Lecture 2

Lipid metabolism and Transport

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Suggested reading:

Marks' Essentials of Medical Biochemistry, Chapter 30, Chapter 31, Chapter 20

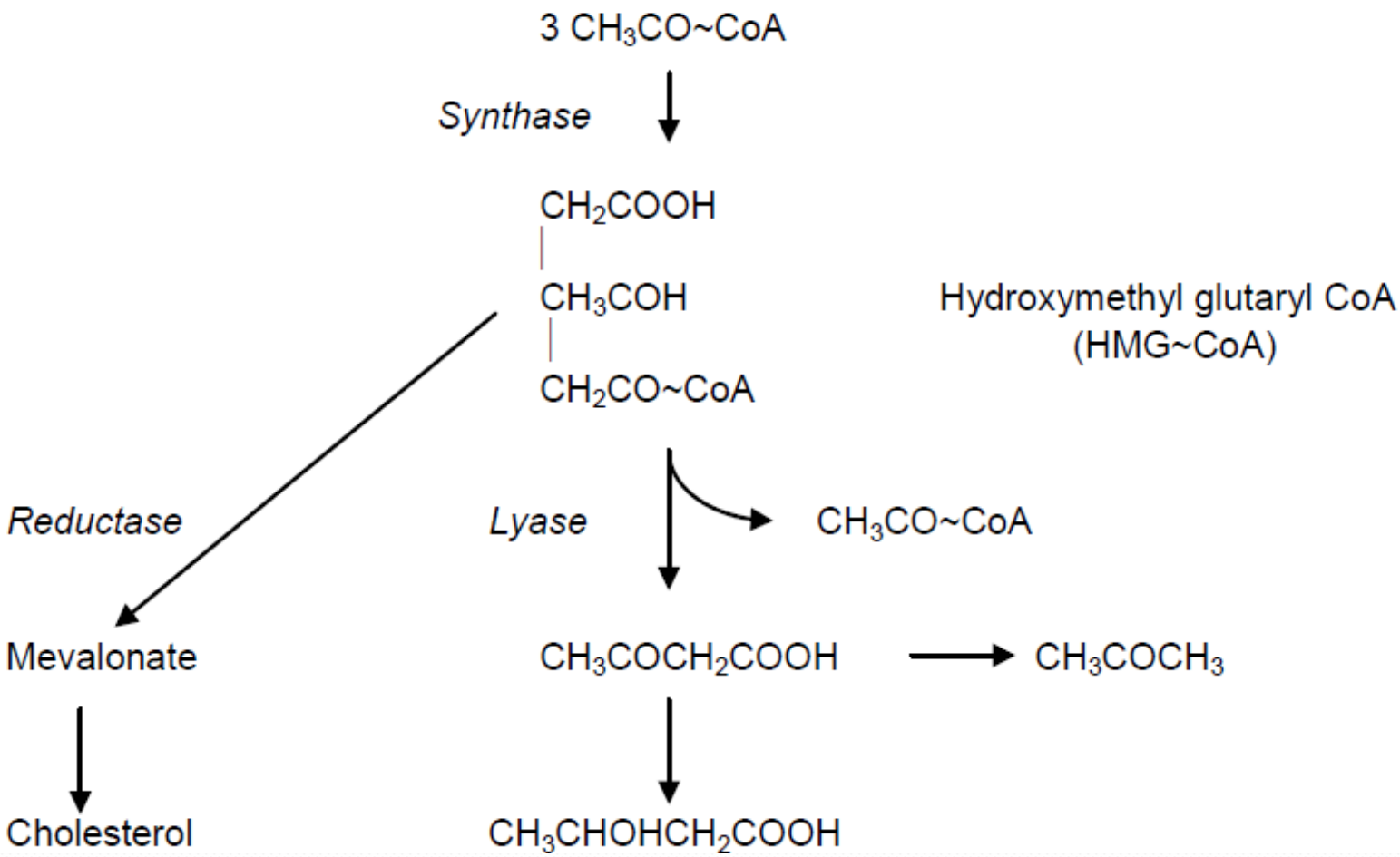
Aims of the session

- Understand how lipids are transported around the body in the blood stream
- Demonstrate how tissue get their lipid from lipoprotein
- Discuss the clinical problems associated with lipid transport .

Ketone bodies

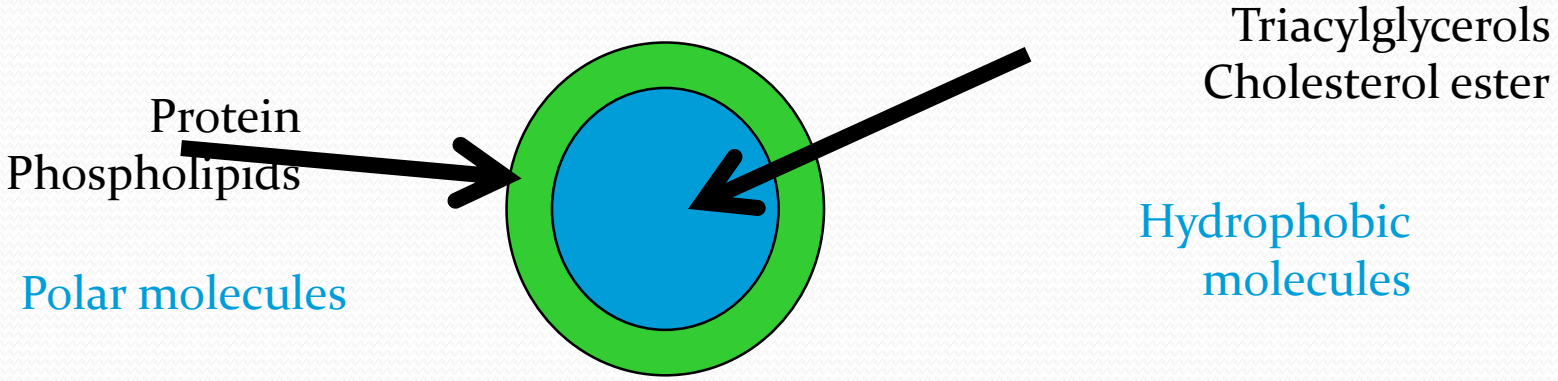
- acetoacetate = $CH_3COCH_2COO^-$
- acetone = CH_3COCH_3
- β-hydroxybutyrate = $CH_3CHOHCH_2COO^-$

