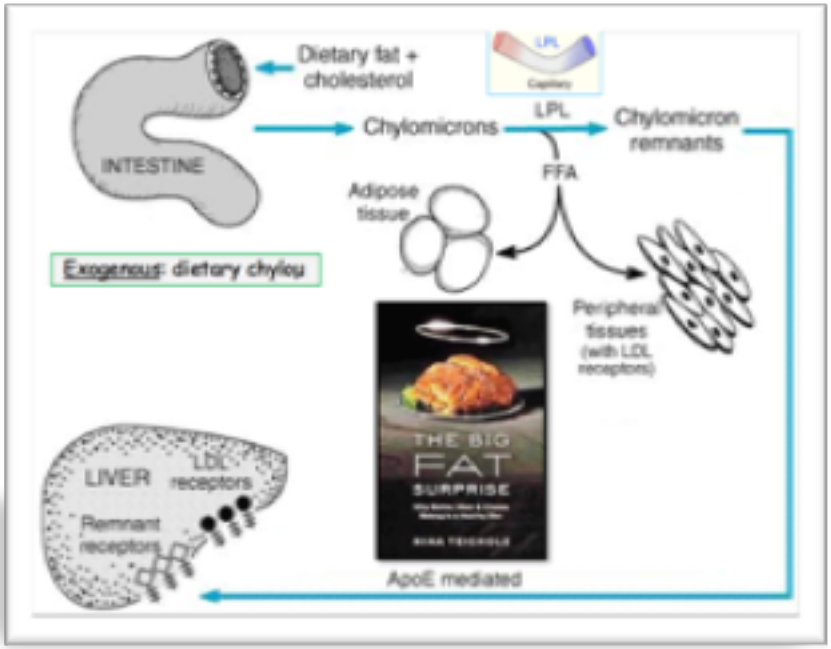

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