Lipoproteins

S.M. Shafiee, PhD

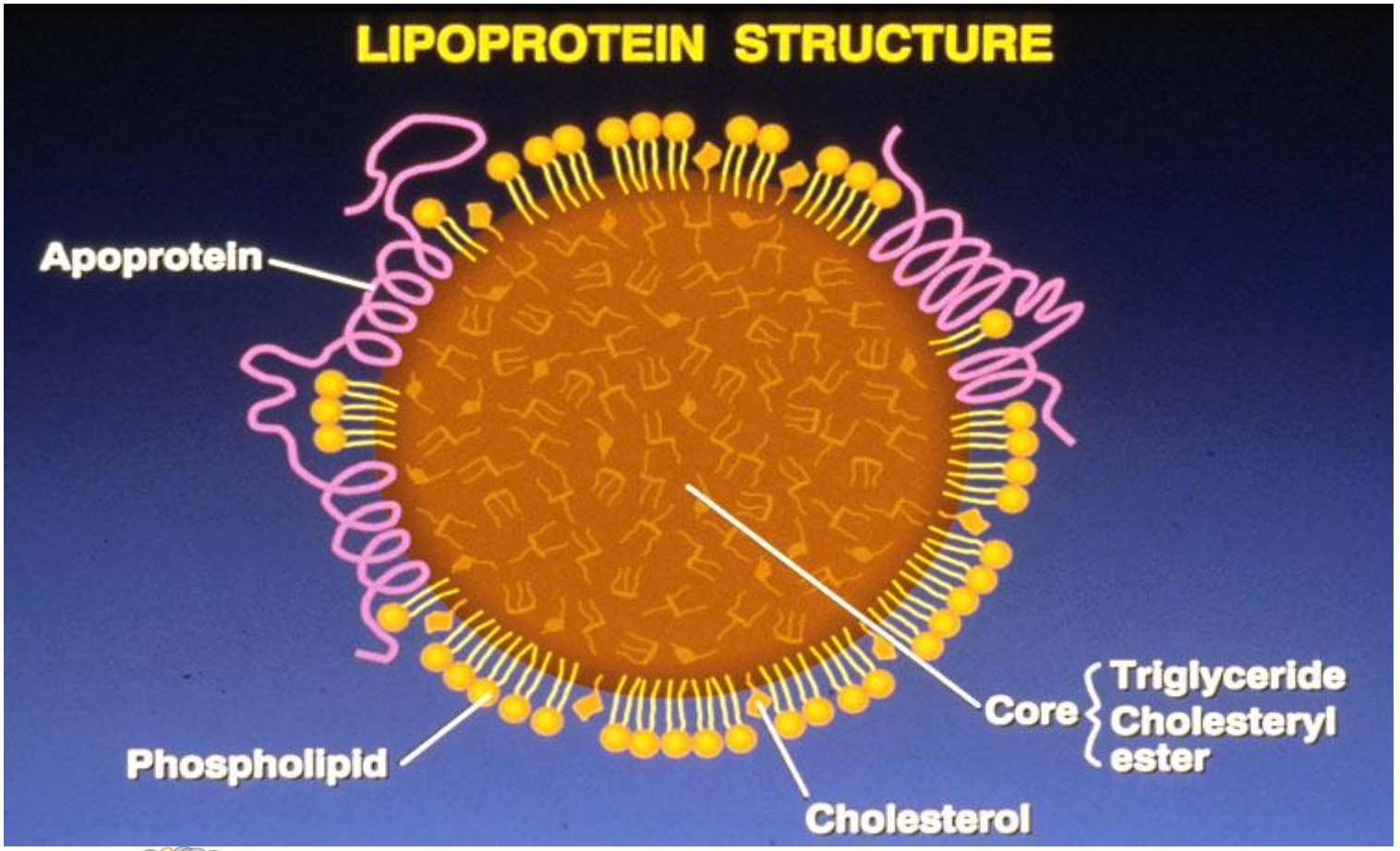
Dept. of Biochemistry, SUMS

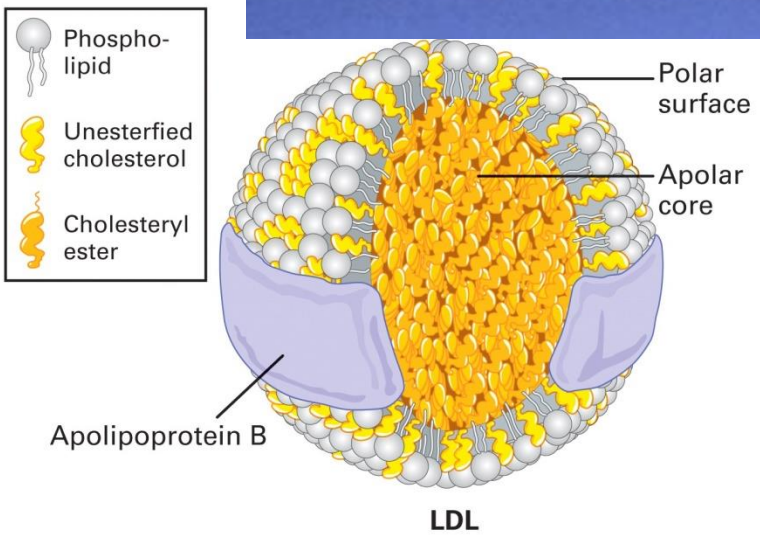
Introduction

Lipid compounds:

Relatively water insoluble

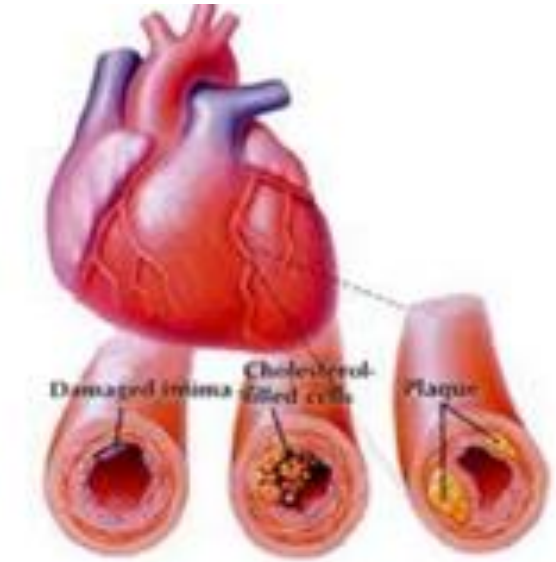
Therefore, they are transported in plasma (aqueous) as Lipoproteins


LIPOPROTEIN STRUCTURE
Apoprotein
Phospholipid
Core
Triglyceride
Cholesteryl ester
Cholesterol


Phospho-lipid
Unesterfied cholesterol
Cholesteryl ester
Polar surface
Apolar core
Apolipoprotein B
LDL

Lipoproteins and Related Clinical Problems

- Atherosclerosis and hypertension
- Coronary heart diseases
- Lipoproteinemias (hypo- and hyper-)
- Fatty liver



Lipoprotein Structure

Protein part: Apoproteins or apolipoproteins

These proteins may be structural or transferred

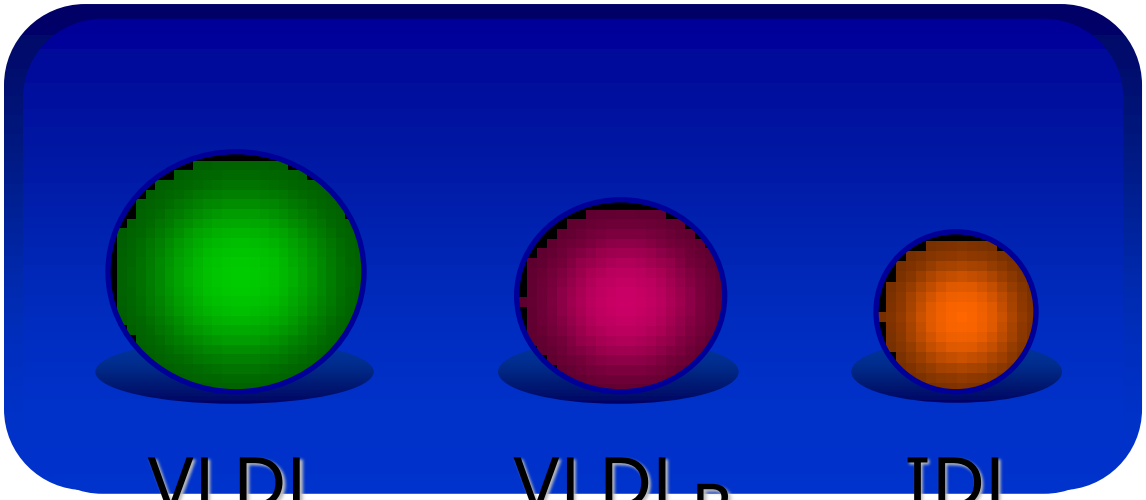
Lipid part:

- According to the type of lipoproteins
- Different lipid components in various combinations

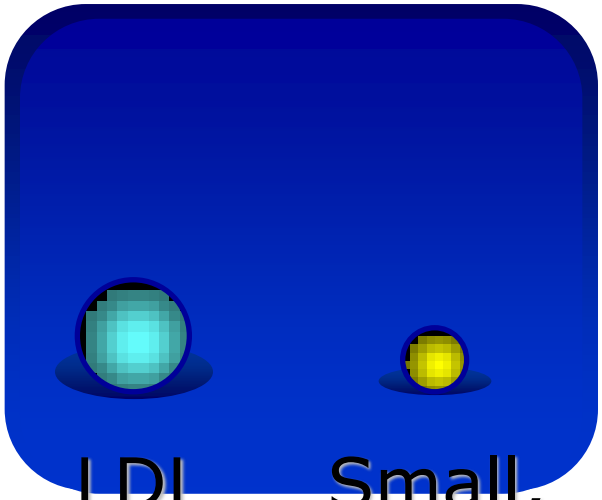
MEASUREMENTS:

Apolipoprotein B

Non-HDL-C



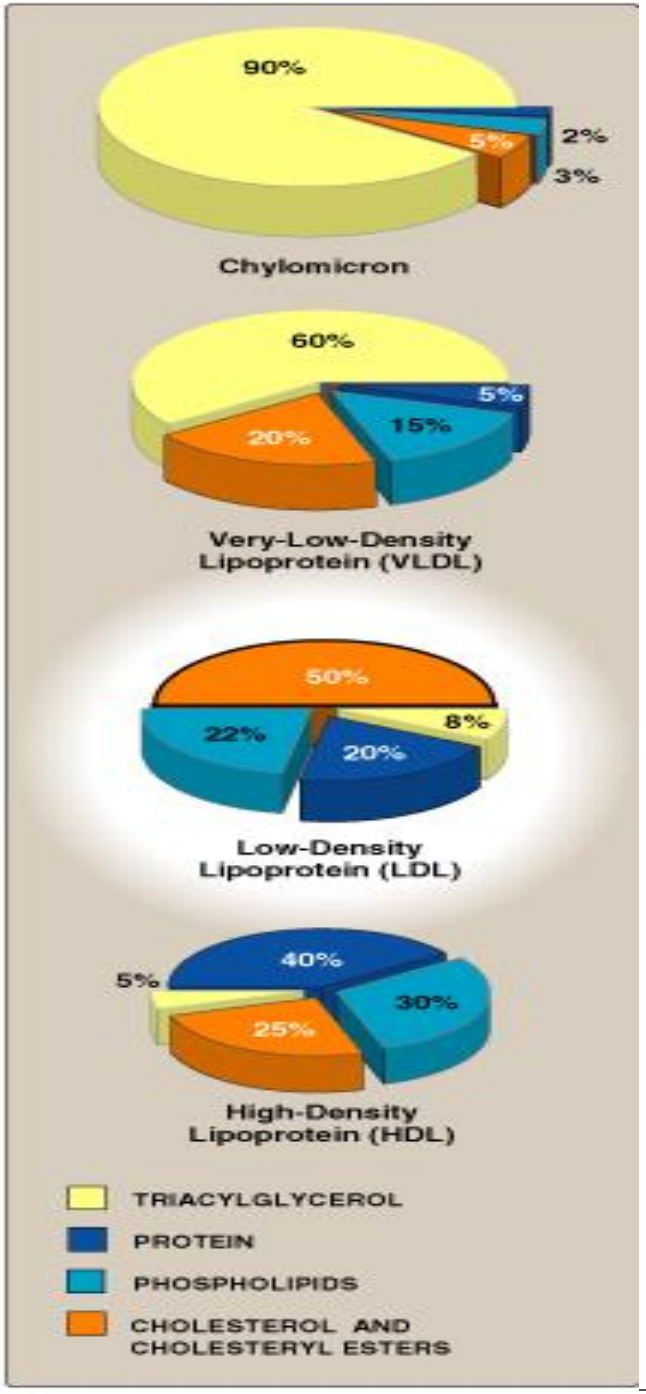
VLDL $VLDL_R$ IDL



LDL Small, dense LDL

TG-rich lipoproteins

Types and Composition of Lipoproteins



Chylomicrons

Very low density Lipoprotein (VLDL)