Synthesis of keton bodies



Transporting lipids

- Need to coat small collections of lipid molecules with polar molecules
  - Coated with proteins
  - Lipoproteins



Plasma lipid concentrations

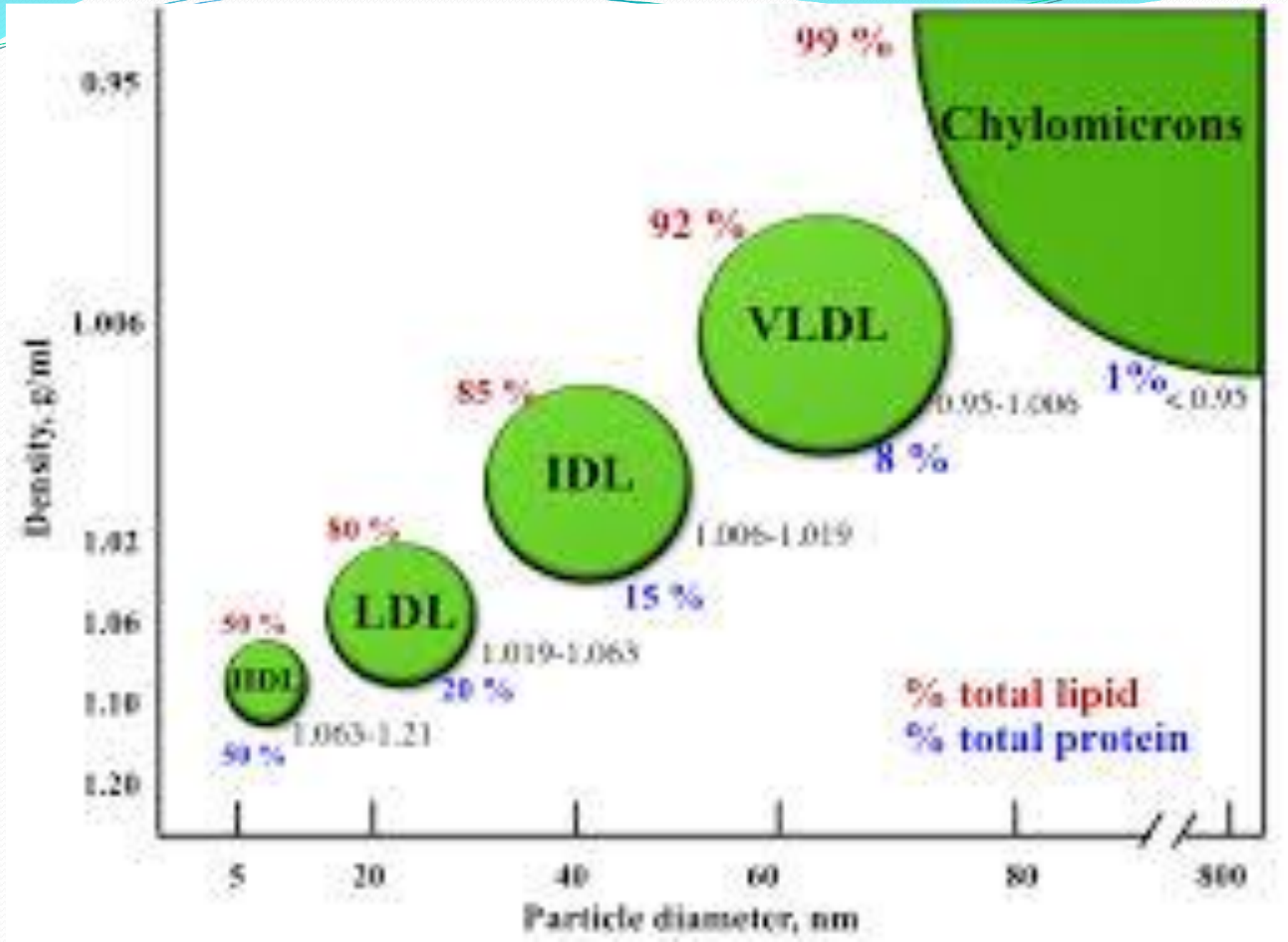
- Triacylglycerides 1.0 $mmol.l^{-1}$
- Phospholipids 2.5 $mmol.l^{-1}$
- Total cholesterol 5.0 $mmol.l^{-1}$
  - (esterified) 3.5 $mmol.l^{-1}$
- Free fatty acids 0.4 $mmol.l^{-1}$
- Total lipids 4000-8500 $mg.l^{-1}$

Lipoprotein particles

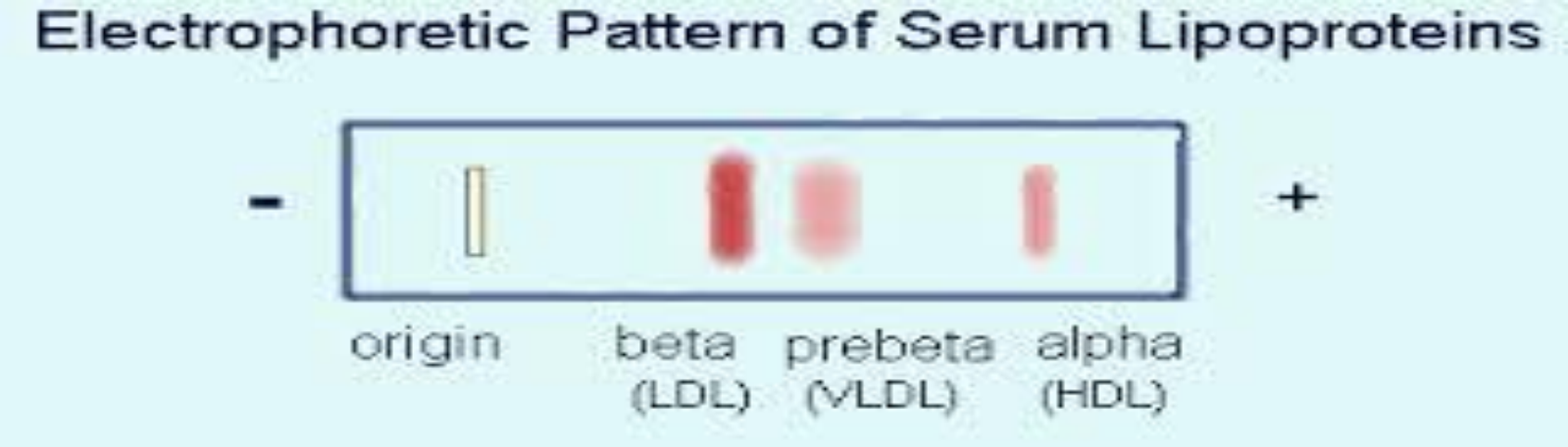
- Different types, varying in
  - Size – 5-100nm
  - Lipid and protein composition (2-55% protein)
  - Density
  - Surface charge
  - Function

