ANSC/NUTR 618
LIPIDS & LIPID METABOLISM
Lipoprotein Metabolism

I. Chylomicrons (*exogenous pathway*)

A. 83% triacylglycerol, 2% protein, 8% cholesterol plus cholesterol esters, 7% phospholipid (esp. phosphatidylcholine)

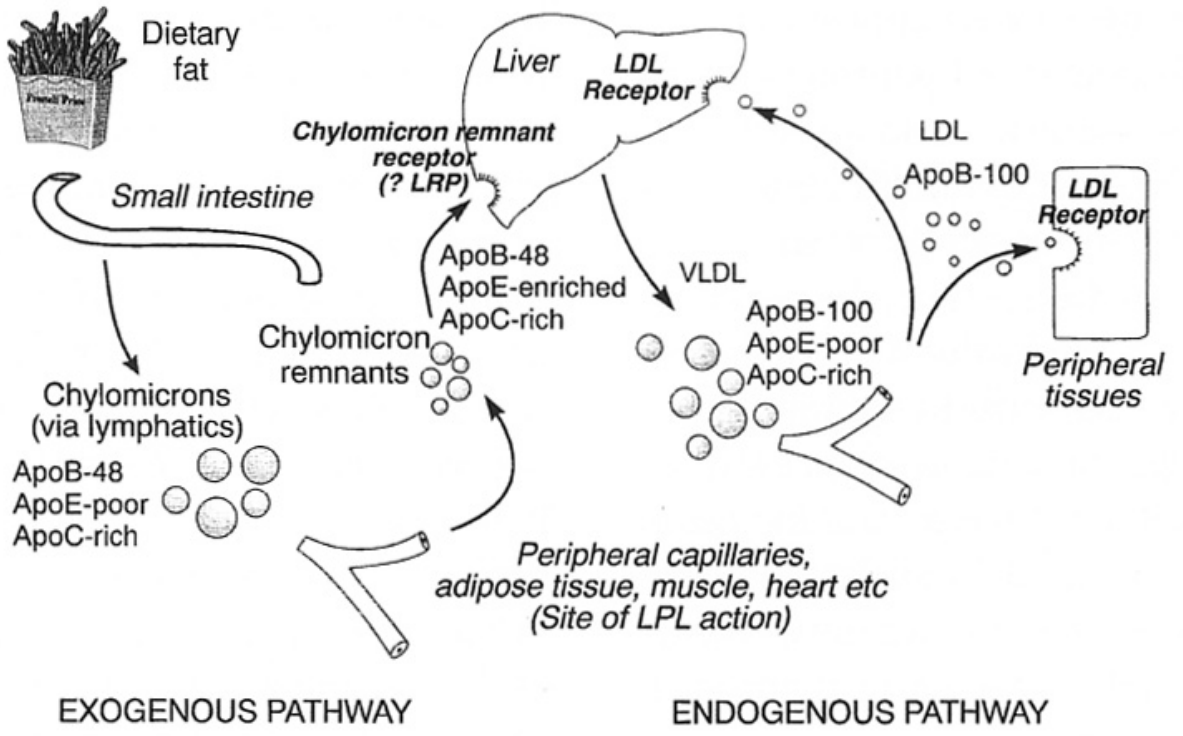
B. Secreted as nascent chylomicrons from mucosal cells with $ApoB_{48}$ and $ApoA_1$

C. Acquire $ApoC_1$, C_2, and C_3 in blood (from high-density lipoproteins)

1. $ApoC_1$ activates lecithin:cholesterol acyltransferase (**LCAT**; in blood) and $ApoC_2$ activates lipoprotein lipase. $ApoC_3$ prevents uptake by the liver.
2. Required for conversion of chylomicrons to remnant particles.

D. Triacylgycerols are removed from chylomicrons at extrahepatic tissues by lipoprotein lipase (**LPL**).

E. Chylomicron remnants are taken up by the LDL-receptor-related protein (**LRP**).



Exceptions: In birds, the lymphatic system is poorly developed. Instead, *pro-microns* are formed, which enter the hepatic portal system (like bile salts) and are transported directly to the liver.

Ruminants do not synthesis chylomicrons primarily due to low fat intake. Rather, their dietary fats are transported from the small intestine as very low-density lipoproteins.