Low density Lipoprotein (LDL)

High density Lipoprotein (HDL)

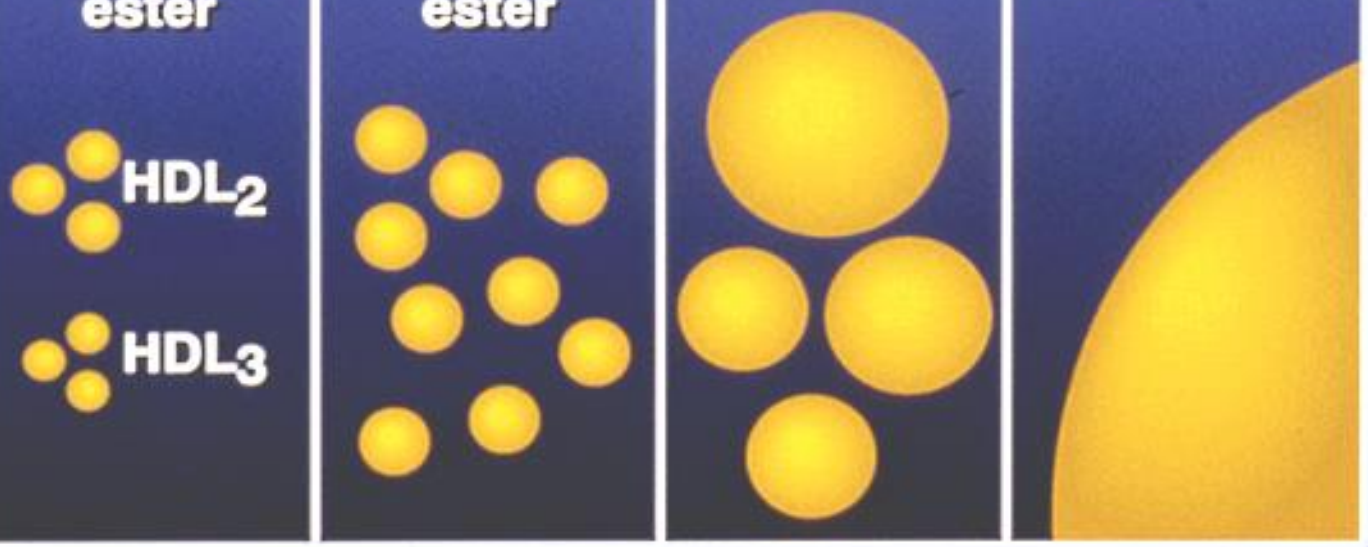
TABLE 1-1 Properties of Human Plasma Lipoproteins

Class	D (nm)	d (g/mL)	Mobility	Composition (%)					Major Apos
				Core		Surface			
				TG	CE	FC	PL	Pro	
Chylomicrons	80–500	<0.93	α_2	86	3	2	7	2	B-48, E, A-I, A-II, A-IV, C
VLDL	30–80	0.95–1.006	Pre-β	55	12	7	18	8	B-100, C-I, C-II, C-III, E
IDL	25–35	1.006–1.019	Slow pre-β	23	29	9	19	19	B-100, E
LDL	21.6	1.019–1.063	β	6	42	8	22	22	B-100
HDL_2	10	1.063–1.125	α	5	17	5	33	40	A-I, A-II
HDL_3	7.5	1.125–1.210	α	3	13	4	25	55	A-I, A-II
Lp(a)	30	1.055–1.085	Slow pre-β	3	33	9	22	33	B-100, apo(a)

apos, apolipoproteins; D, diameter; d, density; CE, cholesteryl ester; FC, free cholesterol; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein(s); LDL, low-density lipoprotein; Lp(a), lipoprotein(a); PL, phospholipid; TG, triglyceride(s); VLDL, very-low-density lipoprotein(s).

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			



Apoproteins

- **Five major classes (A-E) divided by structure & function**
- **Each class has subclasses as Apo A1, Apo CII**

Functions

- **Some are required as structural proteins**
- **Some are activators,**
- **Some are recognition sites.**