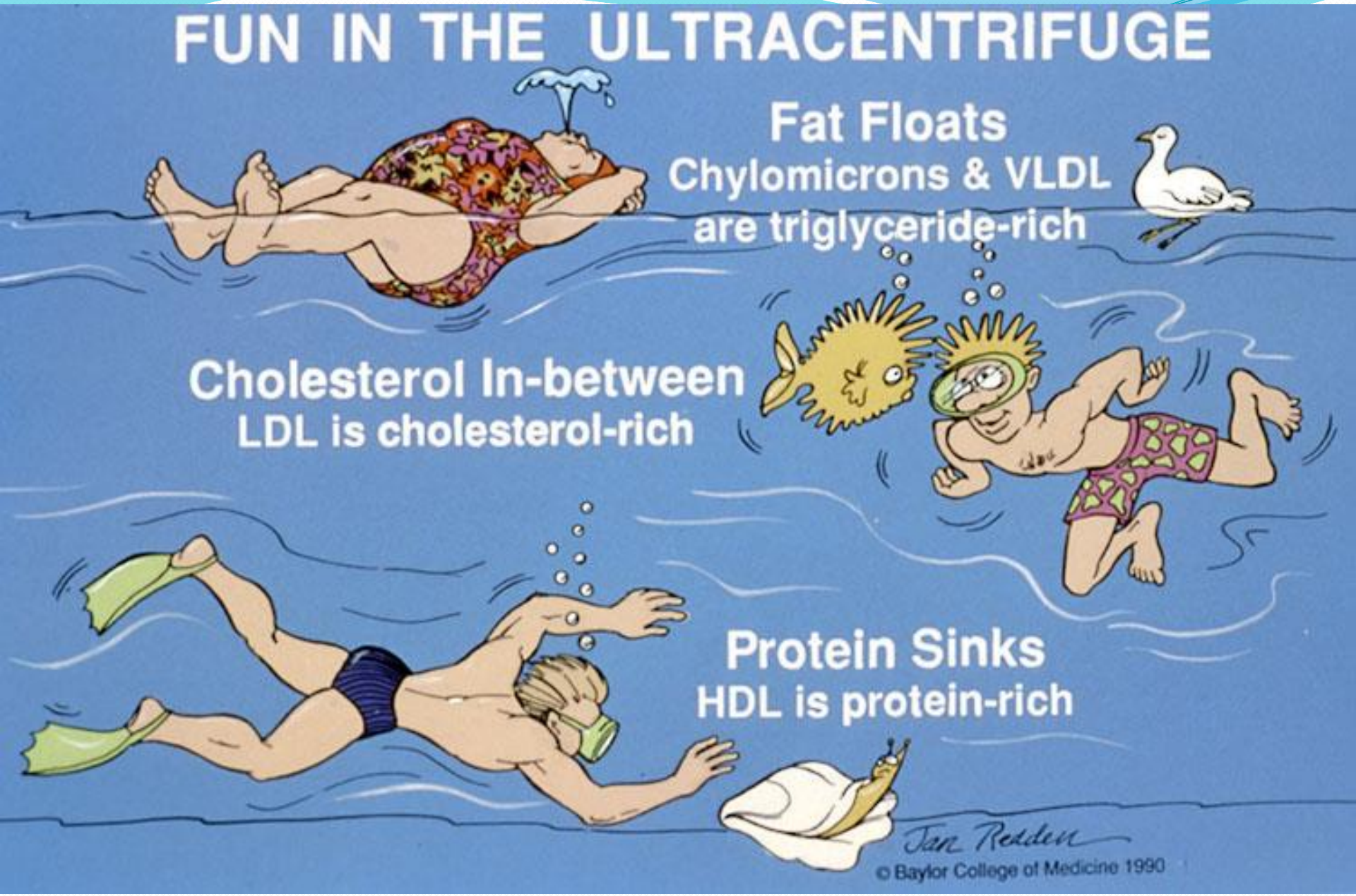
Classes of lipoprotein particle

- Chylomicrons
- Very low density lipoproteins (VLDL)
- Low density lipoproteins (LDL)
- High density lipoproteins (HDL)


99 %
Chylomicrons
1%
< 0.93
92 %
VLDL
0.95-1.006
8 %
85 %
IDL
1.006-1.019
15 %
50 %
LDL
1.019-1.063
20 %
50 %
IIDL
1.063-1.21
50 %
0.95
1.006
1.02
1.06
1.10
1.20
Density, g/ml
5
20
40
60
80
500
Particle diameter, nm
% total lipid
% total protein

