Chapter 1

HYPERLIPOPROTEINEMIA

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Lipoproteins

- Lipoproteins are complexes of proteins and lipids

They transport triacylglycerols (TG) and cholesterol esters (CE) in the blood

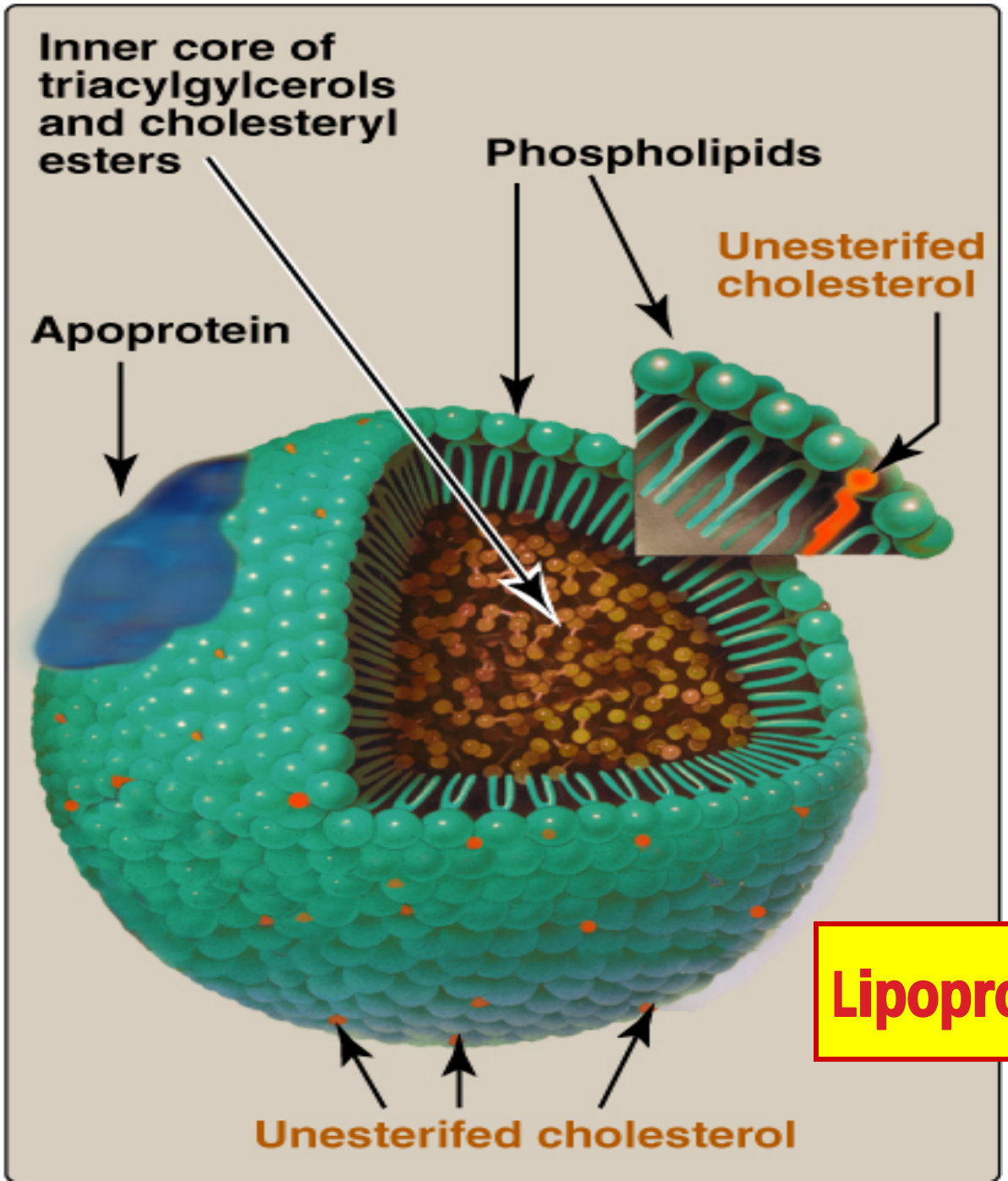
Lipoproteins are classified into chylomicrons, VLDL, LDL, IDL, and HDL based on their density and size

Chylomicrons and VLDL mainly transport TG

IDL, LDL, and HDL mainly transport CE

Lipoprotein particles

- Lipoproteins are spherical particles with a surface monolayer of phospholipids, free cholesterol and apolipoproteins
- The core contains TG and/or CE