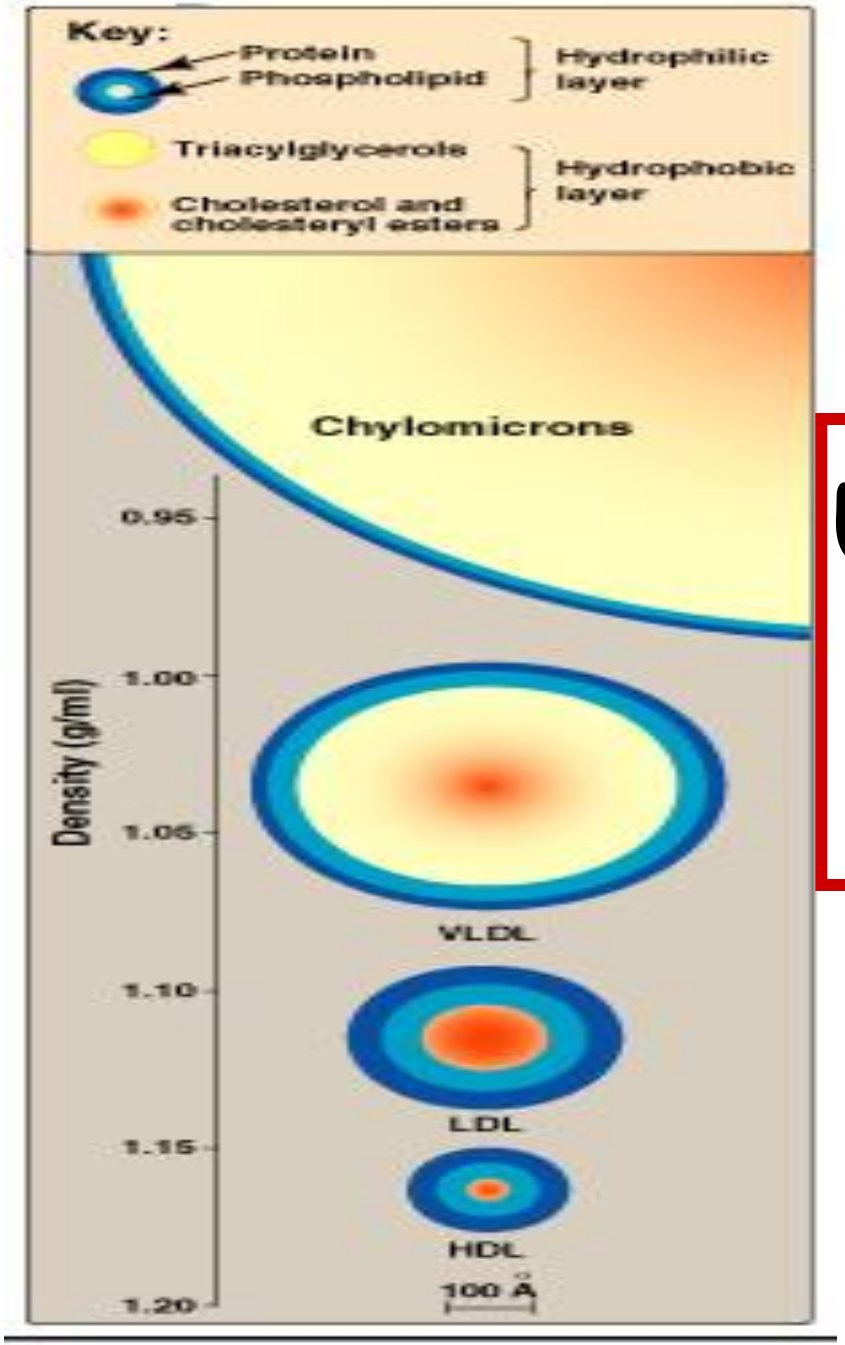
Apolipoproteins

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

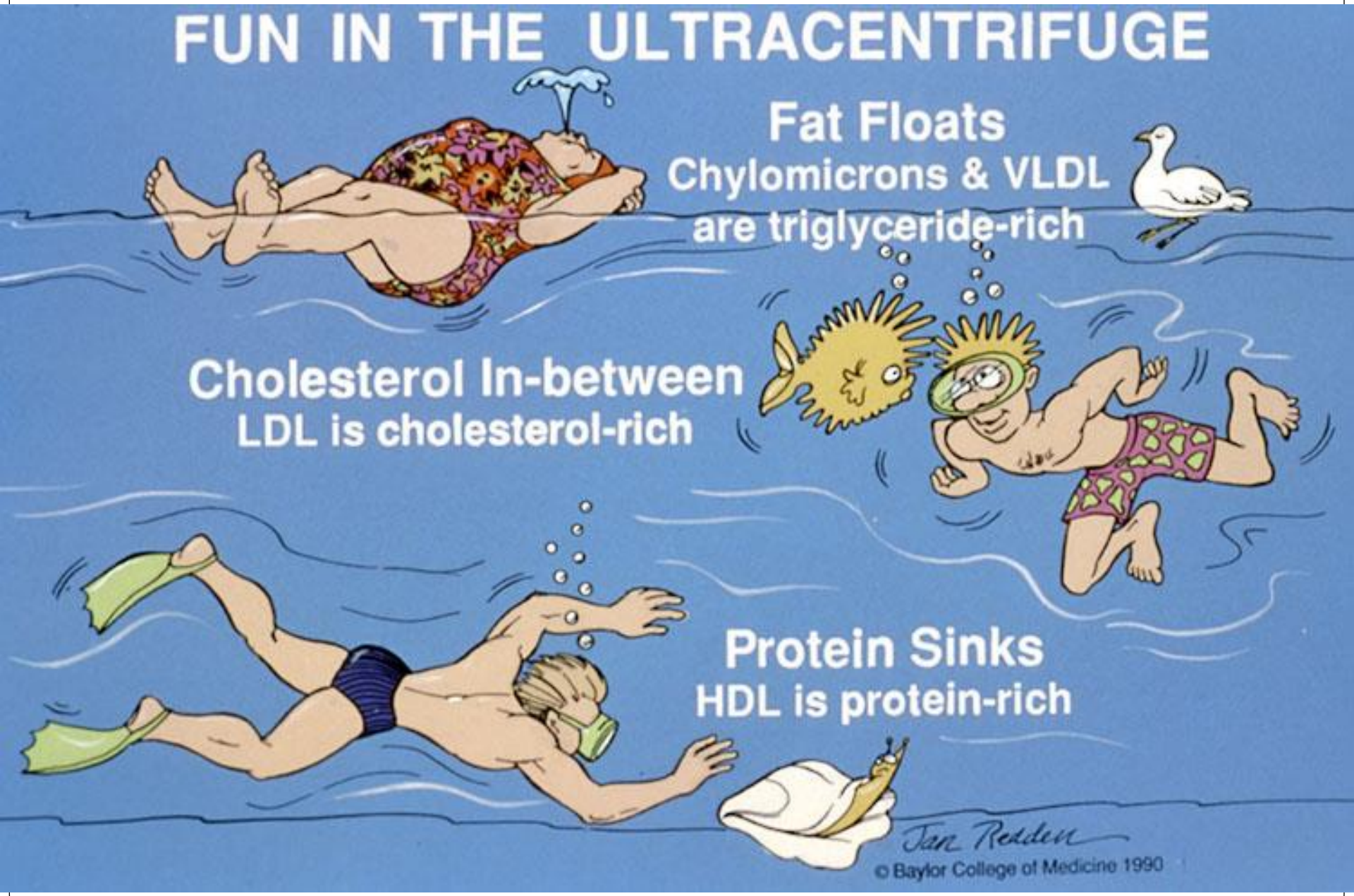
Types of Lipoproteins

- **There are various types of lipoproteins:**

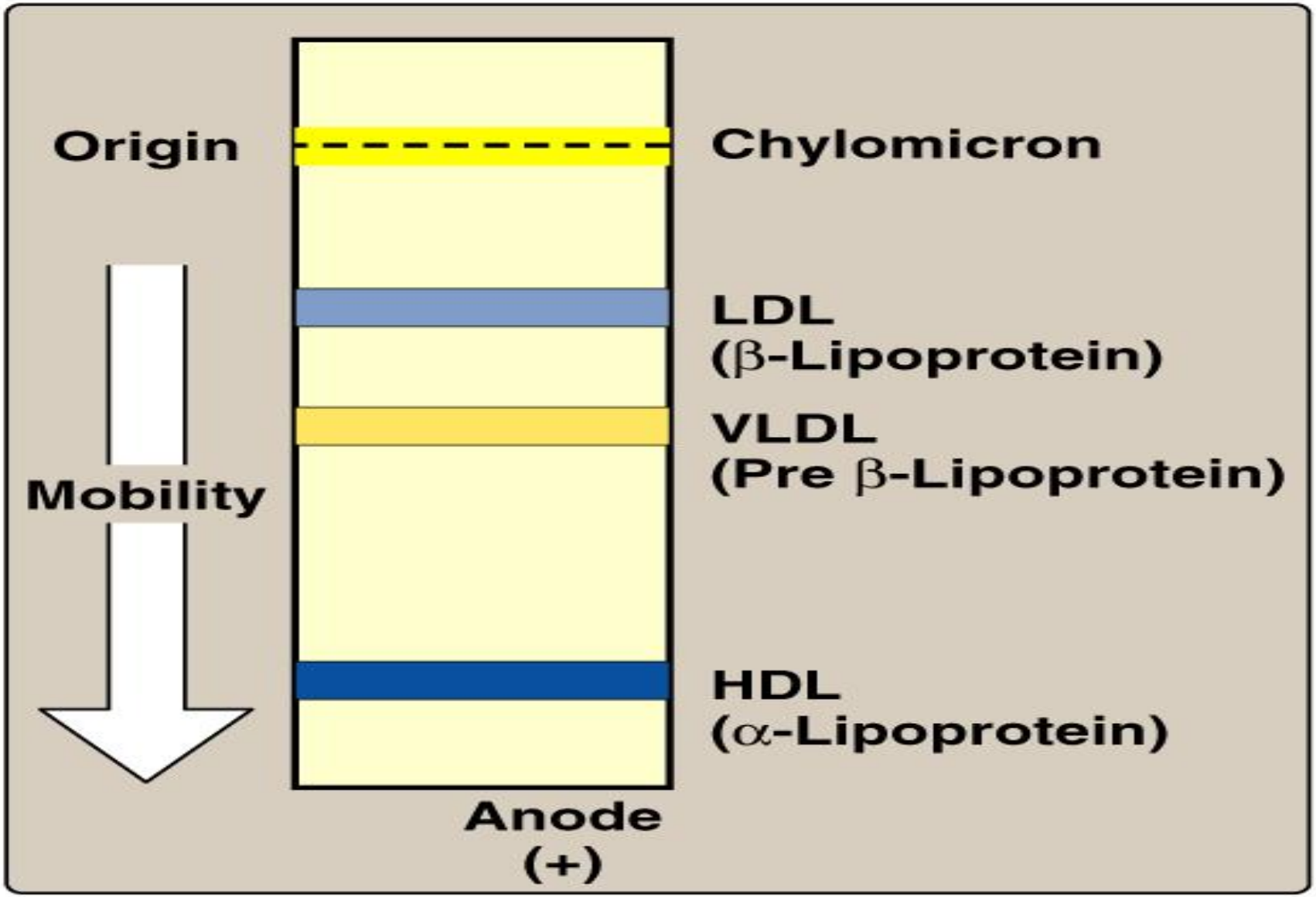
- **They differ in lipid and protein composition and therefore, they differ in:**
  - **Size and density**
  - **Electrophoretic mobility**



Ultracentrifugation of Lipoproteins


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 Reeden
© Baylor College of Medicine 1990

Lipoprotein Electrophoresis

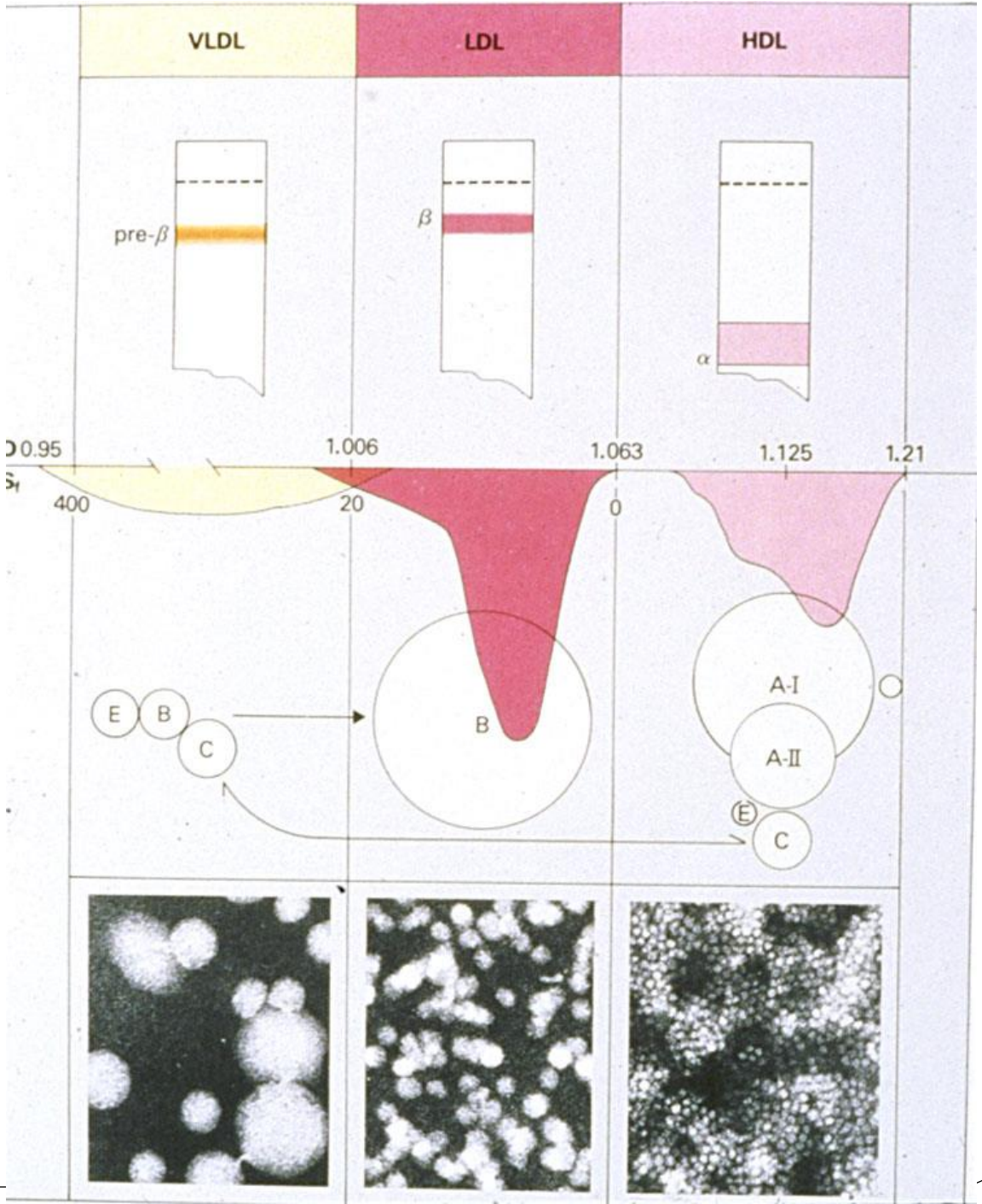


Lipoproteins:
Separation by –

Electrophoresis

Density

Size by
Electron Microscopy



Plasma Lipoproteins

For triacylglycerol transport (TG-rich):

- **Chylomicrons:** TG of dietary origin
- **VLDL:** TG of endogenous (hepatic) synthesis

For cholesterol transport (cholesterol-rich):

LDL

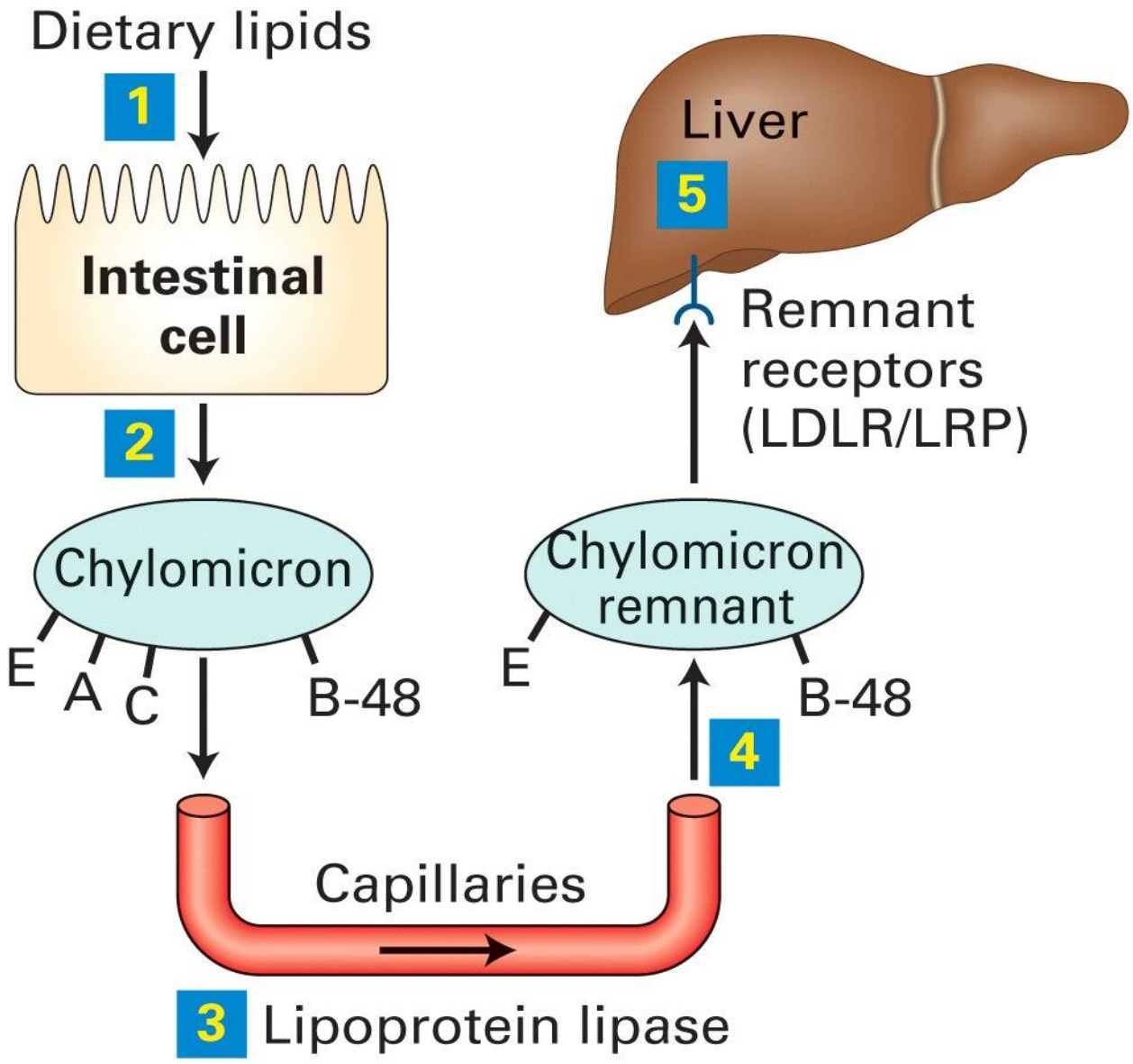
HDL

Chylomicrons

- Assembled in intestinal mucosal cells
- Lowest density
- Largest size
- Highest % of lipids and lowest % proteins
- Highest triacylglycerol (dietary origin)
- Carry dietary lipids to peripheral tissues
- Responsible for physiological milky appearance of plasma (up to 5 hours after meal)