F. Lipoprotein lipase

1. Lipoprotein lipase is synthesized by various cells (e.g., adipose tissue, cardiac and skeletal muscle) and secreted to the capillary endothelial cells.

a. LPL is bound to the endothelial cells by a heparin sulfate bond.

b. LPL requires lipoproteins (i.e., apoC2) for activity, hence the name.

2. TAG within the chylomicrons and VLDL are hydrolyzed to NEFA, glycerol, and 2-MAG.

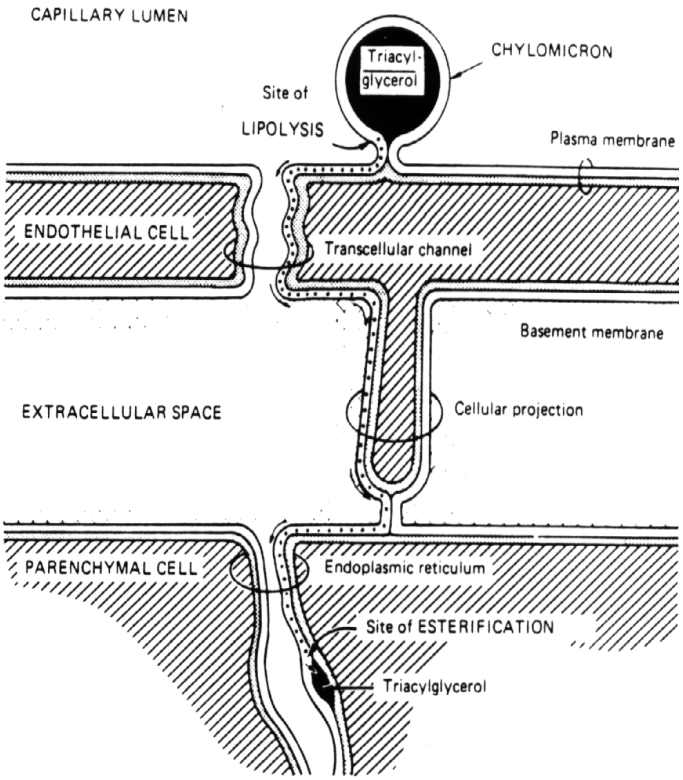
a. NEFA and 2-MAG are taken up the tissues and reesterified to TAG

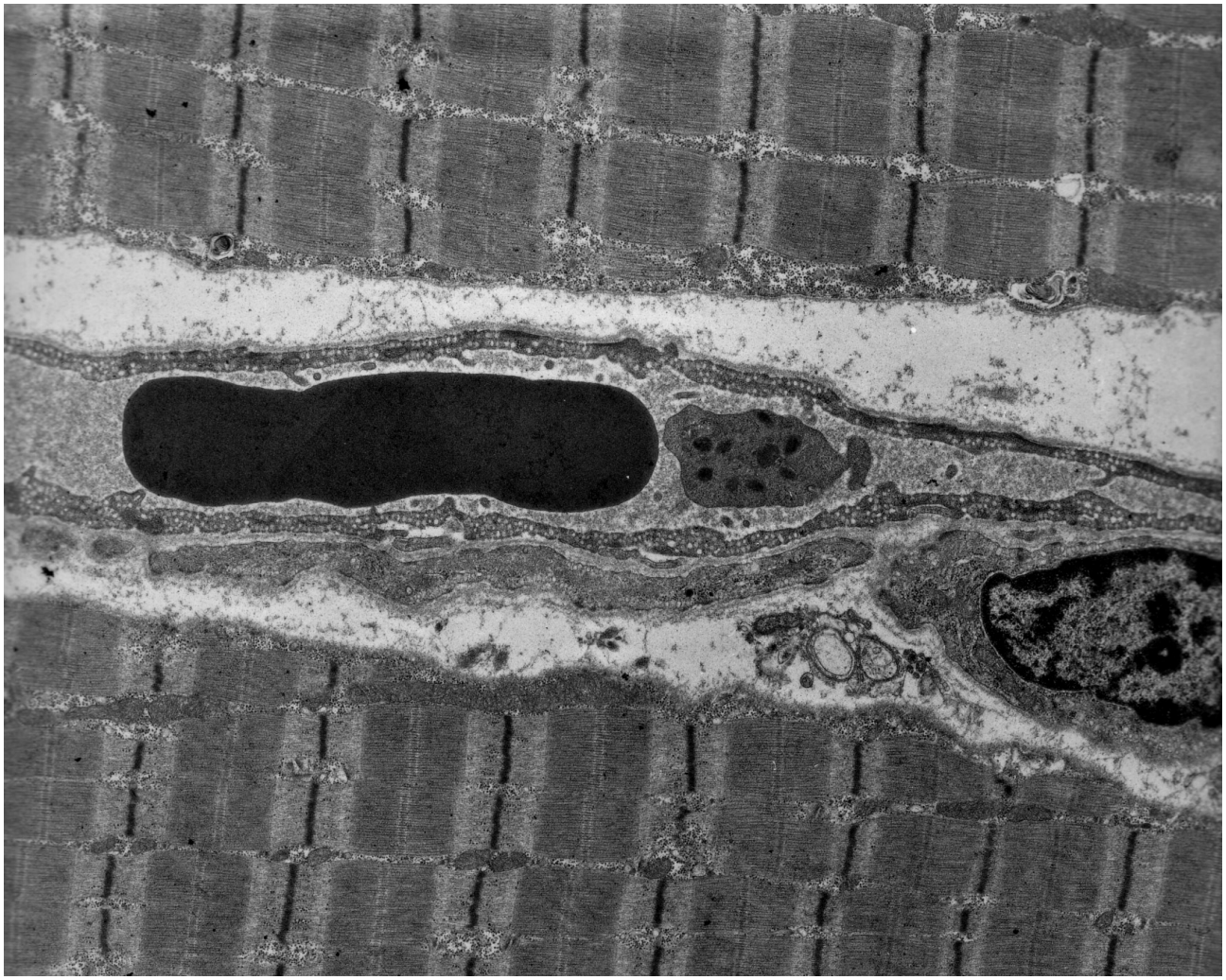
b. Glycerol is taken up by the liver for metabolism and converted to G-3-P by glycerol kinase (not present in adipose tissue).