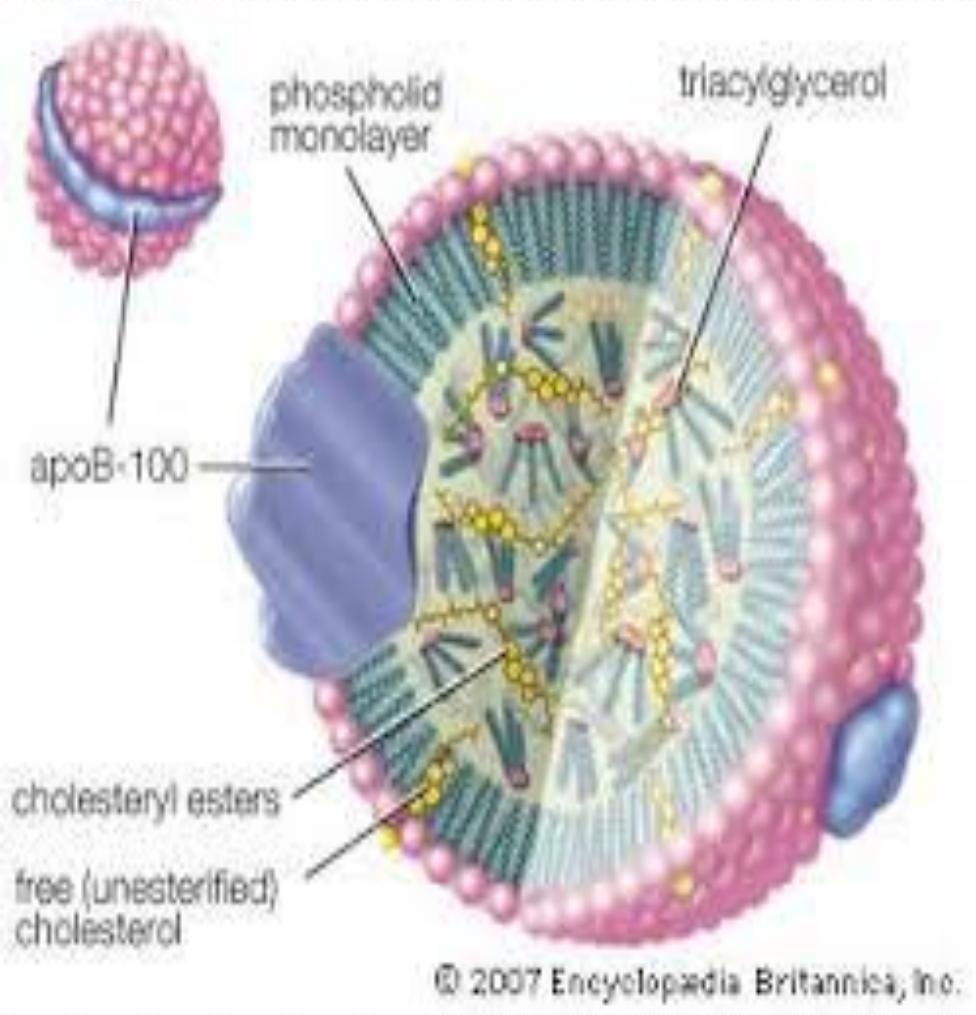
Lipoprotein Electrophoresis




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

Apoproteins

- Each class of lipoprotein particle has its own set of specific apoproteins
  - Have hydrophilic and hydrophobic regions
    - Enabling them to coat lipid particles
  - Functional roles
    - Activation of enzymes
    - Recognition of cell surface receptors



Chylomicrons

- Formed by enterocytes lining the intestine
- Combine triacylglycerols from food with specific apoproteins
- Vary in size – up to 750nm
- Less dense than water
- Carry lipids from diet to tissues
  - Especially adipose tissue
- Only present in blood after a meal

Very low density lipoproteins

- Formed in liver for storage of energy
- Rich in triacylglycerols
- Combine triacylglycerols synthesised in liver with specific apoproteins
  - 30-80nm
  - Density similar to water
- Carry lipid from liver to tissues
  - Mainly adipose tissue

Low density lipoproteins

- Formed in liver
- Cholesterol rich
- Combine cholesterol synthesised in liver with a specific apoproteins
  - 18-25nm
  - Slightly more dense than water
- Carry cholesterol to tissues from liver

High density lipoproteins

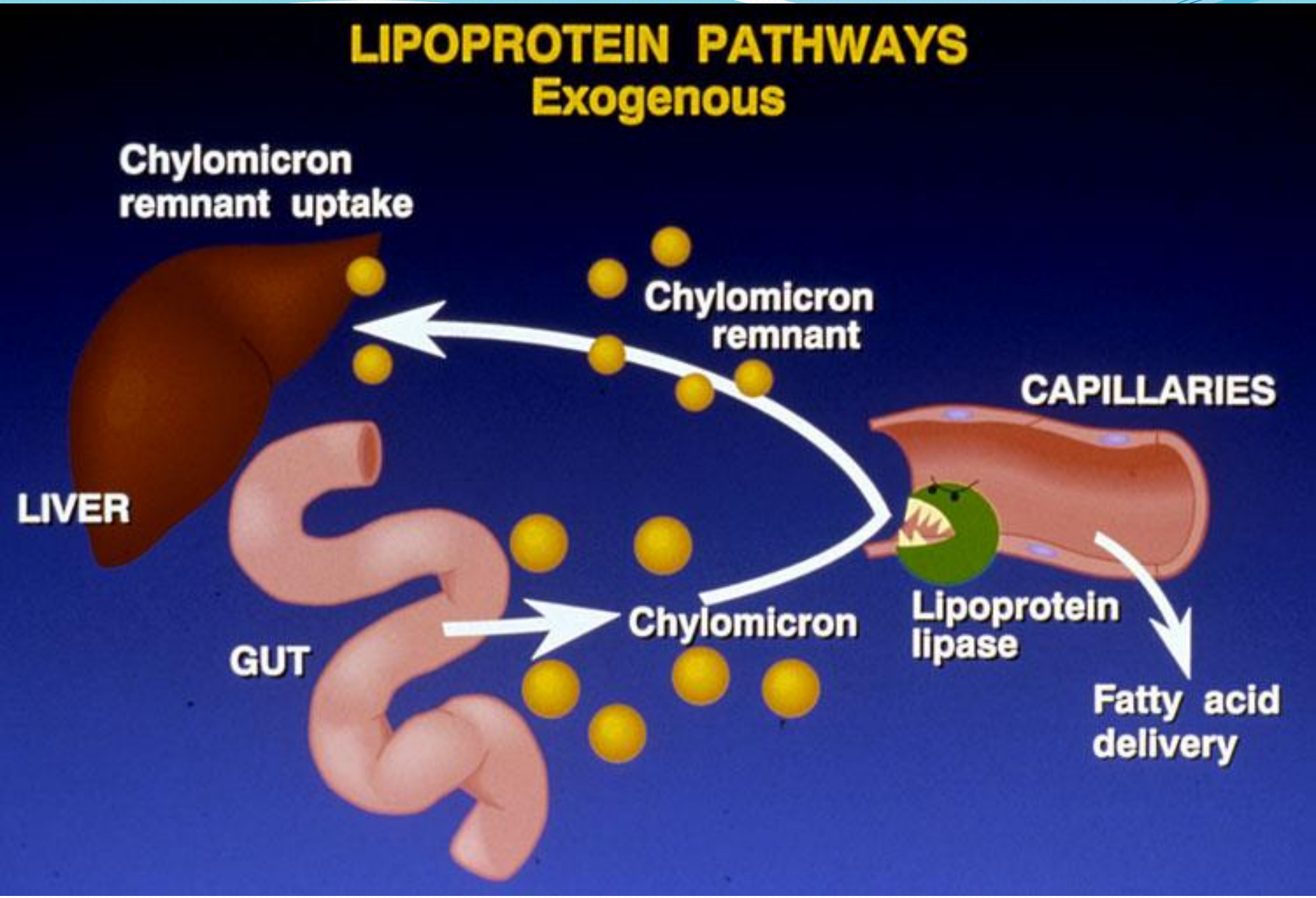
- Formed in tissues
- Cholesterol from tissues combined with specific apoproteins
  - 5-12nm
  - Significantly more dense than water
- Carry excess cholesterol back from tissues to liver