Lipoprotein Lipase

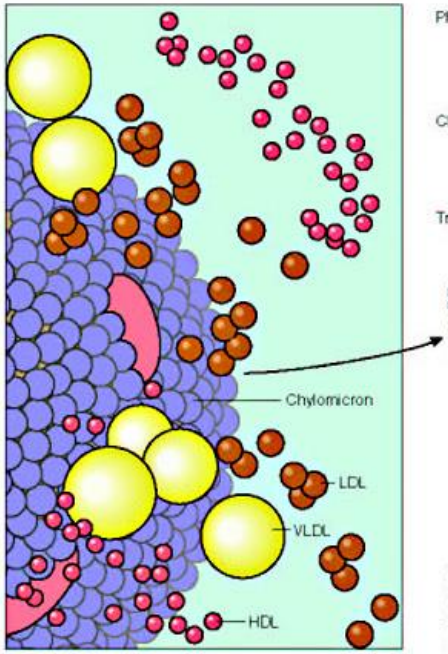
- ***Extracellular*** enzyme anchored by ***heparan sulphate*** to the capillary walls of most tissue esp. those of adipose tissue, cardiac & skeletal muscles
- Clearing Factor
- Its synthesis & transfer to luminal surface of the capillary is ***stimulated by insulin***
- ***Activated*** by apoC-II



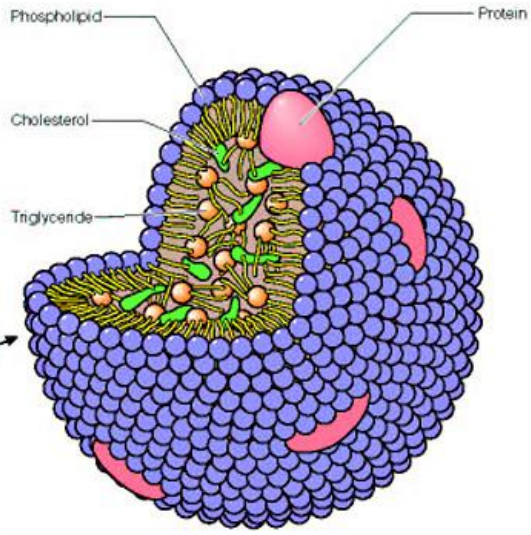
LRP: Low density lipoprotein receptor-related protein

Plasma Lipoproteins Classes & Functions

- Very Low Density Lipoprotein (VLDL)
  - Synthesized in liver
  - Transport endogenous triglycerides
  - 90% lipid, 10% protein
  - Apo B-100
    - Receptor binding
  - Apo C-II
    - LPL activator
  - Apo E
    - Remnant receptor binding



This solar system of lipoproteins shows their relative sizes. Notice how large the fat-filled chylomicron is compared with the others and how the others get progressively smaller as their proportion of fat declines and protein increases.



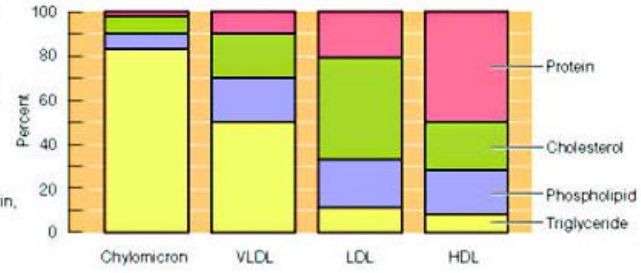
A typical lipoprotein contains an interior of triglycerides and cholesterol surrounded by phospholipids. The phospholipids' fatty acid "tails" point toward the interior, where the lipids are. Proteins near the outer ends of the phospholipids cover the structure. This arrangement of hydrophobic molecules on the inside and hydrophilic molecules on the outside allows lipids to travel through the watery fluids of the blood.

Chylomicrons contain so little protein and so much triglyceride that they are the lowest in density.

Very-low-density lipoproteins (VLDL) are half triglycerides, accounting for their low density.

Low-density lipoproteins (LDL) are half cholesterol, accounting for their implication in heart disease.

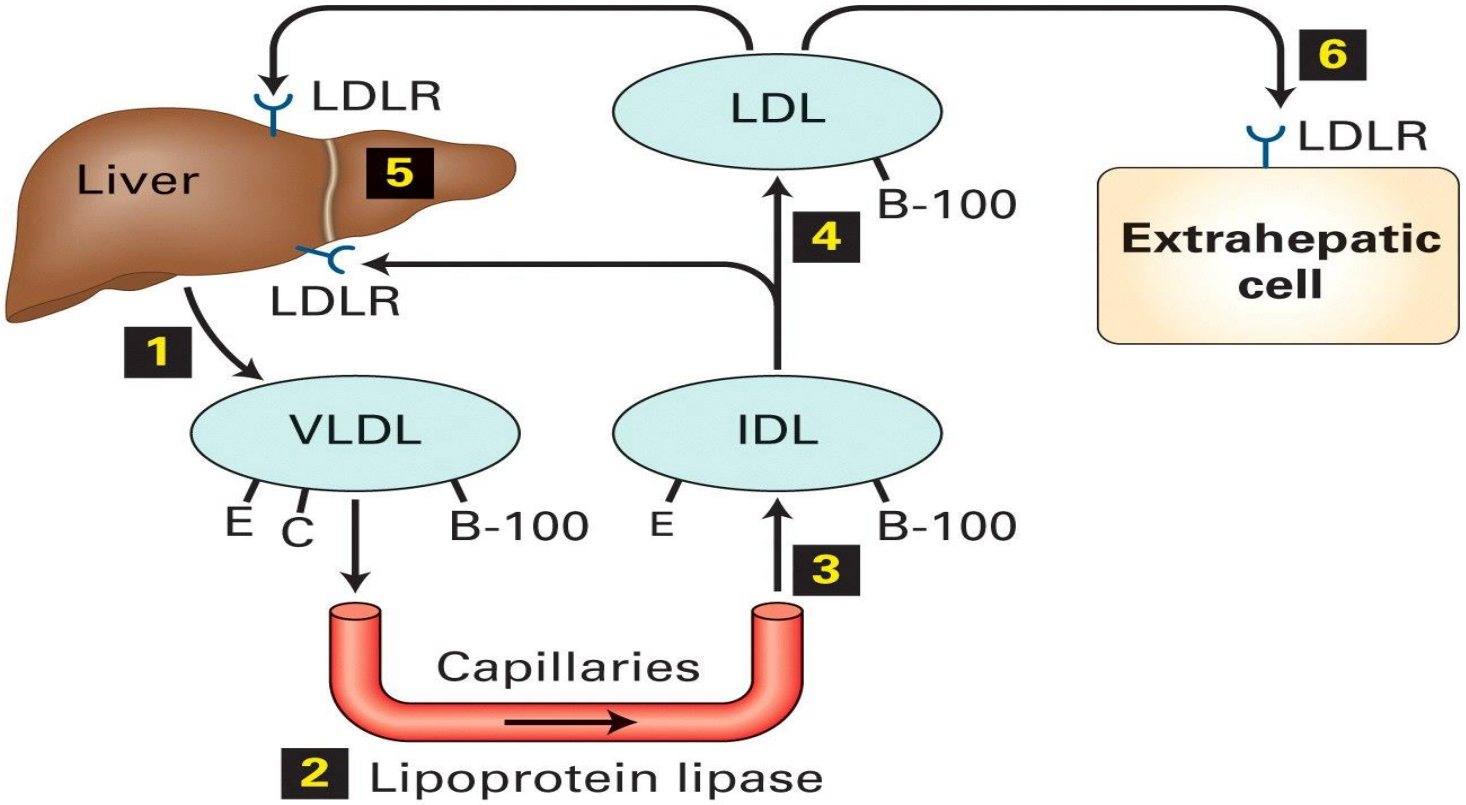
High-density lipoproteins (HDL) are half protein, accounting for their high density.

