METABOLISM and FUNCTIONS of LIPIDS

Lecture III

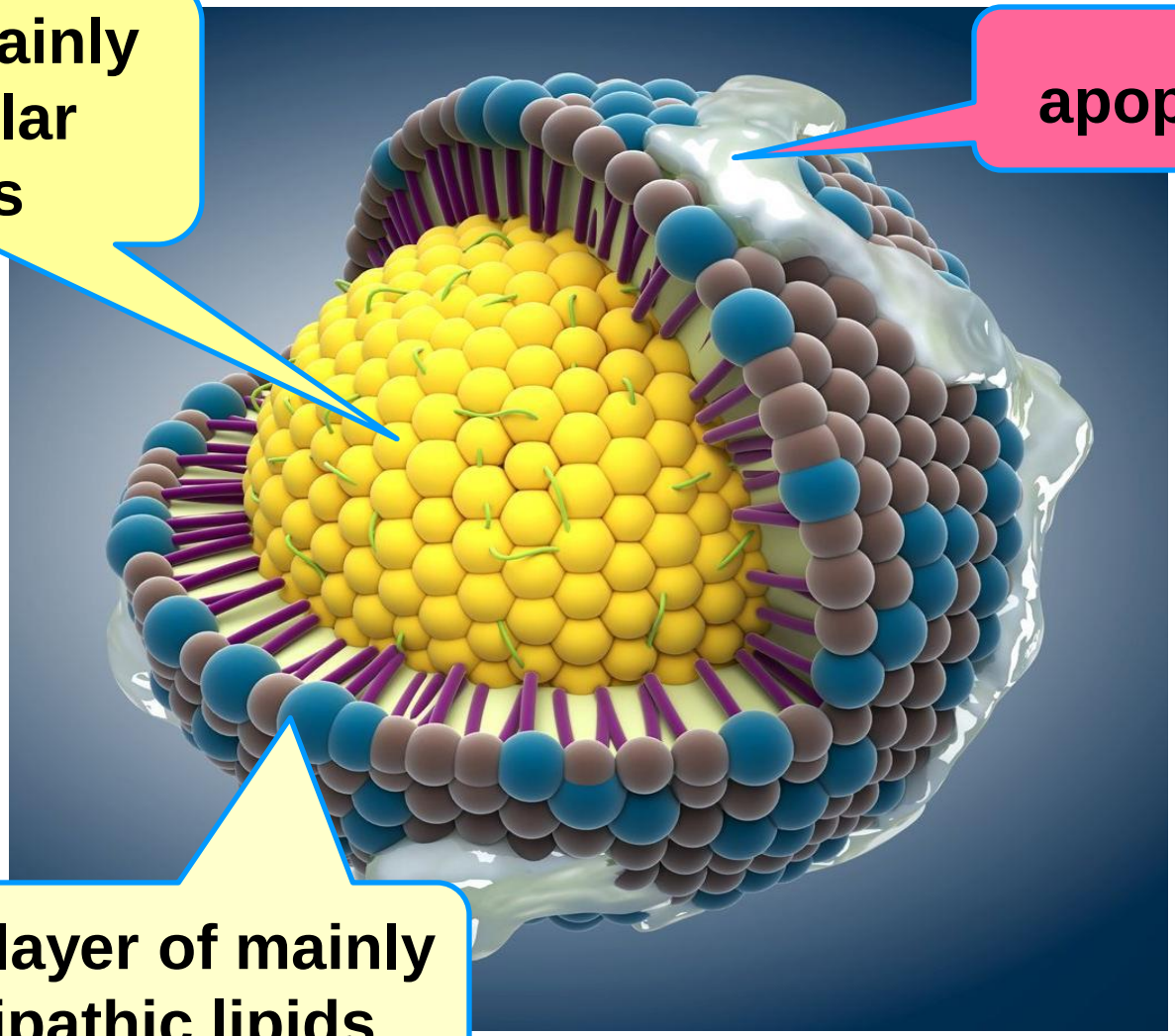
Transport fatty acids in the blood.

Fatty acids released from adipose tissue by hydrolysis of TAG are thrown in the circulation as free fatty acid (FFA). They are carried in non-esterified state in plasma, hence also called NEFA. In circulation, FFA/ NEFA combines with albumin and are carried as albumin-FFA complex.