Getting lipids off lipoproteins

- Cells must bind circulating particles
- And release the lipids
  - Different mechanisms for triacylglycerols and cholesterol

Getting triacylglycerols from chylomicrons and VLDL

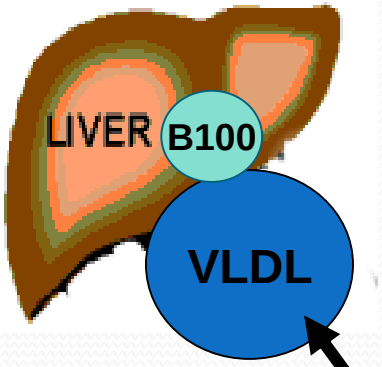
- Endothelial cells of capillaries have lipoprotein lipase on outside of membranes
- Binds chylomicrons and VLDL
- Cleaves triacylglycerols into:
  - Glycerol – remains in circulation
  - Fatty acids – enter tissues for metabolism
- Leave VLDL remnants
  - Usually removed by liver or converted to other types of lipoprotein particles

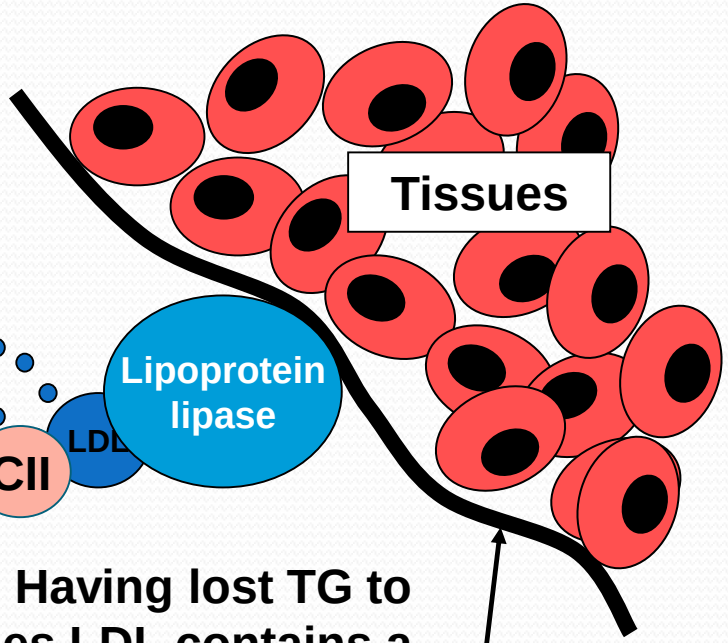

LIPOPROTEIN PATHWAYS
Exogenous
Chylomicron remnant uptake
Chylomicron remnant
CAPILLARIES
LIVER
GUT
Chylomicron
Lipoprotein lipase
Fatty acid delivery

Getting cholesterol from LDL

- Cells have LDL receptors
  - Complex proteins binds LDL at N-terminal domain
  - Receptor/LDL complex taken into cell by endocytosis
  - Cholesterol ester released, and cleaved into cholesterol and fatty acid
- LDL receptor synthesis controlled by cholesterol concentration in cell
  - Uptake stimulated by need

This animation shows how VLDL are metabolised once they enter the circulation from the liver





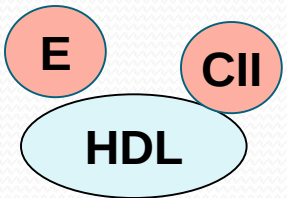
Some LDL taken up by liver (LDL receptors)

Having lost TG to tissues LDL contains a large proportion of cholesterol/cholesterol esters

Capillary wal (endothelia surface)

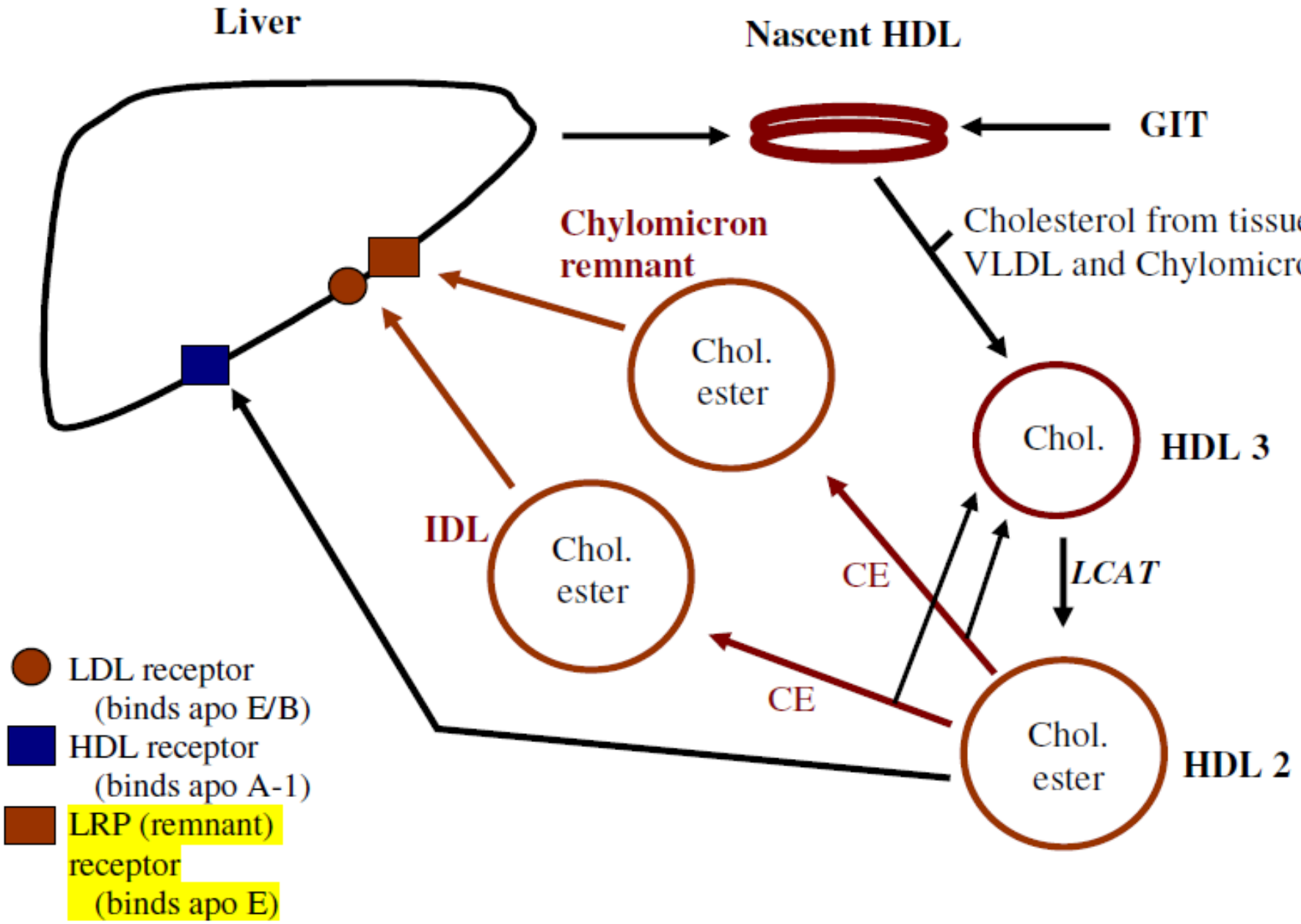
Some LDL taken up by other tissues (LDL receptors).