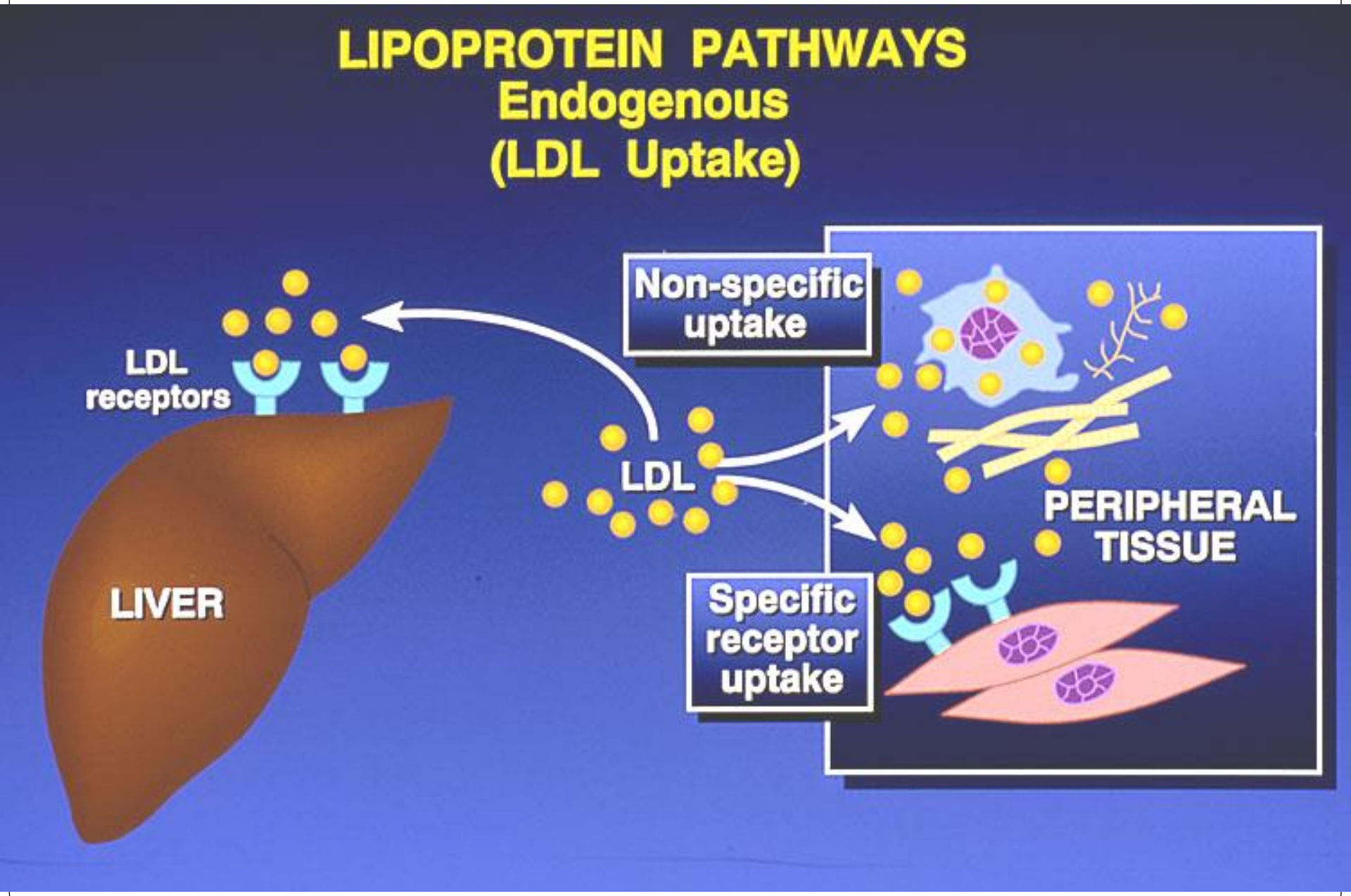


Plasma Lipoproteins Classes & Functions

- Intermediate Density Lipoprotein (IDL)
  - Synthesized from VLDL during VLDL degradation
  - Triglyceride transport and precurser to LDL
  - Apo B-100
    - Receptor binding
  - Apo C-II
    - LPL activator
  - Apo E
    - Receptor binding

Endogenous Lipid Transport




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

Low Density Lipoprotein

- **LDL carries about 70% of total plasma cholesterol**

- **High LDL-C level is well established risk factor for development of coronary heart disease**

Low Density Lipoproteins (LDL)

Produced in the circulation as the end product of VLDLs

Compared to VLDLs:

- **It contains only apo B-100**
- **Smaller size and more dense**
- **Less TG**
- **More cholesterol & cholesterol ester**

Transport cholesterol from liver to peripheral tissues

Uptake of LDL at tissue level by

- **LDL receptor-mediated endocytosis**
- **Recognized by apo B-100**

High Density Lipoproteins (HDL)

- **Produced by intestine and liver**
- **Nascent HDL:**

  Disk-shaped

  Contains apo A-I, C-II and E

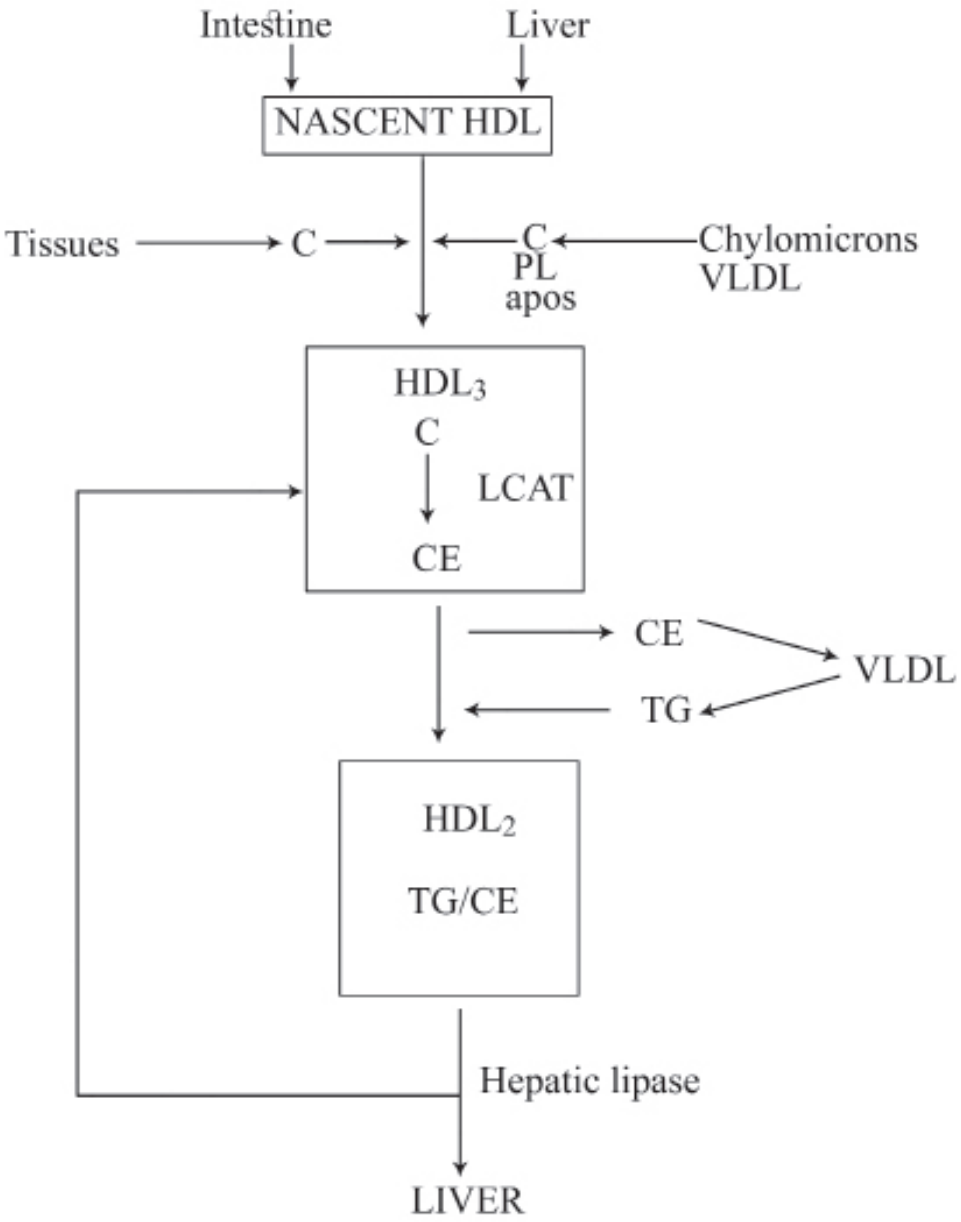
  Contains primarily phospholipid (PC)

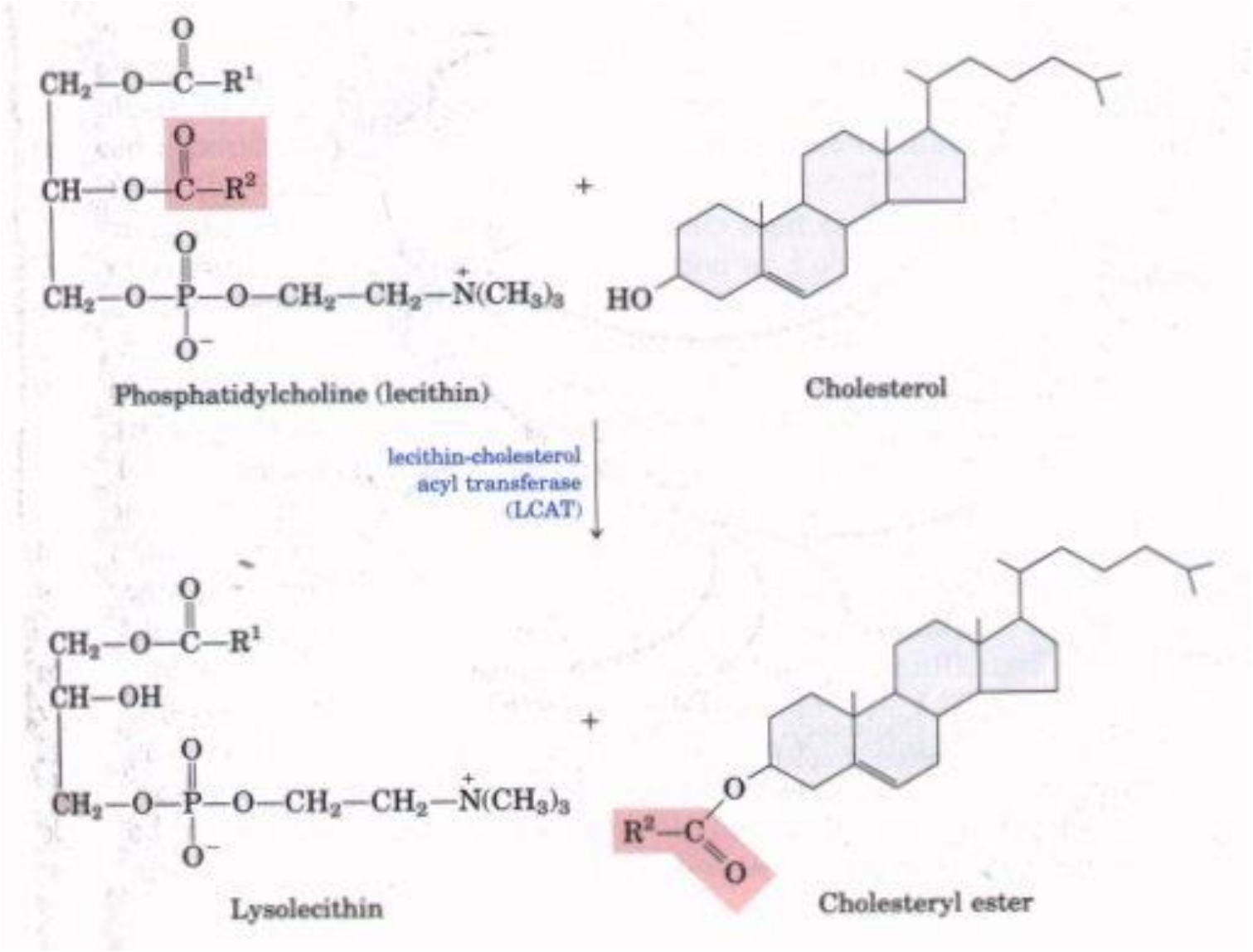
  Contains LCAT (Lecithin Cholesterol Acyl Transferase)
- **Mature HDL (HDL_2):**

  First, the HDL_3 collects cholesterol (C)

  Then, C is converted to CE (Cholesterol- ester)

  The HDL_2 is the spherical mature particle


Intestine
Liver
NASCENT HDL
Tissues
C
C
PL
apos
Chylomicrons
VLDL
HDL3
C
LCAT
CE
CE
VLDL
TG
HDL2
TG/CE
Hepatic lipase
LIVER


Phosphatidylcholine (lecithin)
Cholesterol
lecithin-cholesterol
acyl transferase
(LCAT)
Lysolecithin
Cholesteryl ester

Functions of HDL

- **Reservoir of apoproteins**
  - e.g., Apo C-II and E to VLDL
- **Uptake of cholesterol:**
  - From other lipoproteins & cell membranes