c. G-3-P usually is converted to glucose or used as the backbone for TAG synthesis.

3. Fatty acids and 2-MAG travel *through* the membrane of the capillary endothelial cells to the cell membrane and endoplasmic (sarcoplasmic) reticulum of the target tissue.

4. Fatty acids are oxidized or stored as TAG.





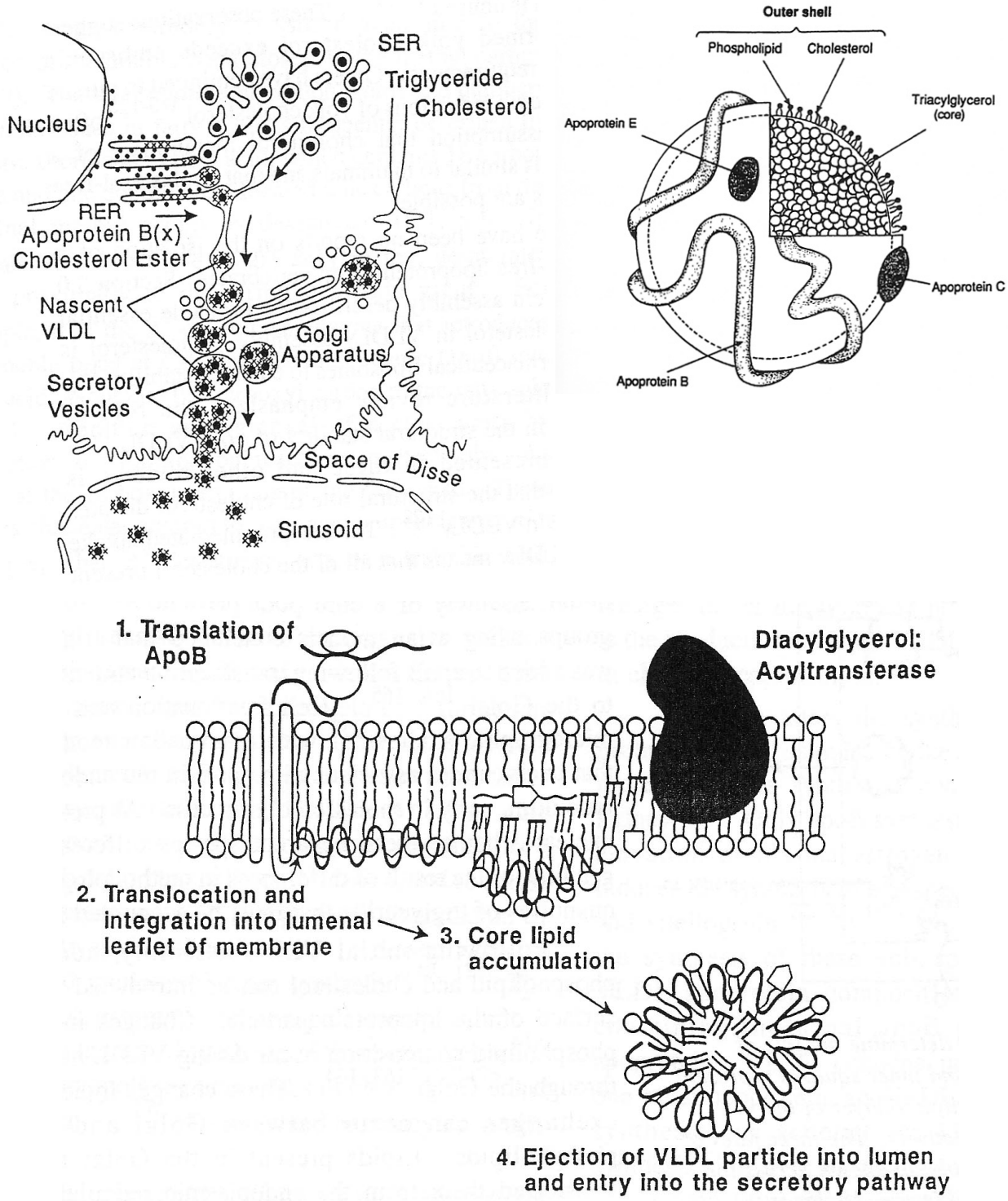
II. Very low-density lipoprotein (VLDL; *endogenous pathway*)

A. 50% TAG, 7% protein, 22% cholesterol ester plus C, 20% phospholipid.

B. Secreted (primarily) from liver with $ApoB_{100}$ and apoE.

C. Lose their TAG at muscle and adipose tissue (via LPL) → **IDL.**

Exception: In birds, VLDL are taken up *unchanged* by oocytes by reverse pinocytosis and are incorporated directly into egg yolks.



D. Synthesis of VLDL (virtually identical to the synthesis of chylomicrons)

a. $ApoB_{100}$ and TAG synthesized on the rough e.r.

b. Portions of the e.r. pinch off and encapsulate the TAG and $apoB_{100}$.

c. VLDL particles are ejected into the sinusoids of liver (like lacteals of small intestine).