Transport of lipids in the blood

Lipids are hydrophobic compounds. Their transport in blood (in an aqueous medium) poses a problem, which is solved by associating the more insoluble lipids with more "polar" ones, such as phospholipids, cholesterol and combining with a specific, protein molecule (called as 'apoproteins'). Thus, the hydrophobic and insoluble lipid is converted by above combination into a hydrophilic and soluble lipoprotein complex.

Generalized structure of plasma lipoprotein

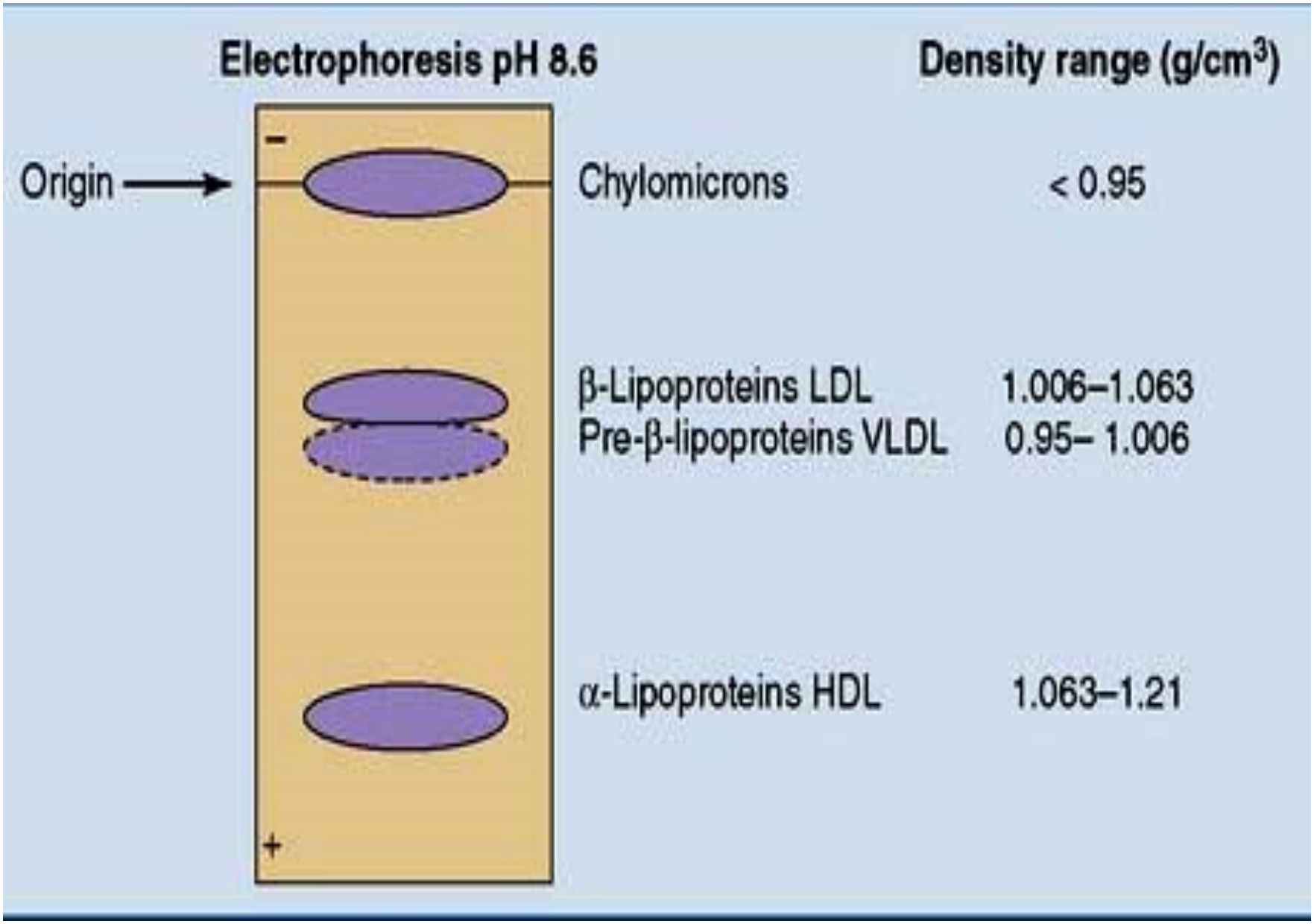


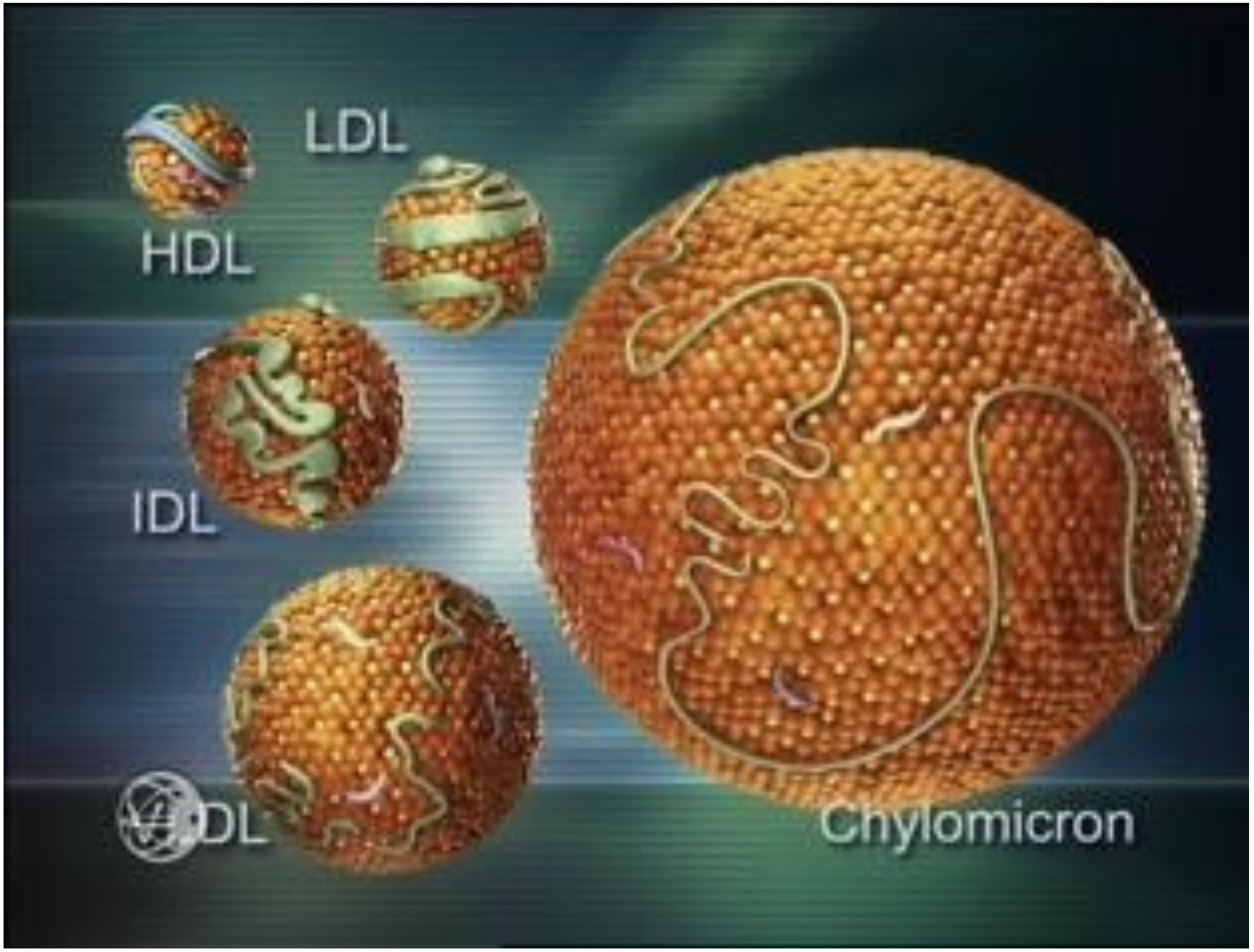
FUNCTIONS OF APOLIPOPROTEINS

- By entering into the “polar” surface layer they make the lipoprotein molecules **hydrophilic**.
- They can form part of the structure of the lipoprotein itself.
- They are enzyme cofactors and can act as activator or inhibitor of the enzymes.
- They act as **ligands** for interaction with lipoprotein receptors in tissues.