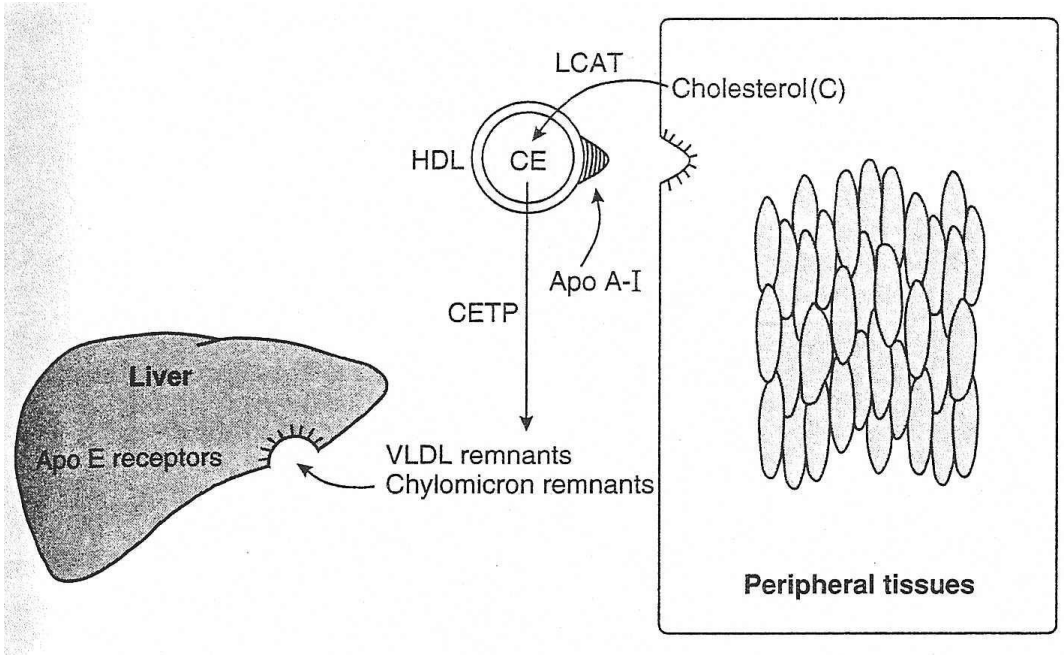
(HDL is suitable for uptake of cholesterol because of high content of PC that can both solubilizes cholesterol and acts as a source of fatty acid for cholesterol esterification)

- **Esterification of cholesterol:**
  - Enzyme:PCAT/LCAT
  - Activator: Apo A-I
  - Substrate: Cholesterol, Co-substrate: PC
  - Product: Cholesterol ester (& Lyso-PC)
- **Reverse cholesterol transport**

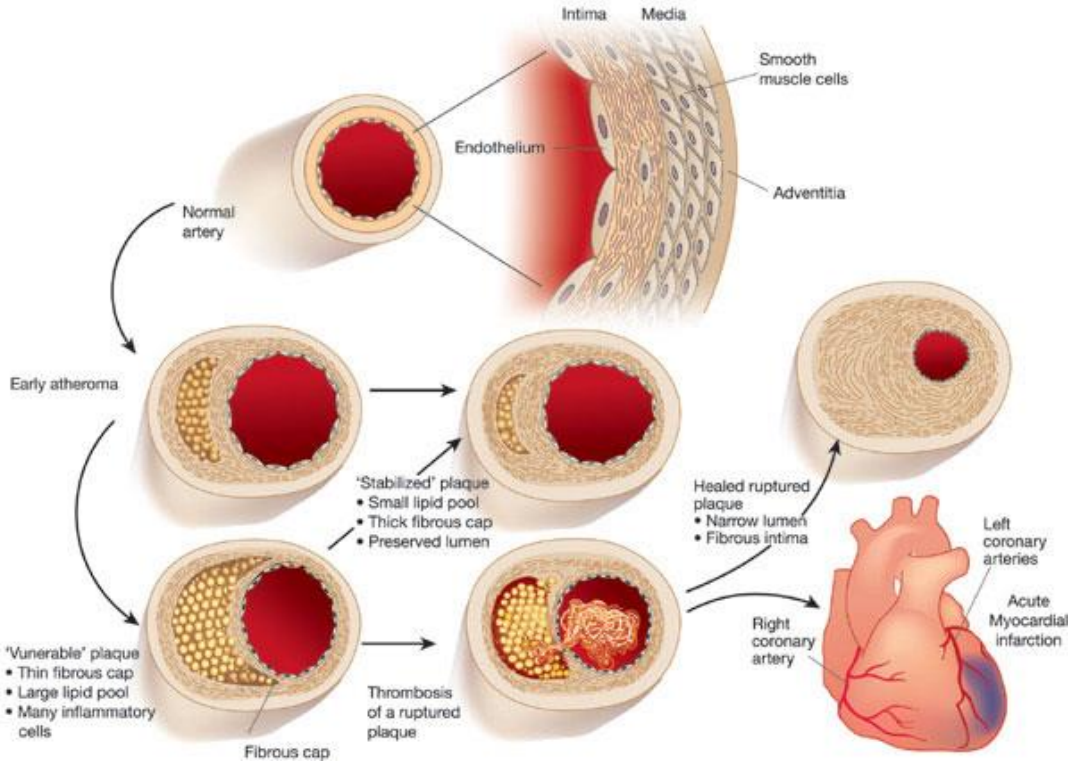
(Cholesterol scavenger)

Reverse cholesterol transport figure 19-6

- Uptake of cholesterol from peripheral tissues (binding by apo-A-I)
- Esterification of HDL-C by LCAT
  - LCAT activated by apoA1
- Transfer of CE to lipoprotein remnants (IDL and CR) by CETP
- removal of CE-rich remnants by liver, converted to bile acids and excreted



Atherosclerosis



Atherosclerosis

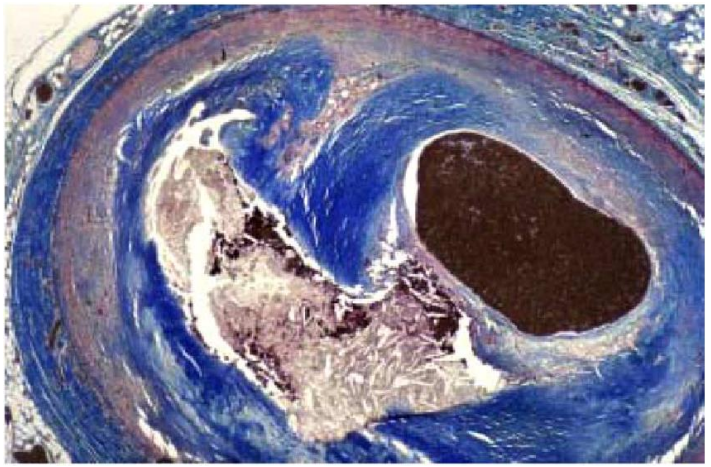
Arteriosclerosis (hardening of the arteries)

3 types:

1. **Atherosclerosis (athero=porridge) plaques of lipid and fibrous tissue in vessel wall**

Less important forms of arteriosclerosis

2. Medial calcification (Monckeberg)
3. Small vessel (arteriolosclerosis) hyaline or hyperplastic



Atherosclerosis

- Disease of cardiovascular system affecting vessel wall.
- It leads to the narrowing of arteries or complete blockage.
- Its main components are endothelial disfunction, lipid deposition, inflammatory reaction in the vascular wall.
- Remodeling of vessel wall.

Triggers for inflammation in atherosclerosis

- LDL retained in the intima (in part by binding to proteoglycan) undergoes oxidative modification.
- Lipid hydroperoxides, lysophospholipides, carbonyl compounds localize in the lipid fraction.
- Oxygen free-radicals inactivate NO rapidly.
- NO + superoxide ($O_2^{\cdot -}$) ⇨ peroxynitrite ($ONOO^-$).
- NO has no longer vasoprotective function.

The process of atherogenesis

- Lipid entry into the arterial wall is a key process in atherogenesis.
- Hypercholesterolemia – factor for VCAM-1 and MCP-1 induction.
- LDL and VLDL are most atherogenic, enter vascular wall more easily.
- LDL – in plasma are protected against oxidation by vit. E, ubiquinon, plasma antioxidants (β-carotene, vit. C).
- Out of plasma, LDL phospholipides and fatty acids oxidize.

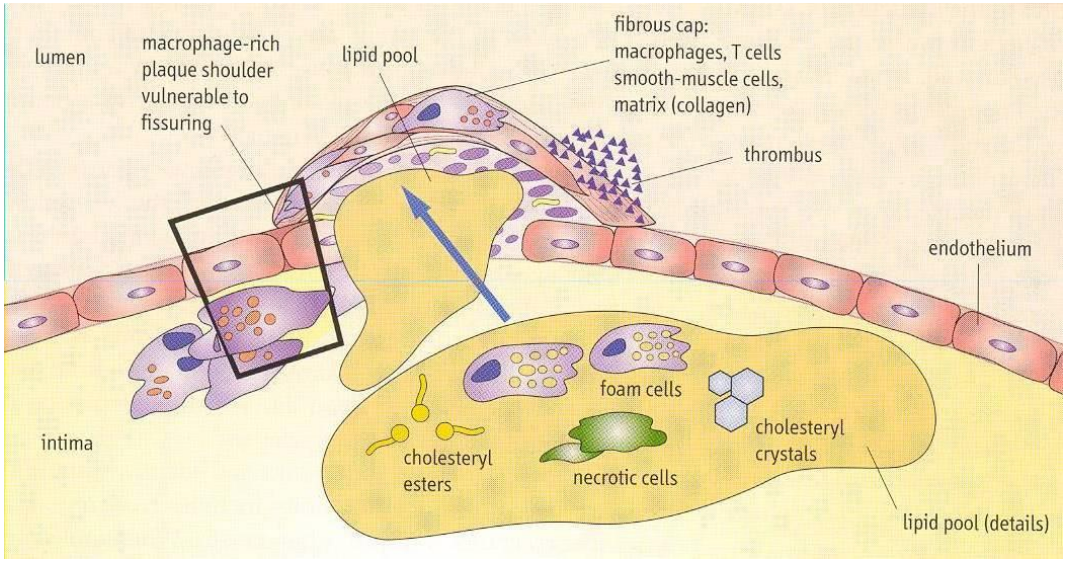
The process of atherogenesis

- Activated macrophages produce enzymes – lipoxygenases, myeloperoxidase, NADPH oxidase ⇨ ROS
- Oxidized LDL are cytotoxic to endothelial cells, mitogenic for macrophages.
- Oxidized LDL apolipoprotein apoB100 bind to the scavenger receptor.
- Scavenger receptors are not subjected to regulation by intracellular cholesterol level.
- Macrophages take up oxidized LDL, overload with lipids.

The process of atherogenesis

- Foam cells ruptured (apoptosis).
- Lipid release to intima and their acumulation becomes centre of atherosclerotic plaques.