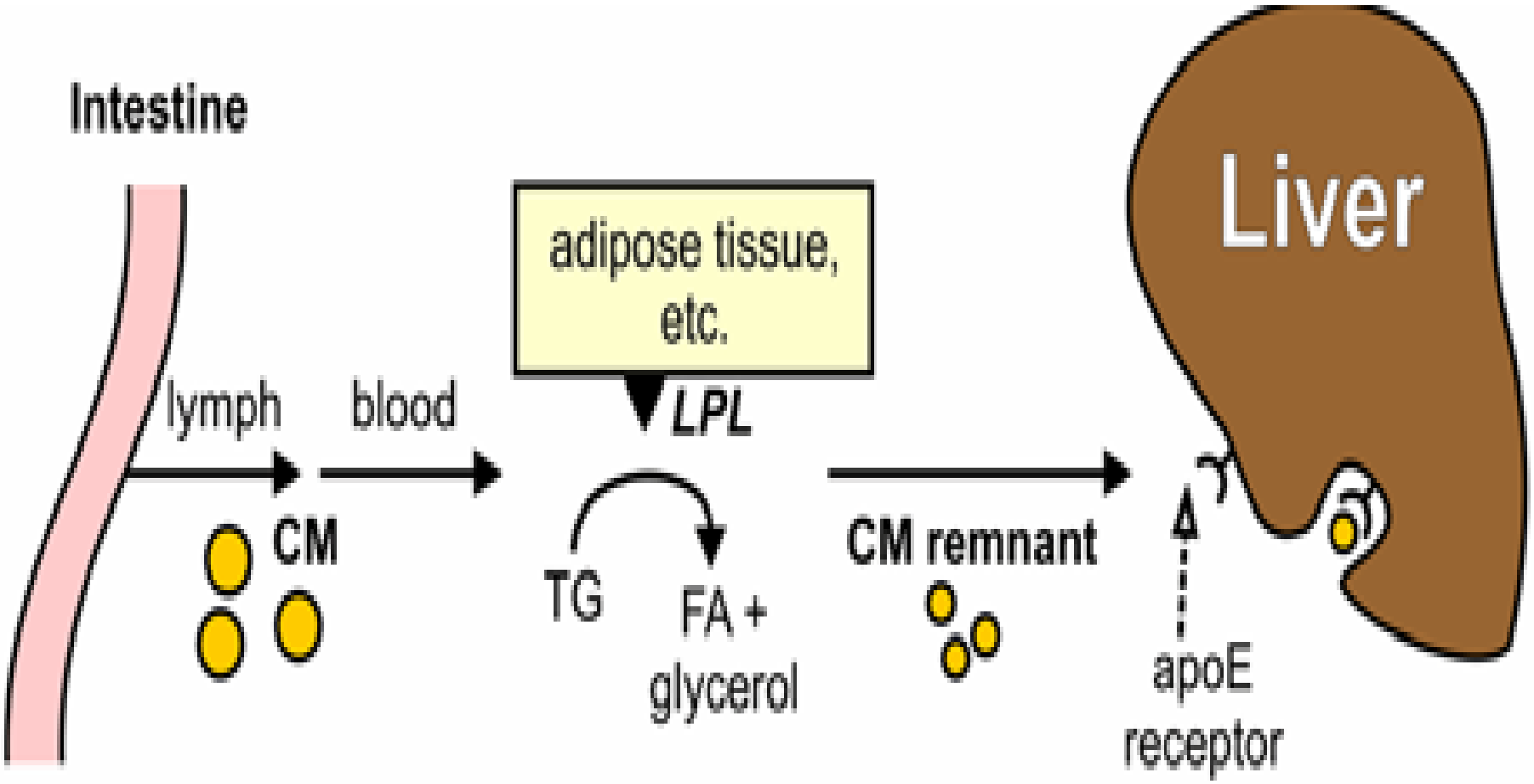
Lipoprotein Structure

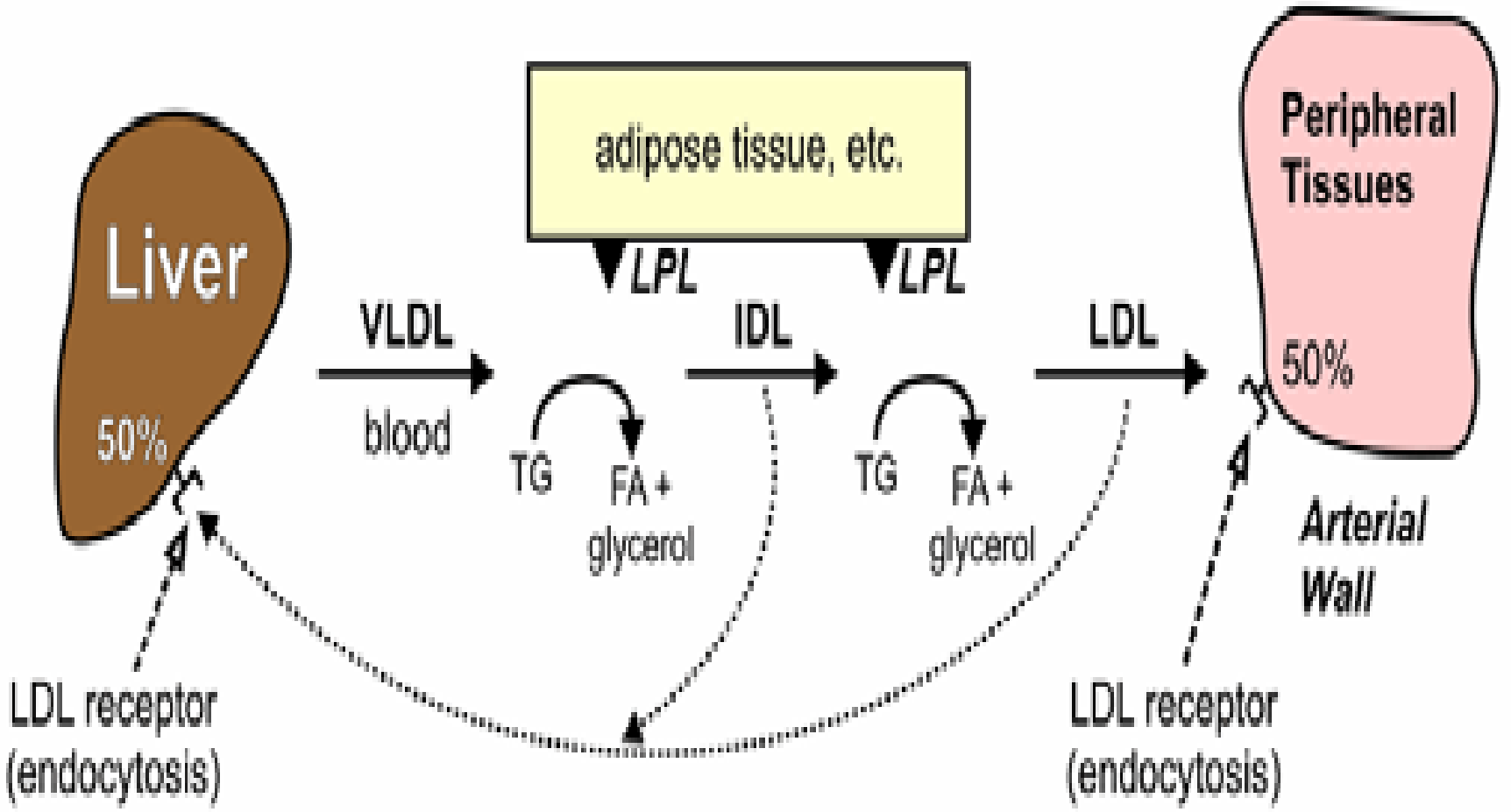
Tissue of origin and function of the plasma lipoproteins