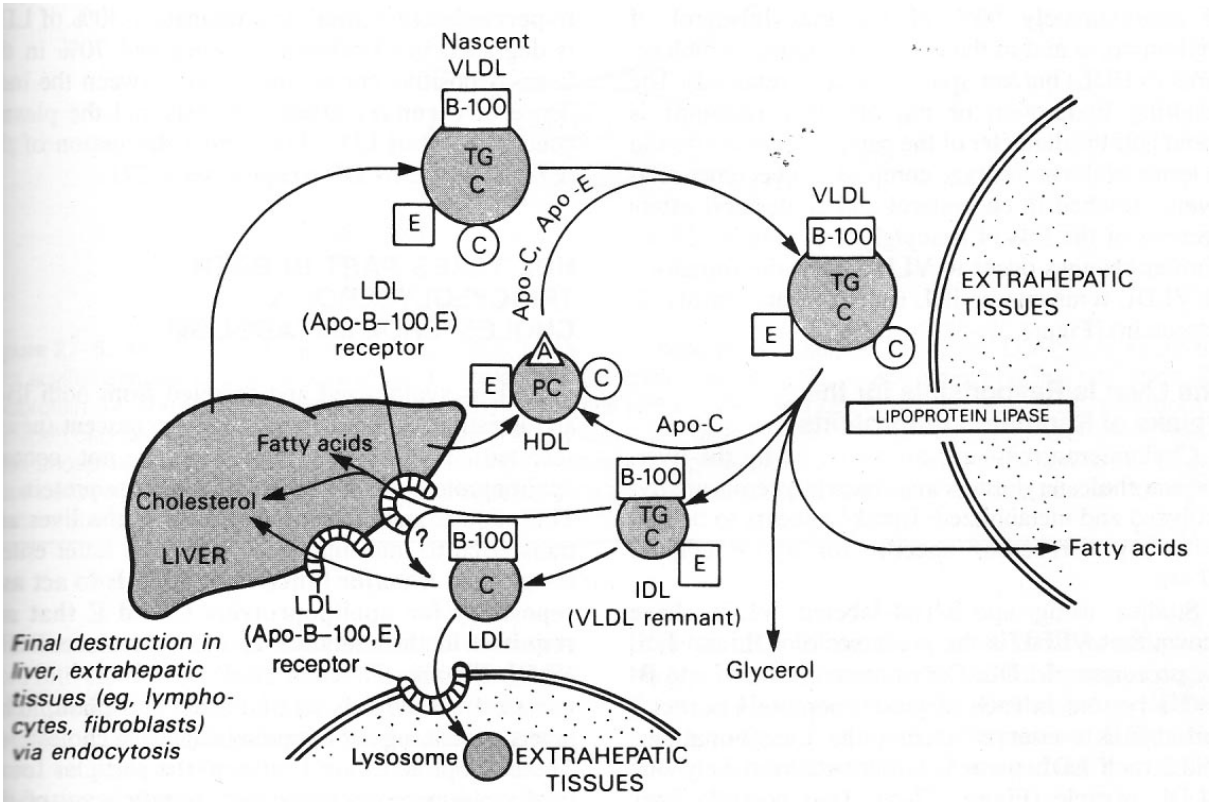
III. Intermediate density lipoprotein (IDL)

A. Produced from VLDL, but retain ApoE.

B. Contain approx. 10% TAG, 20% phospholipid, 20-30% *cholesterol ester*, 8% cholesterol, and 15% protein.

C. Small pieces pinch off → nascent high-density lipoproteins (**HDL).**

4. Remainder = **IDL**, taken up by the liver LDL-receptor *rapidly if it contains ApoE*.



IV. Low density lipoprotein (LDL)

A. Depletion of TAG in VLDL destabilizes particles, produces IDL **without ApoE**.

B. Pinching off of phospholipid and Apo A forms laminar structures (pieces transferred to nascent HDL).

C. Remainder becomes LDL.

D. LDL taken up by tissues with LDL receptors (primarily liver) by receptor-specific endocytosis.

Exception: In birds, the liver secretes a *very* high density lipoprotein termed *vitellogenin* (VTG). Like avian VLDL, VTG is taken up by oocytes for incorporation into egg yolk (apparently by the VLDL receptor).

V. High density lipoprotein (HDL)

A. Nascent HDL is derived from liver and small intestine.

1. Discoid phospholipid bilayer (like cell membranes) is released from liver with $ApoA_1$ and lecithin cholesterol acyltransferase (**LCAT**) (= pre-ß HDL).

2. Chylomicron and VLDL remnants contribute surface constituents to developing HDL particle → *discoidal* pre-ß HDL.

3. Free cholesterol is taken up from "cholesterol rafts" in membranes of extrahepatic cells and binds to $ApoA_1$.

4. Cholesterol is converted to cholesterol ester by LCAT to produce dense HDL_3 particles: lecithin + cholesterol → 2-lyso-lecithin + cholesterol ester.