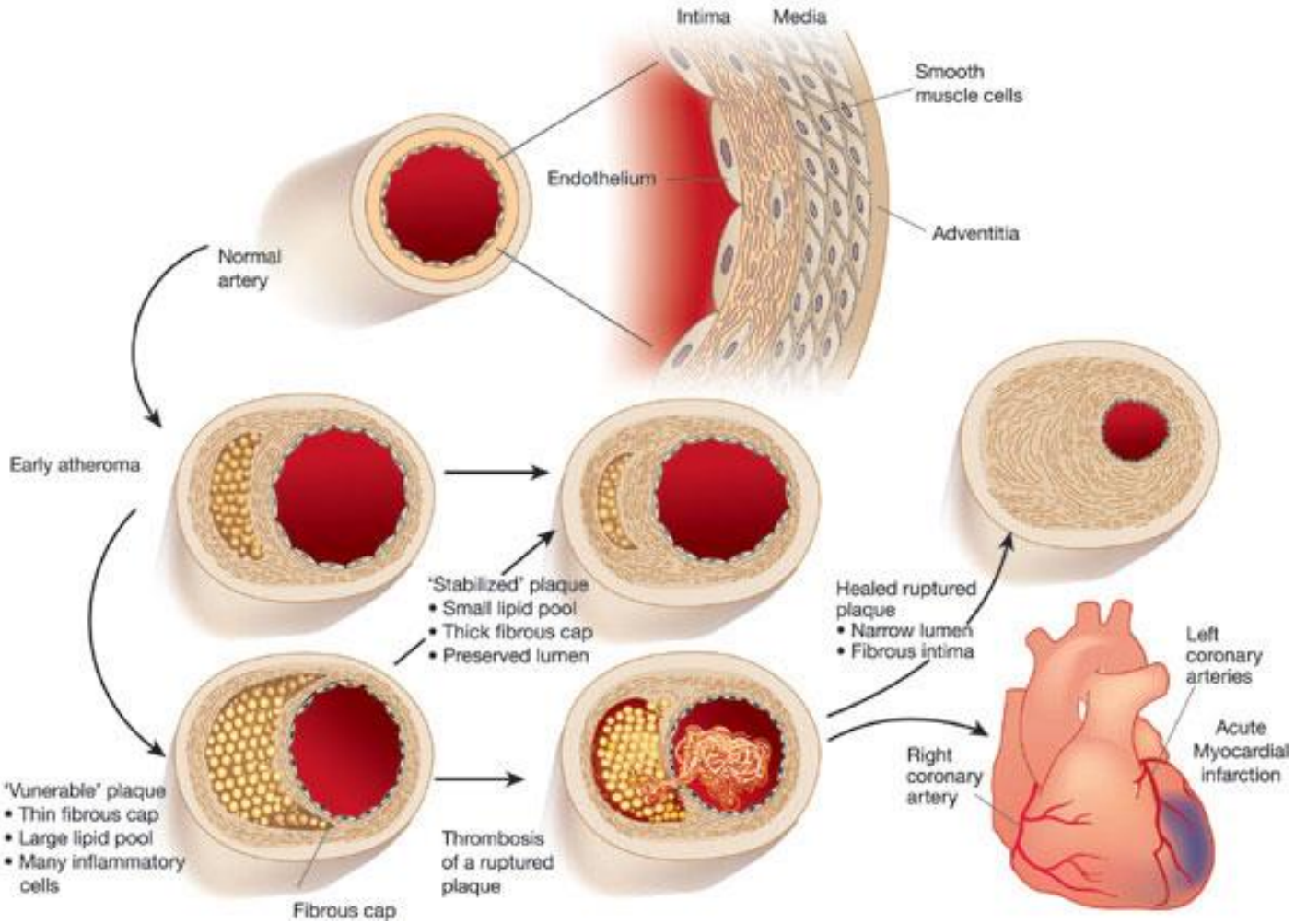
• The lipid center and fibrous cap are the main parts of a mature atherosclerotic plaque.
• Plaque emerges from the structurally changed vascular wall.
• So-called vulnerable plaque ruptures easily.
•The thrombus formed at the rupture site.



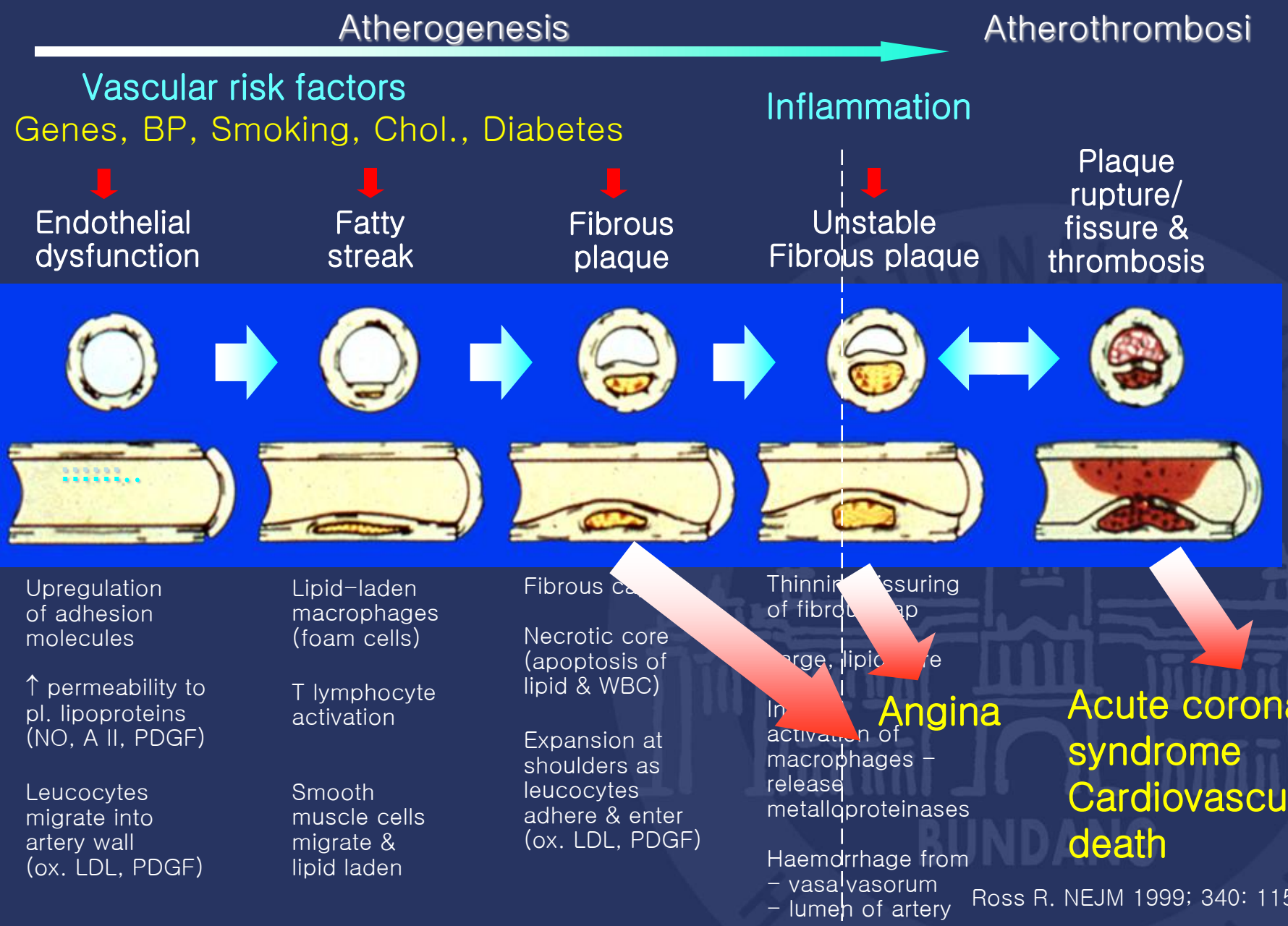
The process of atherogenesis

- Plaque growth – periodically accelerated by a cycle of plaque rupture and thrombosis.
- This happens:
  - Active macrophages and T lymphocytes preferentially reside at the edge of the plaque.
  - Macrophages secrete enzymes degrade extracellular matrix of the cap (MMP – collagenases, gelatinases, and stromelysin)
  - T-cells activated by macrophages secrete IFN-γ and pro-inflammatory cytokines IL-1, IL-2, and TNF-α.