Class	Origin	Physiologic function
Chylomicrons	Intestine	Absorption of dietary fat
Chylomicron remnants	Plasma	Delivery of dietary fat to liver
VLDL	Liver	Transport of trigliceride from liver to other tissues
IDL	Plasma	Initial product formed in VLDL catabolism
LDL	Plasma	Cholesteryl ester transport
HDL	Liver, Intestine	Removal of excess cholesterol from tissue and lipoproteins; remodeling of lipoproteins

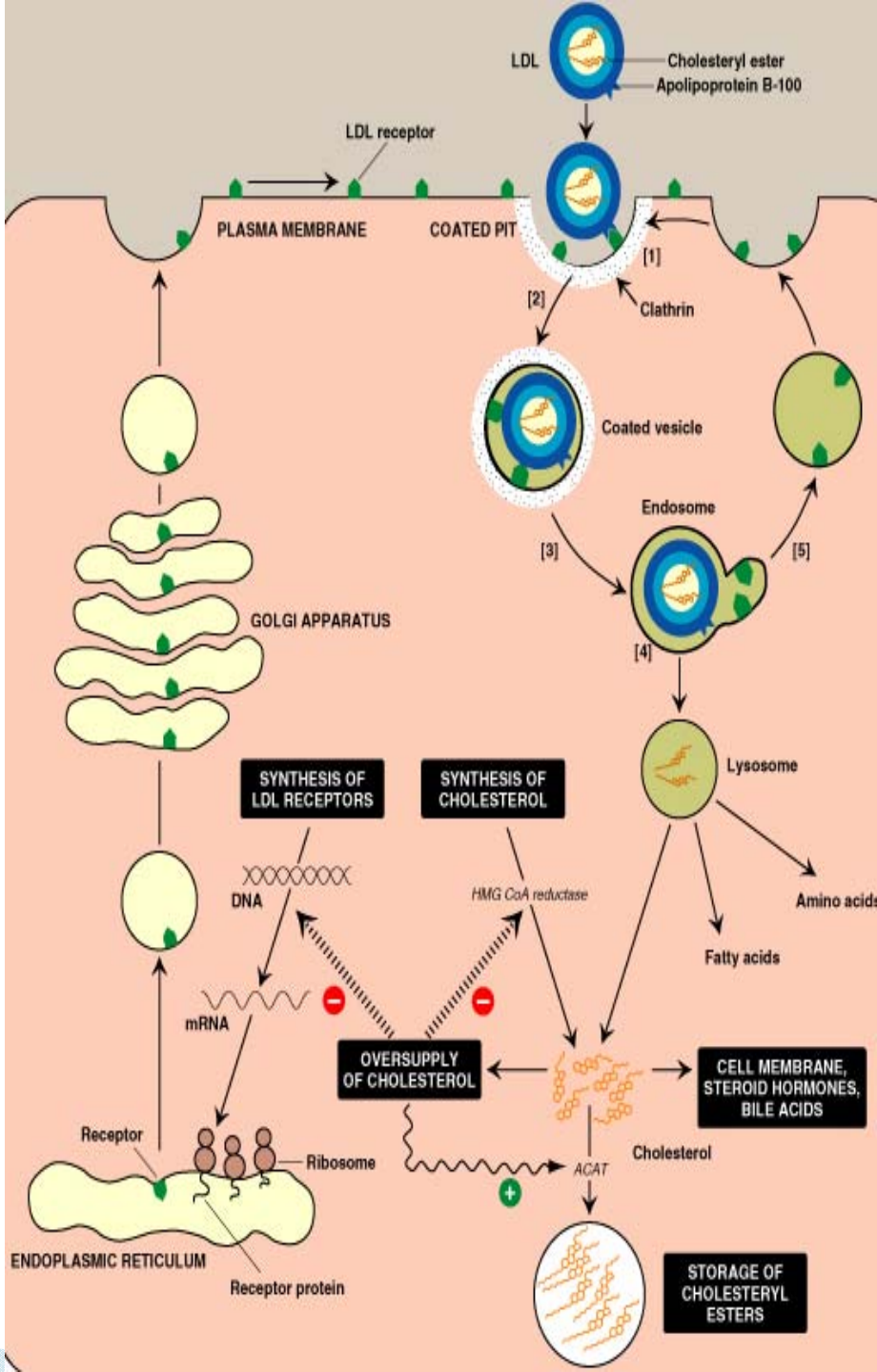
Enzymes mediating lipoprotein metabolism