LDL delivers cholesterol and TG to the extra hepatic tissues.



Loading HDL

- Some HDL synthesised as ‘shells’ in liver
  - Nascent HDL
- Other comes from VLDL remnants
- Both types sequester cholesterol from capillaries
- Mature into HDL particles
- Carry cholesterol back to liver and other cells


Liver
Nascent HDL
GIT
Chylomicron remnant
Cholesterol from tissues, VLDL and Chylomicrons
Chol. ester
Chol.
HDL 3
IDL
Chol. ester
CE
LCAT
CE
Chol. ester
HDL 2
LDL receptor (binds apo E/B)
HDL receptor (binds apo A-1)
LRP (remnant) receptor (binds apo E)

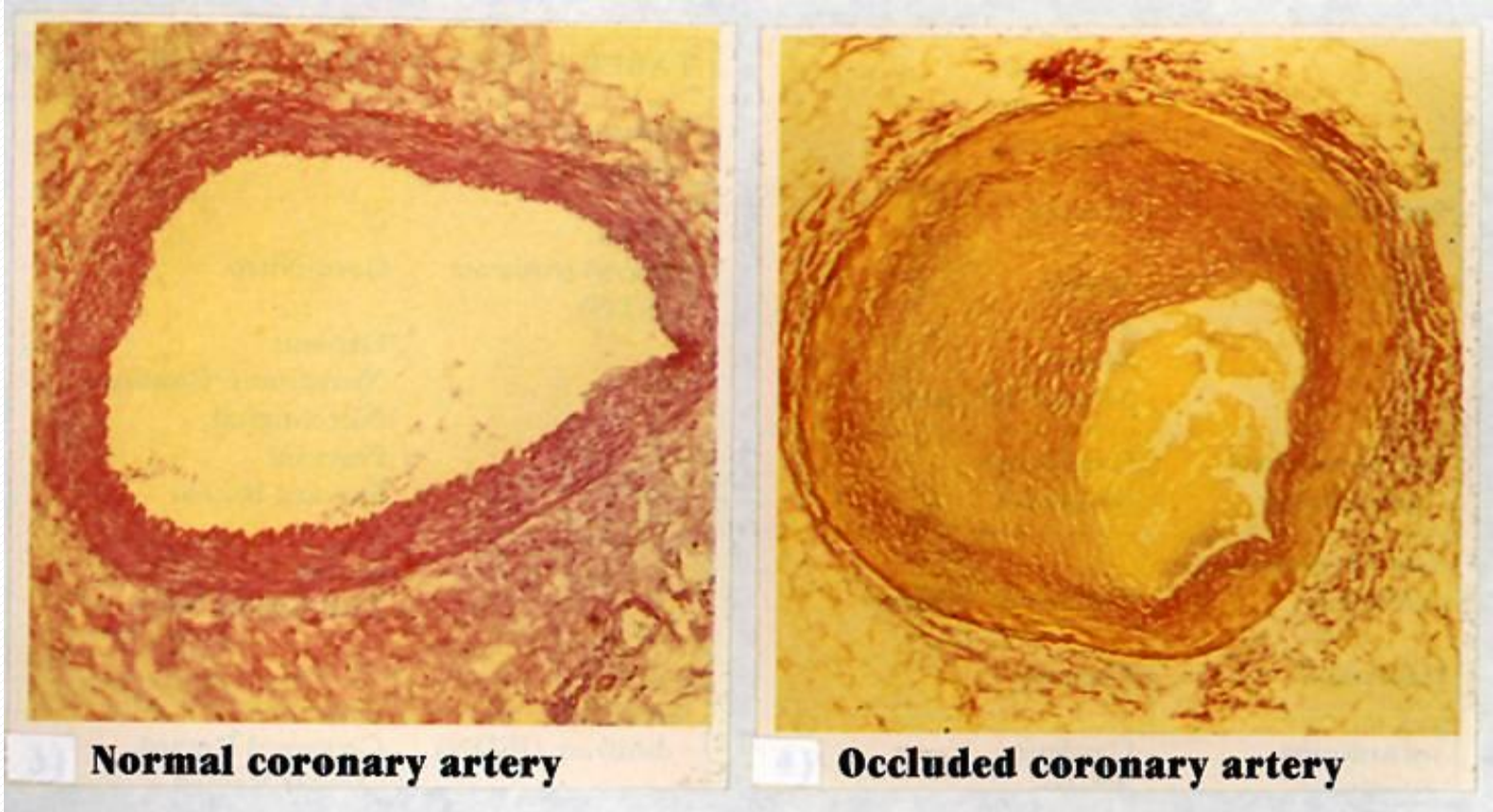
Disposal of Cholesterol

- Some converted to hormones
- Some excreted by conversion to bile acids
  - More polar molecules
  - Important for digestion of fats in gut