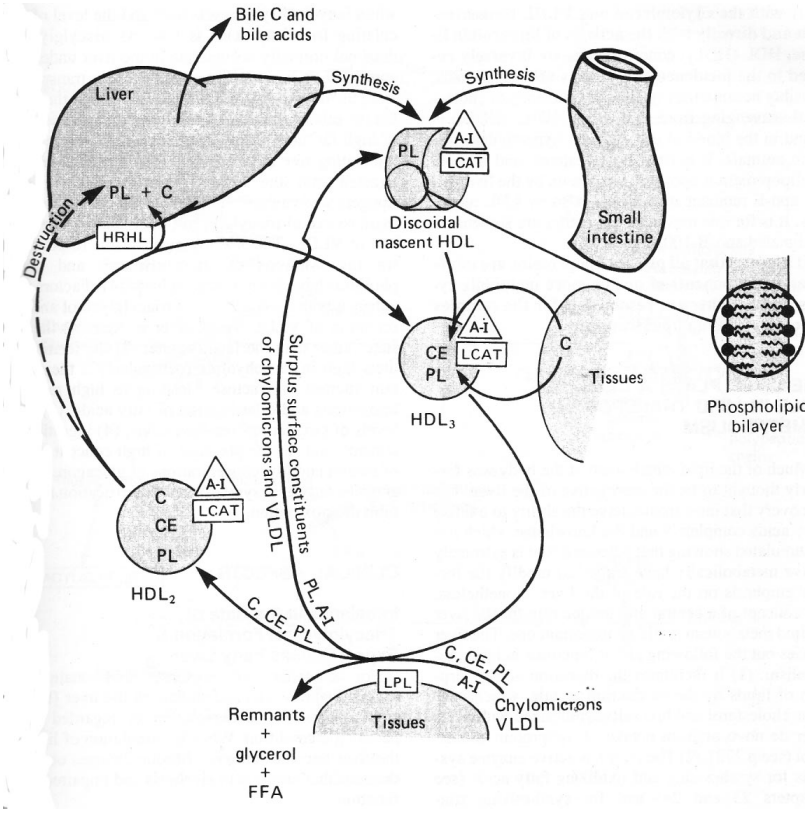
a. Lecithin (phosphatidyl choline) is derived from surface phospholipids of HDL.

b. Lyso-lecithin is released and lecithin is resynthesized in the liver.

c. Accumulation of cholesterol ester produces less dense HDL_2.

5. Uptake of cholesterol from chylomicron and VLDL remnant particles helps to fill the core.

6. HDL remove cholesterol from other tissues (such as arterial walls) to fill their cholesterol ester core.



B. Metabolism of HDL_2 to HDL_3.

1. HDL_2 cholesterol may be absorbed by liver by a specific scavenger receptor, $SR\text{-}B_1$.

   a. Cholesterol ester is taken up and hydrolyzed by liver cells.

   b. The smaller HDL_3 particle is not internalized.

   c. The cholesterol-depleted HDL_3 particle leaves the receptor and re-enters the cycle.

2. Cholesterol esters alternatively can be transferred to VLDL remnants, chylomicron remnants, or LDL via cholesterol ester transfer protein (**CETP**).

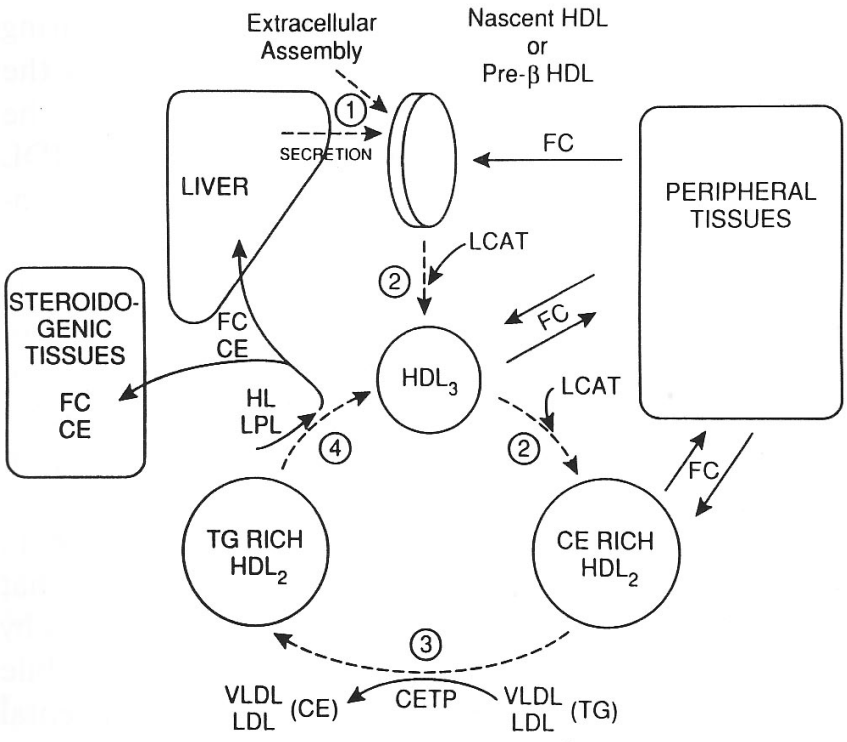
   a. CETP is synthesized by liver and adipose tissue.

   b. CETP mediates the exchange of TAG and CE between VLDL and chylomicrons (sources of TAG) and HDL_2.

   c. VLDL and chylomicrons acquire CE, and HDL_2 acquires TAG.

   d. These particles may be taken up by the liver.