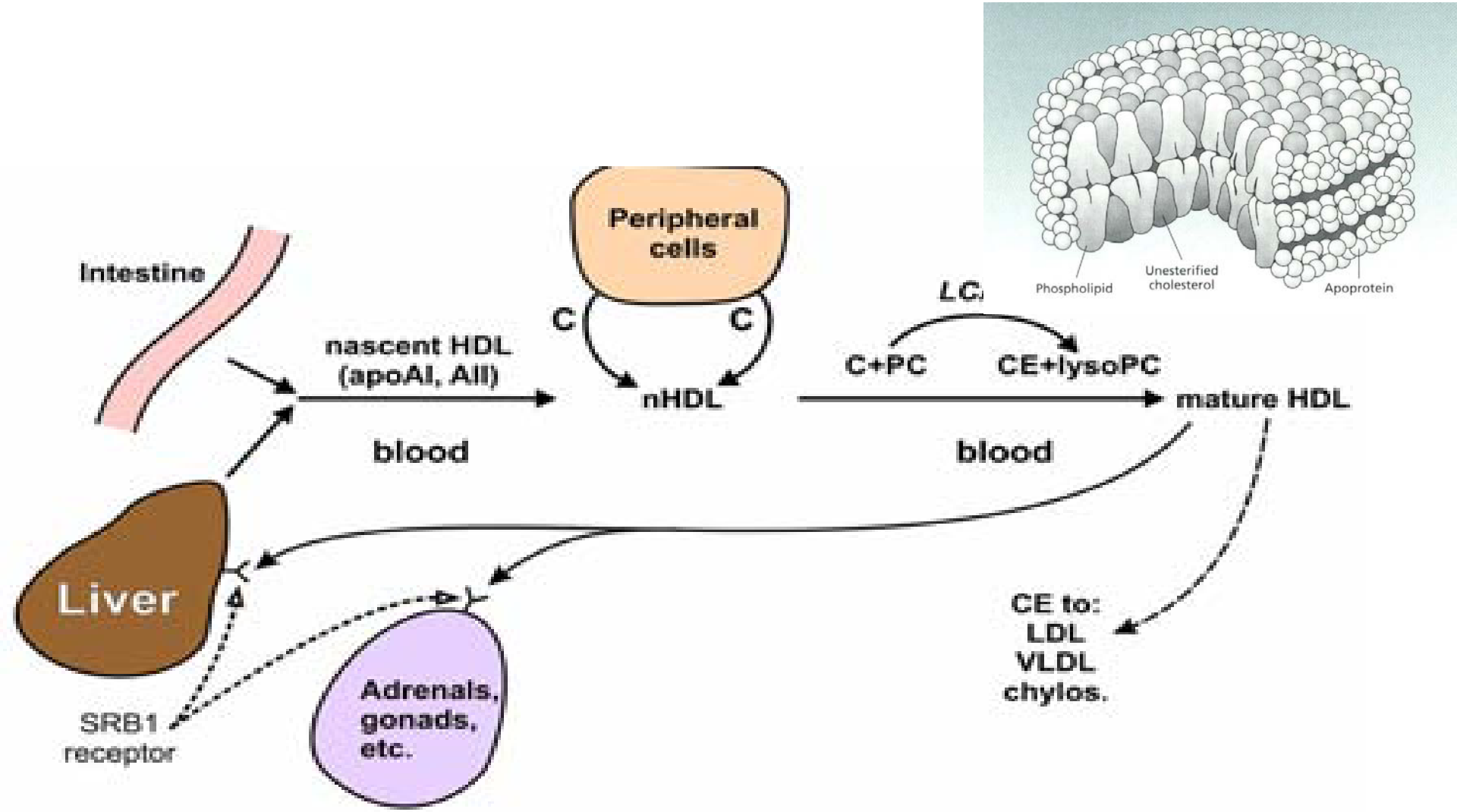
Enzyme	Substrate(s)	Reaction	Site of action	Metabolic role
Lecithin-cholesterol acyltransferase (LCAT)	Cholesterol and phosphatidyl choline	Cholesterol esterification	Plasma lipoproteins, especially HDL	Reverse cholesterol transport
Lipoprotein lipase	Triglyceride in VLDL and chylomicrons	Hydrolisis	Capillary surface	VLDL and chylomicron degradation
Hepatic lipase	Triglyceride and phospholipids in HDL_2 and IDL	Hydrolysis	Liver sinusoids	HDL_2 and IDL catabolism
Acid lipase	Trigliceride and cholesteryl ester	Hydrolysis	Lysosomes	Catabolism of lipoproteins incorporated into tissues by receptor-mediated endocytosis


Intestine
lymph
blood
CM
adipose tissue, etc.
LPL
TG
FA + glycerol
CM remnant
Liver
apoE receptor


adipose tissue, etc.
LPL
LPL
Liver
50%
VLDL
blood
IDL
LDL
TG
FA +
glycerol
TG
FA +
glycerol
Peripheral
Tissues
50%
Arterial
Wall
LDL receptor
(endocytosis)
LDL receptor
(endocytosis)

- LDL receptors exist in the liver (50%), and in most peripheral tissues (50%). (apoB-100/apoE receptors)
- The complexes of LDL and receptor are taken into the cells by endocytosis, where LDL is degraded but the receptors are recycled




Intestine
Peripheral cells
C
C
nascent HDL
(apoAI, AII)
nHDL
LCAT
C+PC
CE+lysoPC
mature HDL
blood
blood
Liver
SRB1
receptor
Adrenals,
gonads,
etc.
CE to:
LDL
VLDL
chylos.
Phospholipid
Unesterified
cholesterol
Apoprotein

hyperlipoproteinemia

- It is also known as hyperlipidemia or hyperlipoproteinemia
- In this case it is defined as a presence of raised or abnormal levels of lipids and/or lipoproteins in the blood

This is abnormality is common in the general population, and is one of the most important modifiable risk factors for coronary heart disease (CHD).

Dyslipidemia is generally characterized by increased fasting concentrations of total cholesterol (TC), LDL cholesterol (LDL-C), and triglycerides (TG), in conjunction with decreased concentrations of HDL cholesterol (HDL-C)

Desirable Levels

- Desirable Lipid levels in Adults:

Total cholesterol	< 5.5 mmol/L	< 200 mg/dl
HDL – C	> 1.1 mmol/L	➢35 mg/dl
Triglycerides	< 1.9 mmol/L	< 200 mg/dl
LDL – C	< 3,4 mmol/L	< 130 mg/dl

- On diagnosing hyperlipoproteinemia, hyperlipidemic status should be evaluated to determine whether it is primary lipoprotein disorder or secondary to any of a variety of metabolic diseases.
- The diagnosis of primaryhyperlipoproteinemia is made after secondry causes have been excluded.