Scavenger receptors

- Macrophages pick up LDL damaged by oxidation via ‘scavenger receptors’
- Cytoplasm becomes loaded with lipid
  - Form ‘foam cells’
- Accumulate in intima of blood vessels
  - ‘fatty streak’
- Eventually form Atheroma

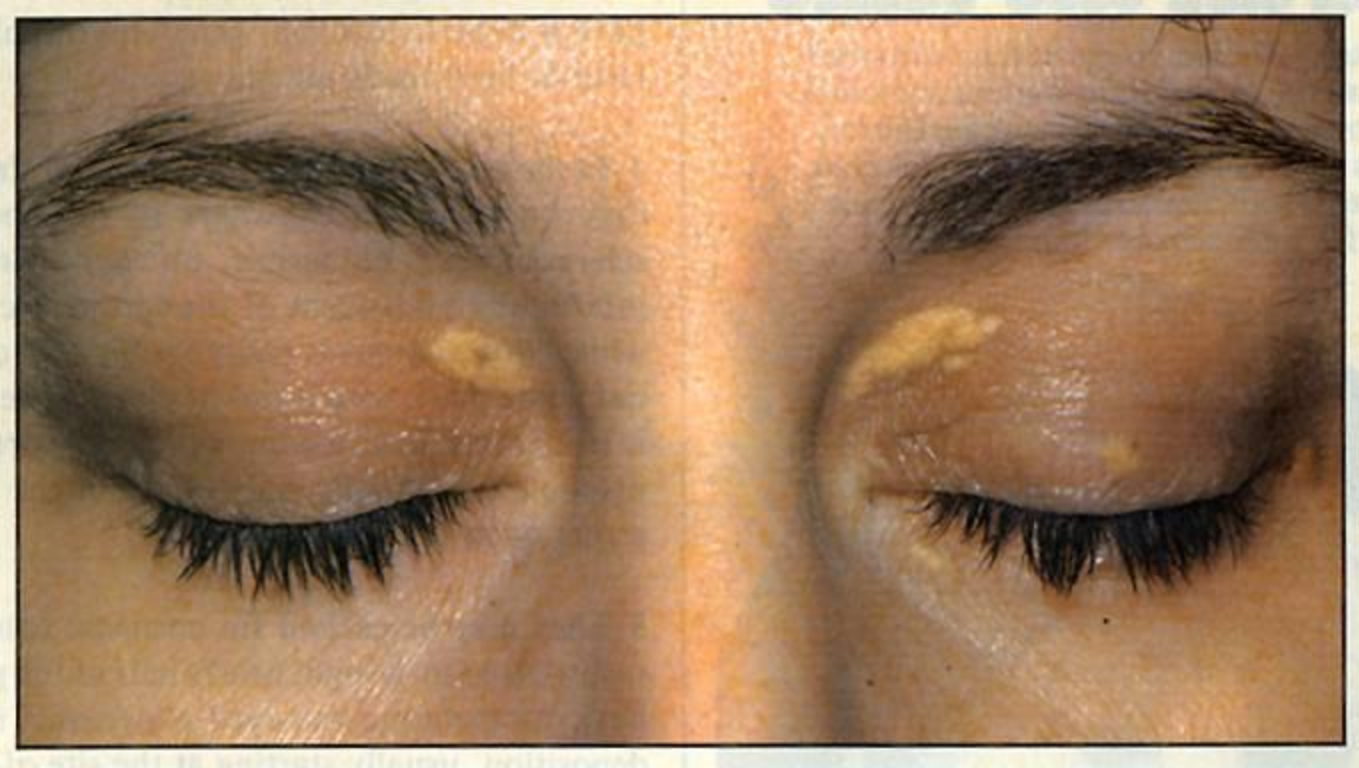
Atheroma



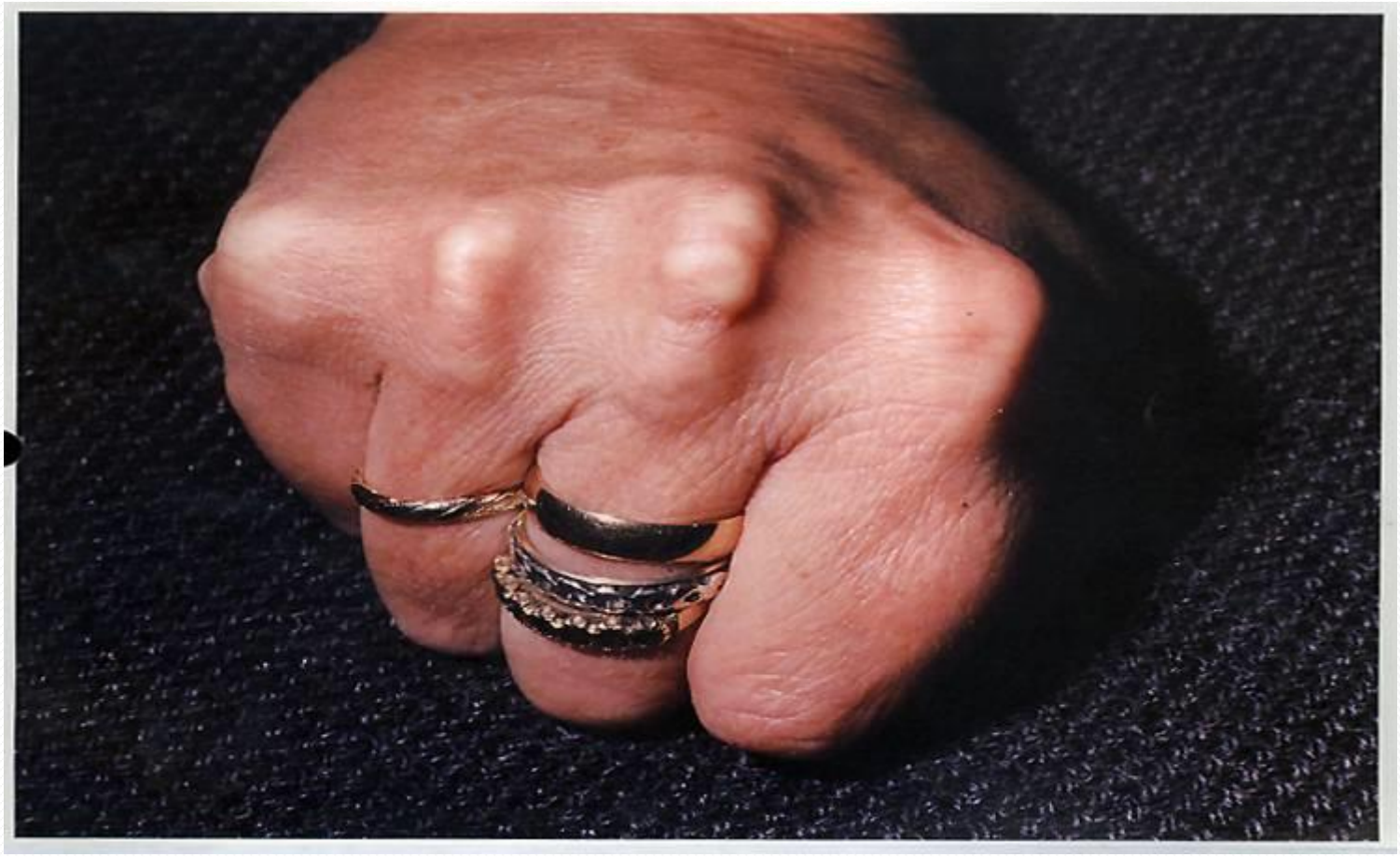
Hyperlipoproteinaemias

- Raised levels of one or more lipoprotein classes
  - Variety of causes
    - Over-production
    - Under-removal
  - Defective
    - Enzymes
    - Receptors
    - Apoproteins

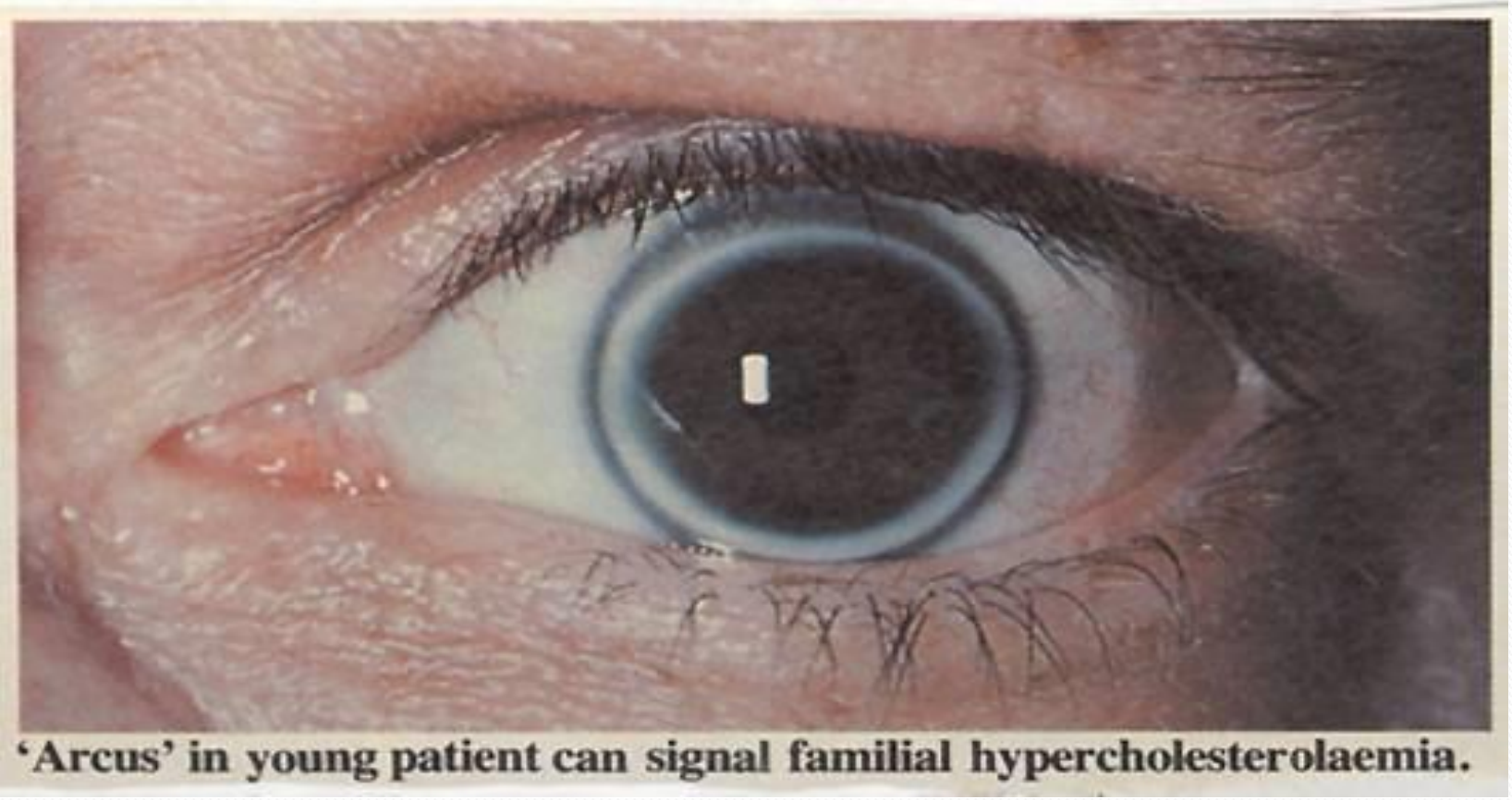
Xanthelasma



Tendon Xanthoma



Corneal arcus



'Arcus' in young patient can signal familial hypercholesterolaemia.

Hyperlipoproteinaemias

- Complex classification depending on which lipid values are increased

Familial hypercholesterolaemia

- Relatively common
  - Mutation in LDL receptor gene
    - Fewer, less effective receptors on cells
  - Less LDL removed from capillary blood
  - LDL levels rise
    - More LDL to be damaged
  - Macrophage scavenger receptors unaffected
  - Much more macrophage accumulation of damaged and undamaged cholesterol
  - Greatly increased risk of atheroma

Treatment of hyperlipoproteinaemias

- Diet
  - Reduce cholesterol, saturated lipids
- Lifestyle
  - Increase exercise
    - Stop smoking to reduce cardiovascular risk
- Drugs
  - Statins – reduce cholesterol synthesis by inhibition of HMG CoA reductase