3. On the surface of the hepatocytes, heparin-releasable hepatic lipase (**HRHL**) hydrolyzes TAG and surface lipids of the HDL → more dense HDL_3.



VI. Proteins associated with apolipoproteins

Apolipoprotein or enzyme	Function
A_1	Cholesterol efflux from cells. Activates LCAT.
A_2	May inhibit hepatic lipase (HL). Inhibits A_1, LCAT.
A_4	Activates LCAT.
B_{48}	Recognition of chylomicron remnants by liver receptors and subsequent clearance.
B_{100}	Recognition of LDL by LDL receptors and subsequent clearance.
C_1	Activates LCAT.
C_2	Activates LPL.
C_3	Blocks uptake of chylomicron remnants by liver. May inhibit LPL.
D	May be involved in CE transfer.
E	Required for clearance of chylomicron remnants and IDL by liver. Can overcome inhibition of uptake by apoC_3.
Lecithin-cholesterol acyltransferase (LCAT)	Transfers cholesterol from extrahepatic sites to HDL_2 via transesterification between lecithin (phosphatidyl choline) and cholesterol. This reaction is less important in HDL_3.
Cholesterol-ester transfer protein (CETP)	Transfers cholesterol esters from CE-rich HDL_2 to VLDL and LDL, resulting in TAG-rich HDL_2 and CE-enriched VLDL and LDL.

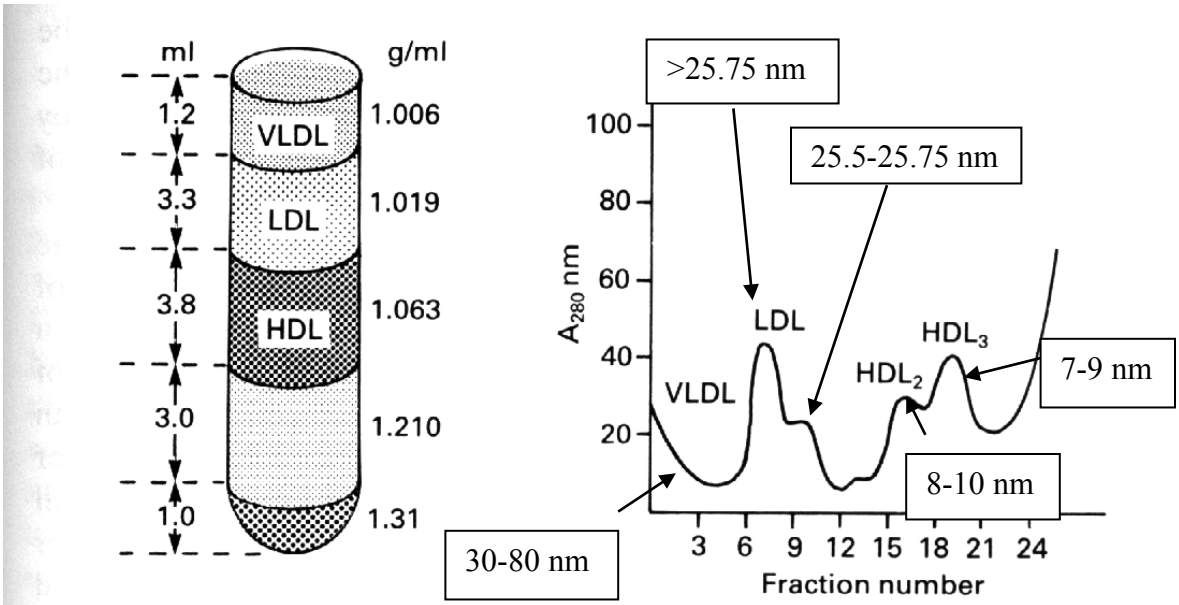


Figure 5.17 Separation of plasma lipoproteins by gradient ultracentrifugation.