Hereditary Hyperlipoproteinamias

- Familial Lipoprotein lipase deficiency (Type I Hyperlipoproteinemia).
- Characterized by high levels of chylomicrons and triglycerides and a deficiency of lipoprotein lipase, an enzyme that accelerates the breakdown of lipoproteins.
- Disease onset is usually in infancy.
- Type 1 has a pure elevation of triglycerides in the chylomicron fraction.These people sometimes get pancreatitis and abdominal pains, but they do not seem to have an increase in vascular disease .

Dysbetalipoproteinemia (Type III):

- also called broad beta disease
- Accumulation of IDL, VLDL and chylomicron remnant.
- Elevated level of total cholesterol and triglycerides.
- The disorder caused by Apo-E or Apo-E receptor. Diabetes, hypothyroidism are associated with type III disorders.
  Type 3 appears in one in 10,000 people and elevates both triglycerides and cholesterol with consequent vascular disease , Disease onset is usually in adults.

Hereditary Hyperlipoproteinamias

- Type II Familial hypecholesterolemias:
- Type II, broken into two subtypes, type II-a and type II-b. Have elevated cholesterol. Some have elevated triglycerides also.
- The familial (genetic) versions of Type 2 often develop xanthomas, which are yellow fatty deposits under the skin of the knuckles, elbows, buttocks or heels. They may also have xanthelasmas, smaller yellow patches on the eyelids. Both subtypes display high levels of blood cholesterol. People with type II-b also have high levels of triglycerides in their blood. Disease onset is usually after age 20.

Abetalipoproteinemia Type IV

- Elevates only triglycerides and does not increase the risk of vascular disease
- Genetic defect in the synthesis of Apo-B.
- Both chylomicron and VLDL are affected.
- Fat malabsorbtion occurs because chylomicron can not be formed by intestine.
- Disease onset is usually during puberty or early adulthood.
- Multiple type hyperlipoproteinemia Increased level of VLDL and LDL which is resulted from the overproduction of VLDL. The biochemical defect is unknown.

Diseases of Lipoprotein Metabolism Caused by Single Gene Defects

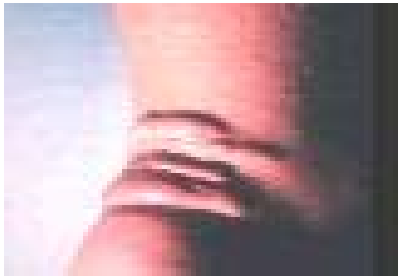
Disease	Lipoprotein abnormality	Lipid abnormality	Metabolic basis	Clinical implications
Familial hyper-cholesterolemia Type II	LDL elevated	Cholesterol elevated	Decrease clearance of LDL from plasma. Familial form results from genetic deficiency or abnormality in LDL receptor.	Risk factor for atherosclerosis
Familial hyper-triglyceridemia Type IV	VLDL elevated	Triglyceride elevated	Uncertain; VLDL overproduction or decreased catabolism.	Questionable as to whether this is an independent risk factor for atherosclerosis
Familial combined hyperlipidemia Type IV	LDL and VLDL elevated	Cholesterol and triglyceride elevated	Uncertain; overproduction of apo-B-100	Risk factor for atherosclerosis
Familial dysbeta-lipoproteinemia Type III	β-VLDL and IDI elevated	Cholesterol and triglyceride elevated	Decreased clearance of remnants; defective binding of apo E to LDL receptor	Risk factor for atherosclerosis
Familial lipoprotein lipase deficiency Type -I	Chylomicrons and VLDL elevated	Triglycerides elevated	Deficiency of lipoprotein lipase or apo-C-II	Acute pancreatitis
Hypoalpha-lipoproteinemia	HDL reduce	None	Uncertain; occasionally caused by genetic apo-A-I/apo-C-II deficiency	Risk factor for atherosclerosis

Phenotype	Elevated Particles	Lipid Abnormality	Possible Defect	Frequency	ATS
I	Chylomicron	TG	LP lipase	Very rare	Not seen
IIa	LDL	LDL-C	LDL-R defect	Common	***
IIb	LDL and VLDL	LDL-C, TG	HMG-CoA reductase	Common	***
III	IDL	TC, TG	Apo-E deficiency	Rare	***
IV	VLDL	TG	VLDL overproduction	Common	*
V	Chylomicron and VLDL	TG	Apo-CII deficiency	Uncommon	*