The process of atherogenesis

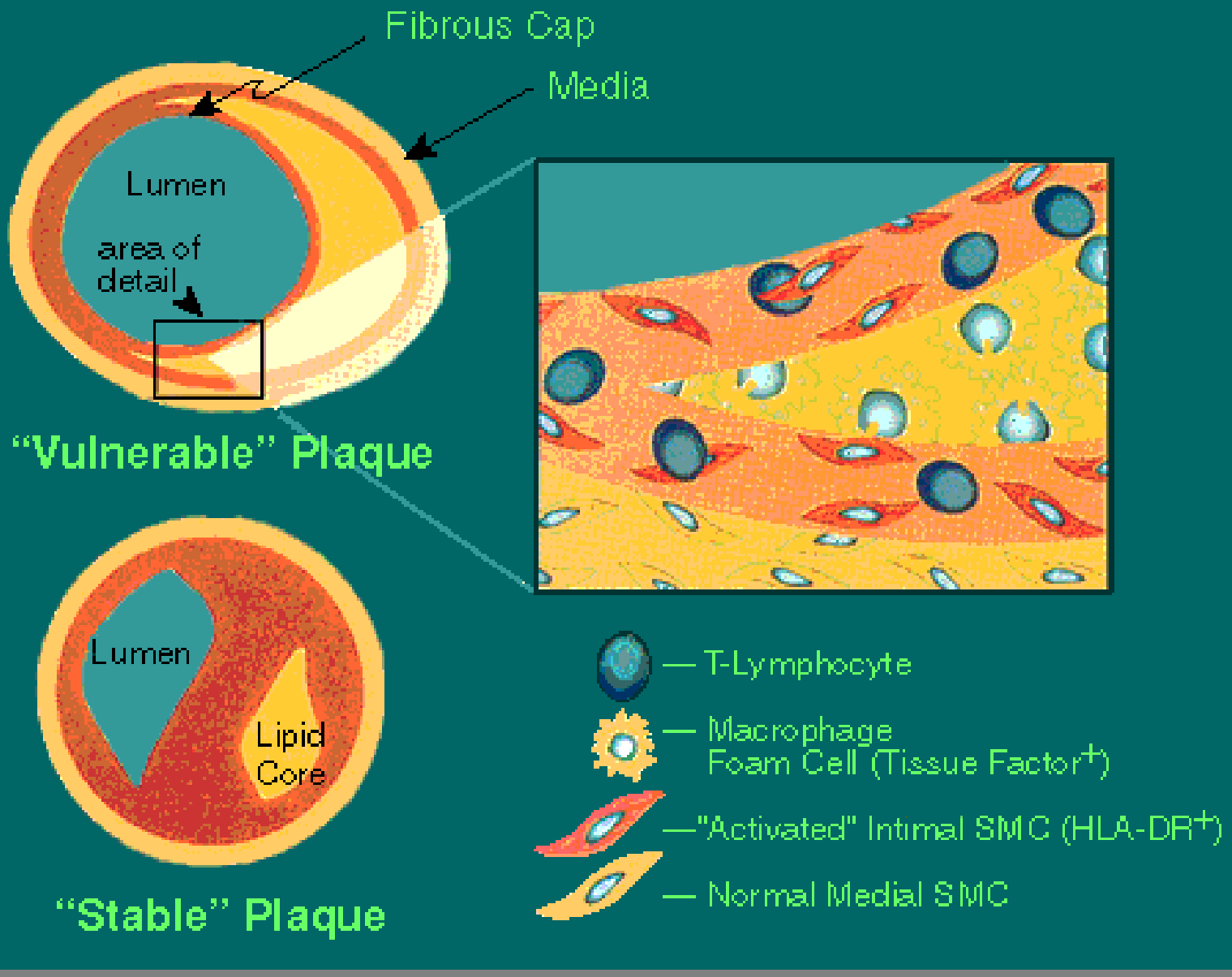


Causes / mediators of atherothrombosis

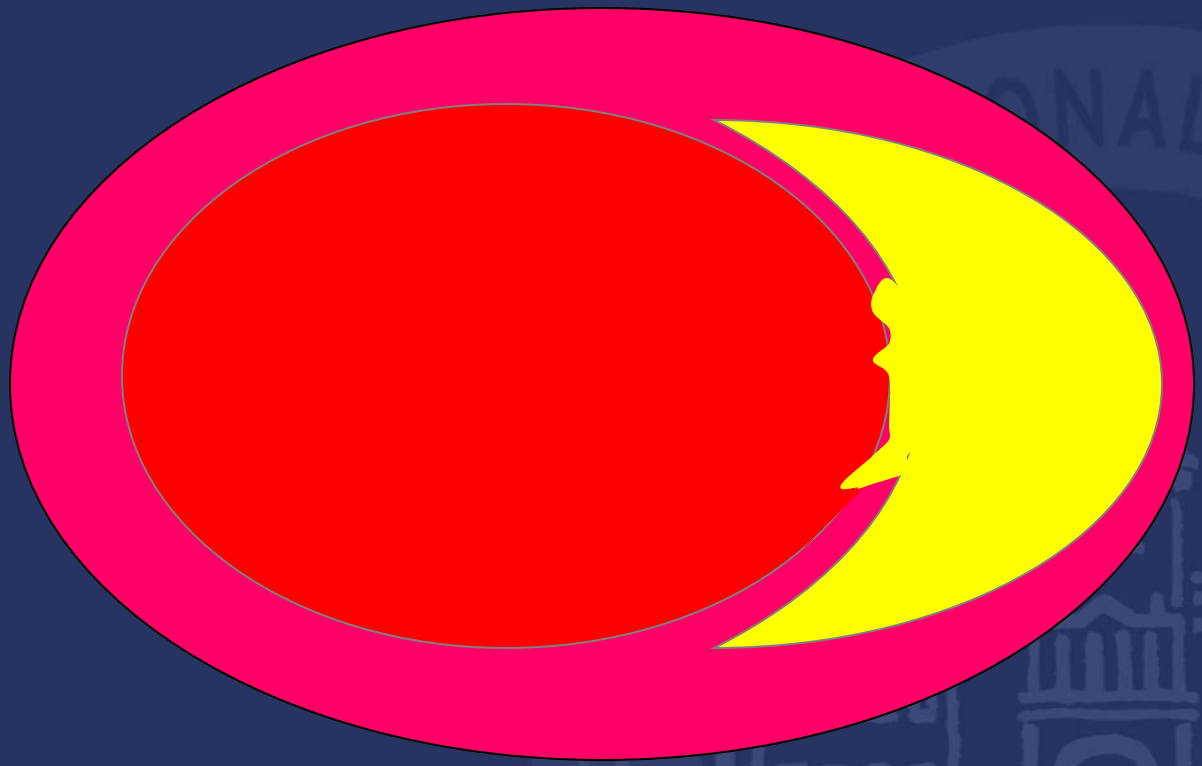


Ross R. NEJM 1999; 340: 115-126

Stable and Rupture-prone plaque

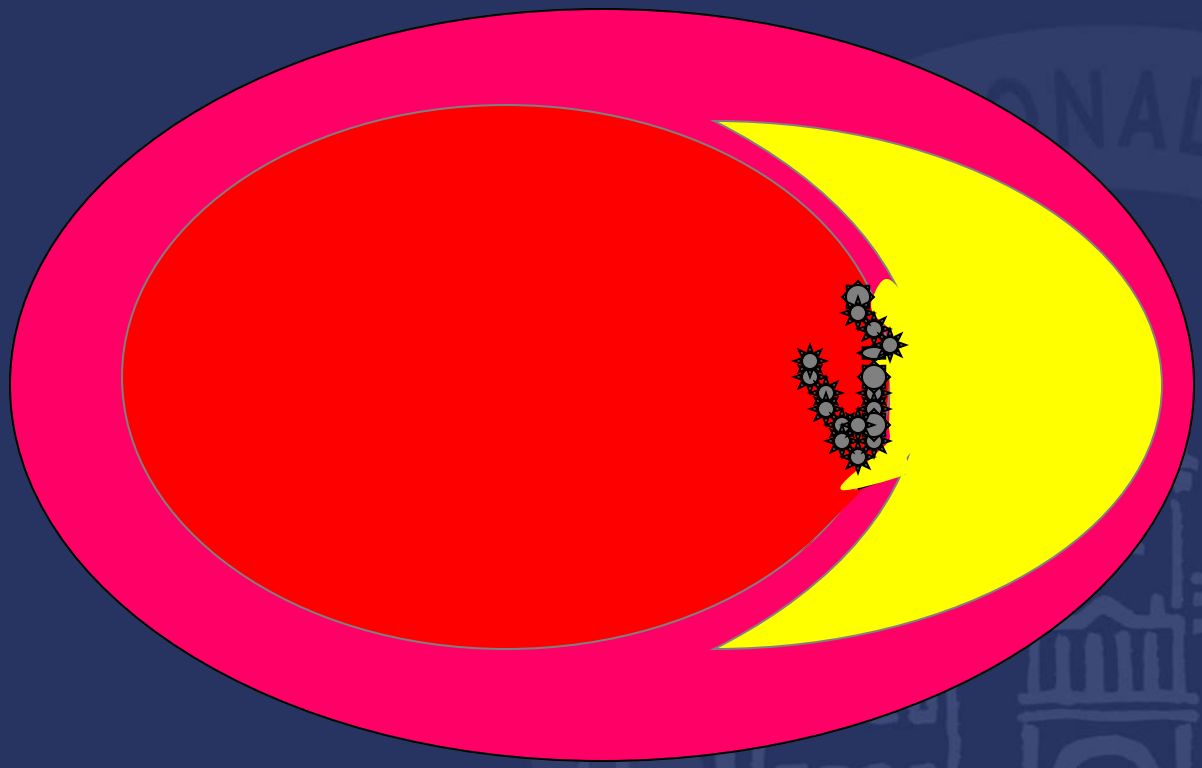


Rupture of a coronary plaque



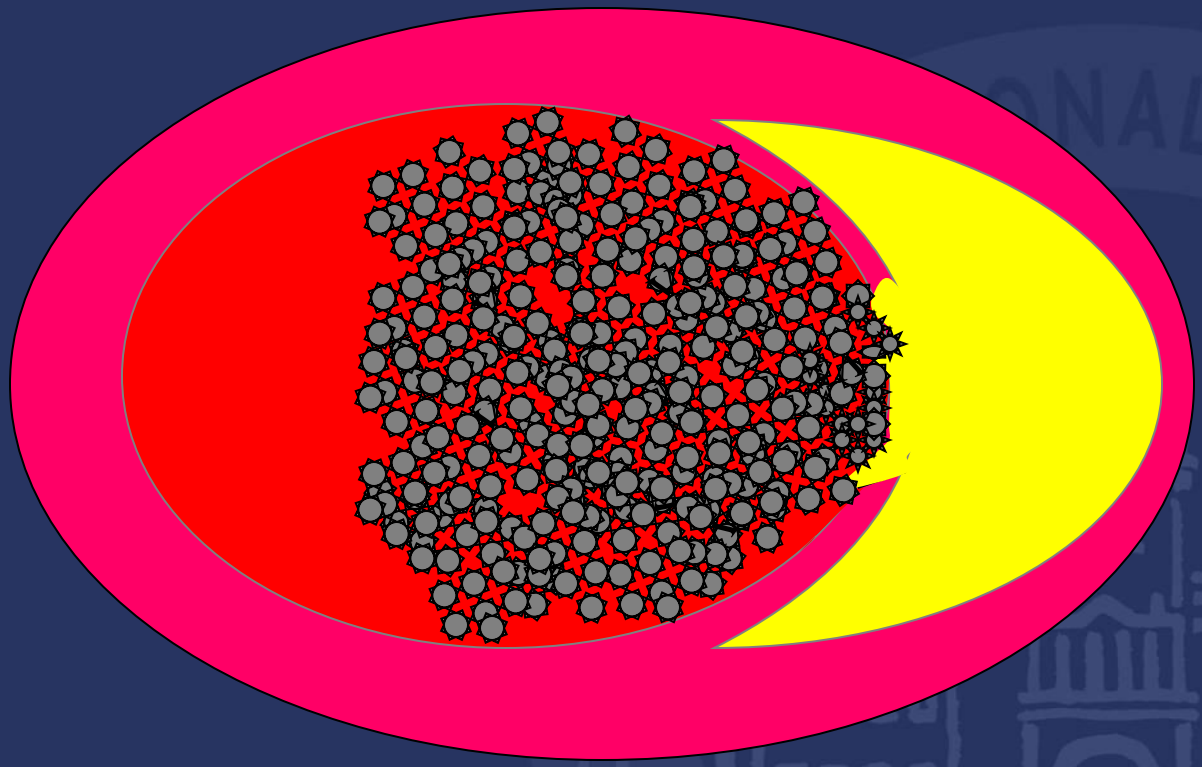
The fibrous cap ruptures and the lipid core is exposed to the blood stream

Rupture of a coronary plaque– Thrombosis

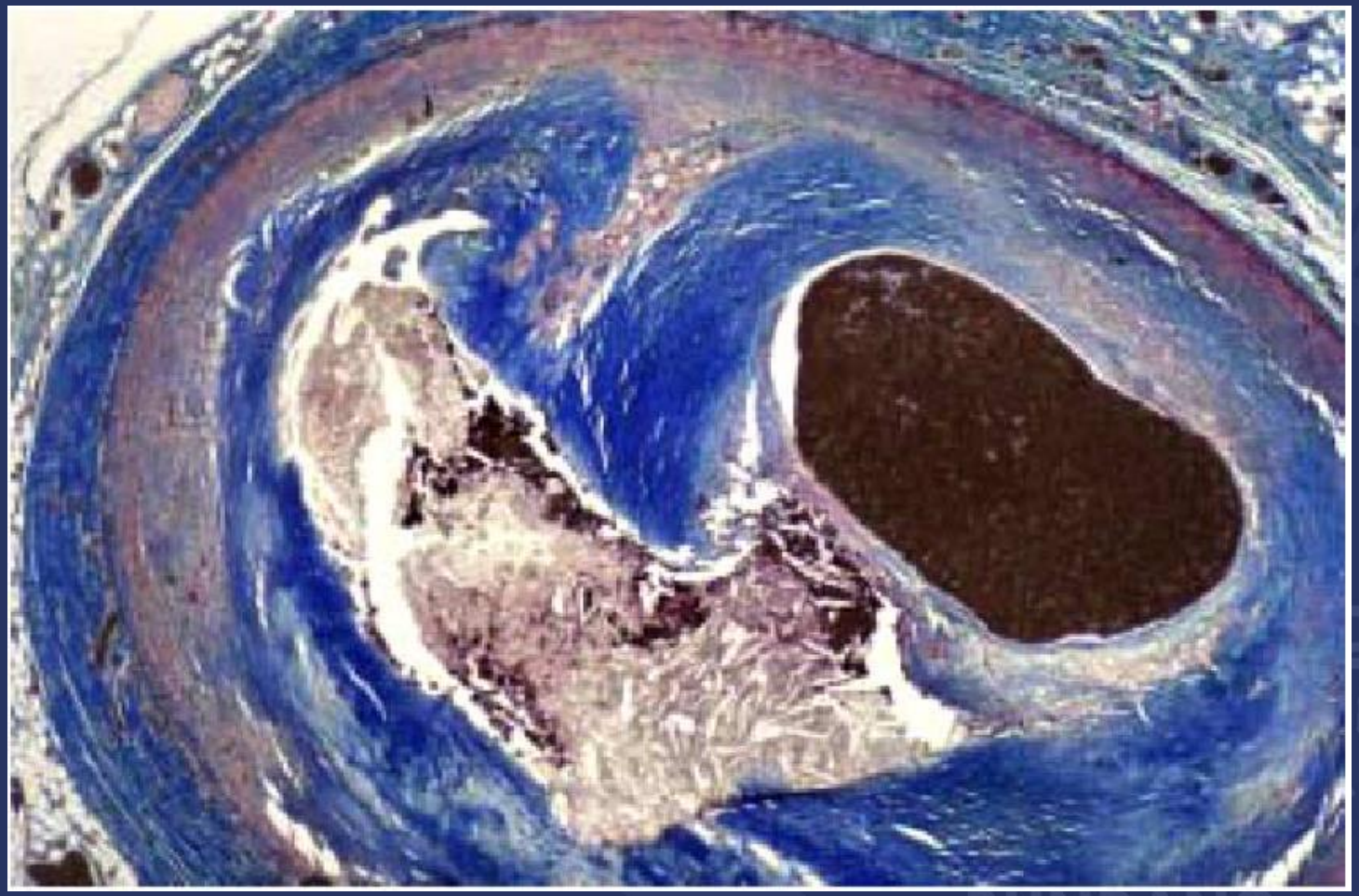


Platelets aggregate around the exposed lipid core and initiate thrombus formation

Thrombosis propagation



Rupture-prone plaque



Eroded plaque with thrombosis