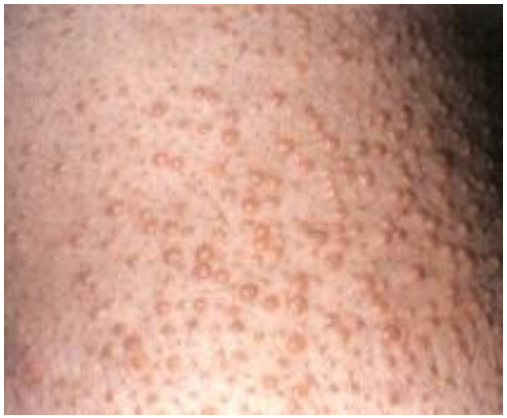
Secondry Hyperlipoproteinemia

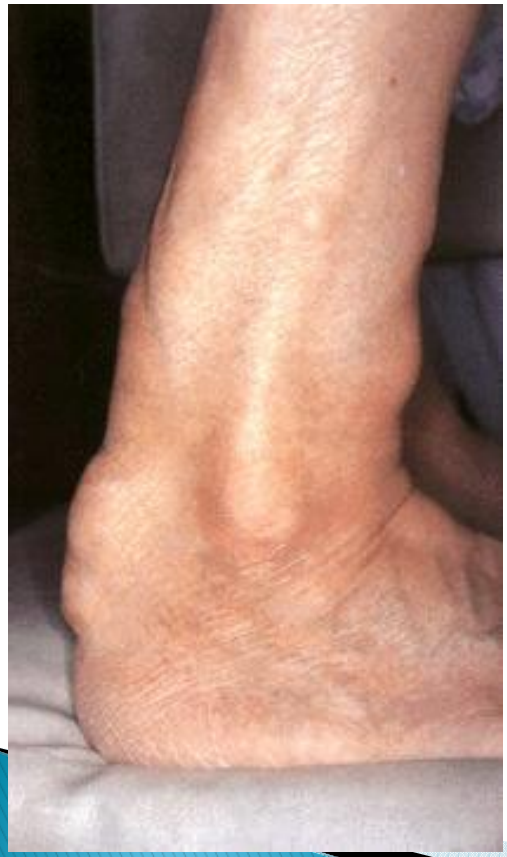
- Diabetes mellitus, because it alters the way the body handles its energy needs, also affects the way it handles fats. The result is elevated triglycerides and reduced HDL cholesterol. This effect is amplified by obesity
- Hypothyroidism is a common cause of lipid abnormalities. The thyroid hormone affects the rate of many chemical processes in the body, including the clearing of fats from the blood. The consequence is usually an elevation of cholesterol
- Kidney disease affects the blood's proteins and consequently the composition of the fat packages. It usually raises the LDLs
- Liver disease, depending on its stage and severity, can raise or lower any of the blood fats
- Alcohol raises triglycerides. Cigarettes smoking lowers HDL cholesterol, as does malnutrition and obesity.
- Glycogen storage disease, and congenital biliary atresia.

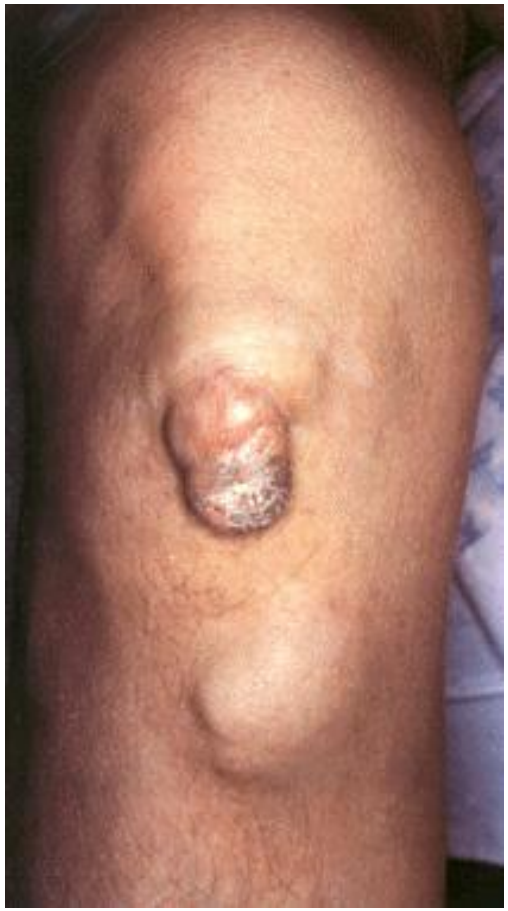
Symptoms

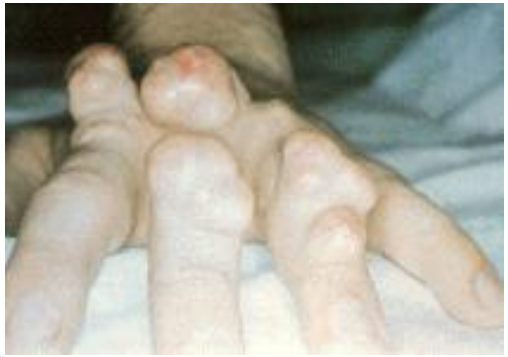


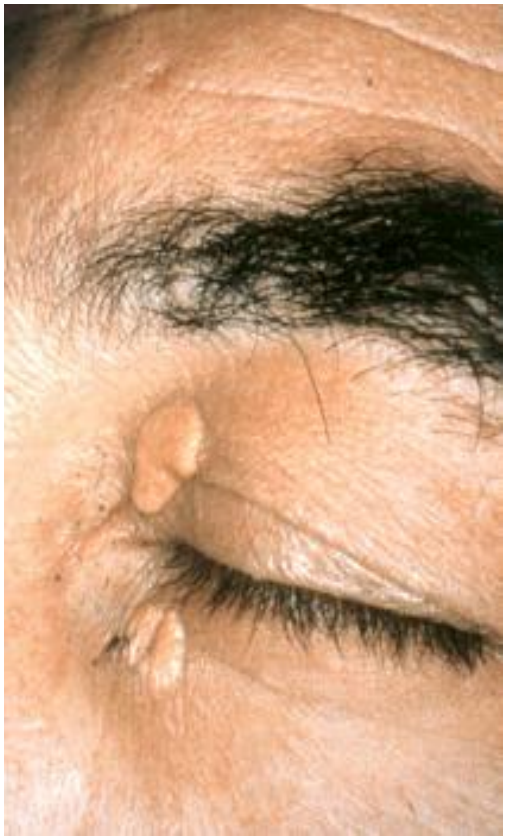
- Usually high lipid levels are asymptomatic
- Occasionally when fat levels are high, it can be deposited in skin and tendons forming bumps called xanthomas (eyes and Achilles tendon)
- Very high triglyceride levels may cause liver to enlarge
- High lipids increase the risk of developing pancreaitis, which causes severe abdominal pain and is sometimes fatal

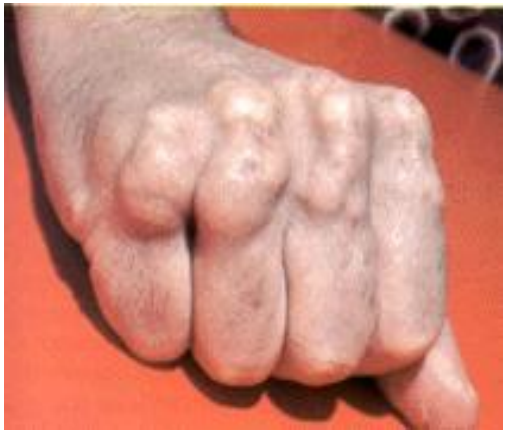








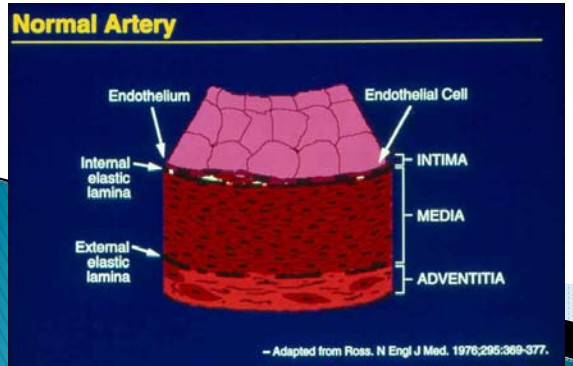


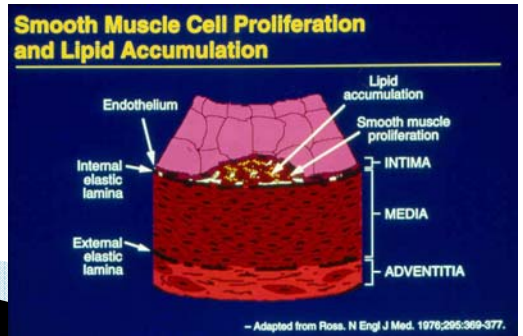


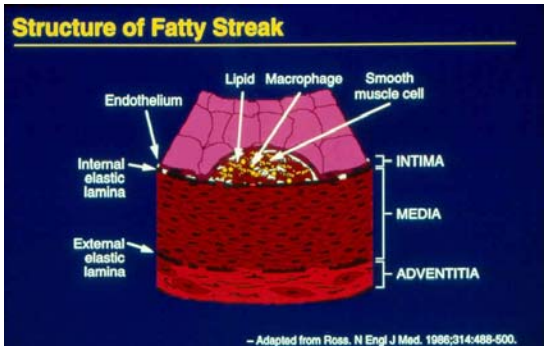
- Human coronary atherosclerosis is a chronic inflammatory disease that is superimposed on a background of lipid abnormalities .

Proinflammatory oxidized low-density lipoprotein (LDL) may be a unifying link between lipid accumulation and inflammation in the vessel wall.

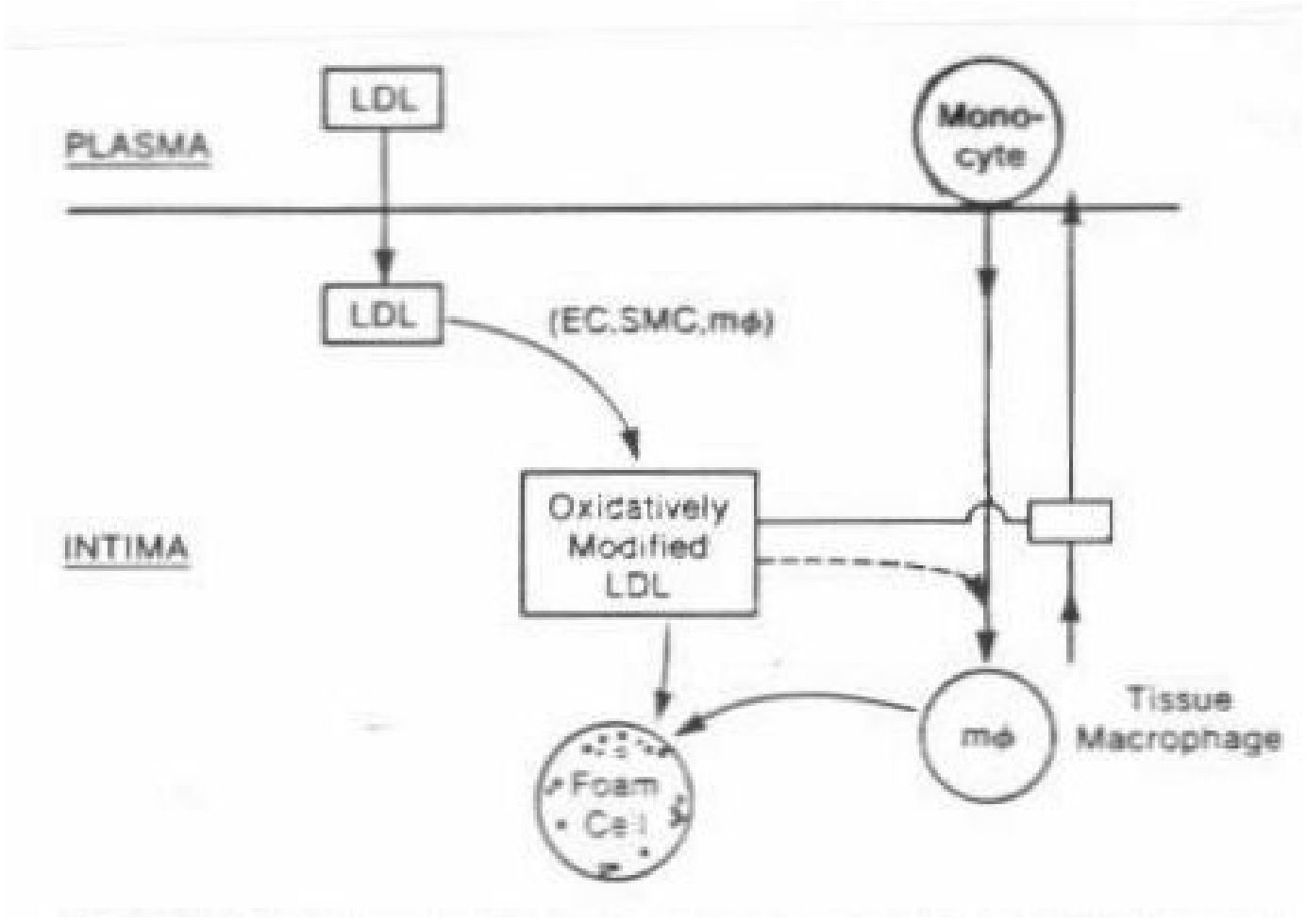
In humans, oxidized LDL in plasma and within atherosclerotic lesions is strongly associated with coronary artery disease, acute coronary syndromes, and vulnerable plaques



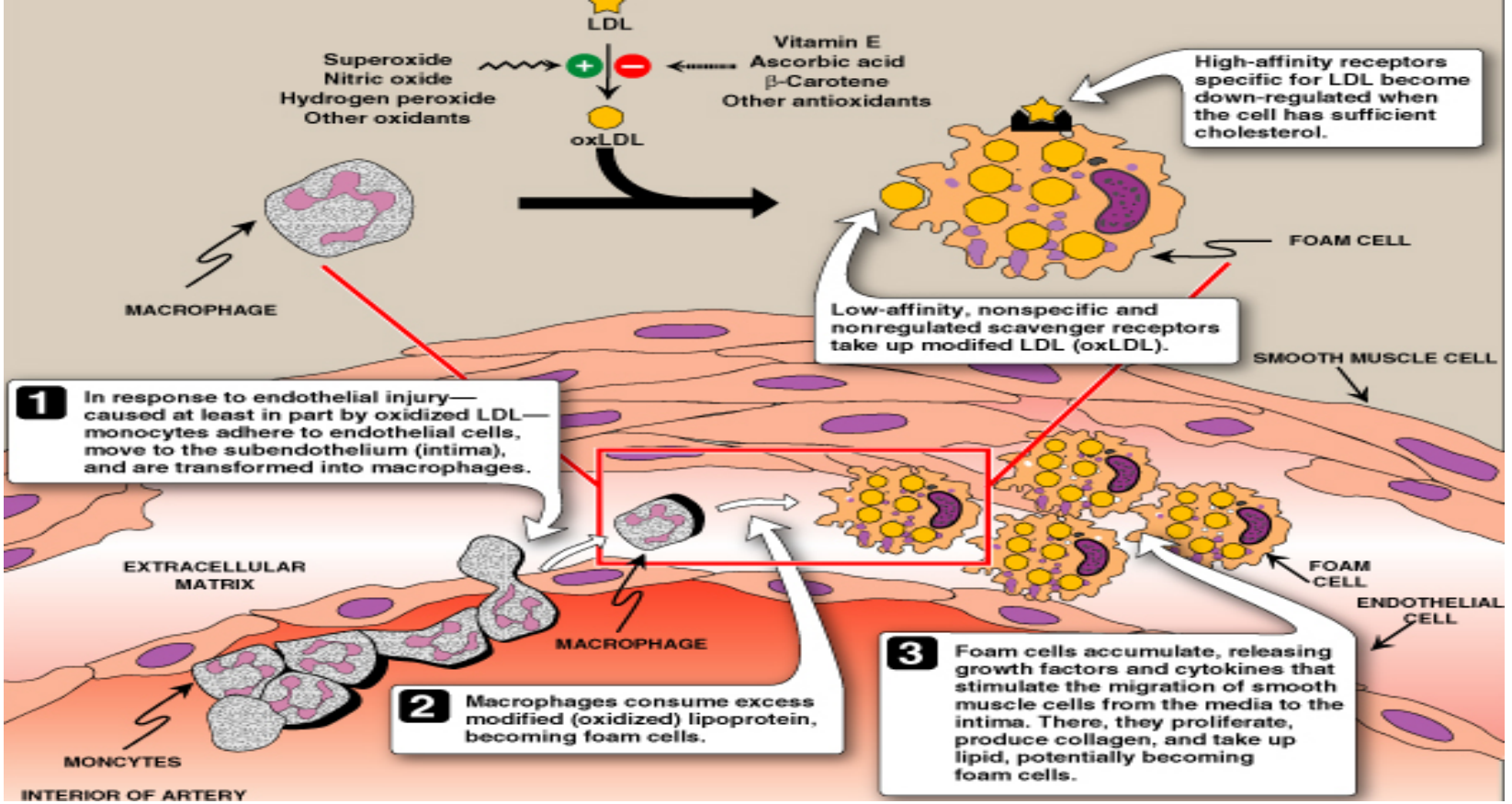




Possible effect of LDL



This scheme suggests that oxidatively modified LDL may enhance the accumulation of macrophages by attracting circulating monocytes while inhibiting tissue macrophage motility



- Oxidation of LDL-cholesterol occurs in endothelial and other cells when polyunsaturated fats become peroxidated.[34,35] Cellular generation of free radicals and the presence of low concentrations of copper or iron lead to oxidative modification.[34,35]
- Oxidatively modified LDL is highly cytotoxic and is also a potent chemoattractant for monocytes.[34,35]
- Once the attracted monocytes migrate between the endothelial cells, they are converted to macrophages and act as scavengers. These macrophages are then able to take up lipid, becoming foam cells.[31]

Contributing Factors

- Levels of lipoproteins and lipids (LDL) increase slightly with age. Other factors associated with increase of these are:
  - familial history
  - Obesity
  - diet high in saturated fat
  - Inactivity
  - alcohol consumption

Lipoprotein-related Diseases

(B) Hypolipoproteinemia

Congenital abetalipoproteinemia

- Defect in TAG-transfer protein
- Inability to load Apo B with lipids
- No CM or VLDL formation
- TAG accumulation: intestine & liver

(C) Fatty Liver (hepatic steatosis)

- Decreased secretion of VLDL
- Obesity, DM, Chronic alcoholism

THANK YOU