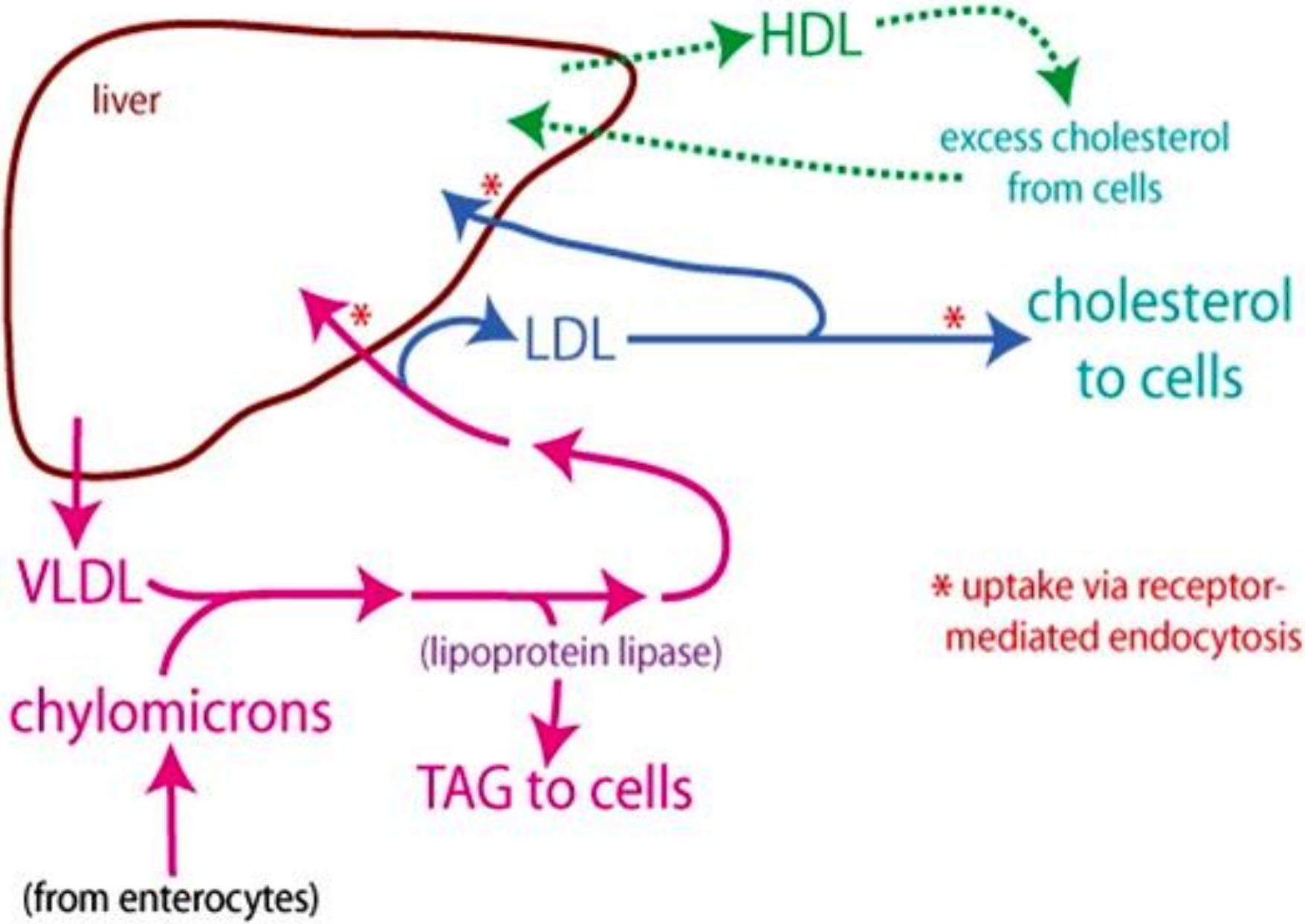
Classification of plasma lipoproteins

Lipoprotein fractions separated by ultracentrifugation	Lipoprotein fractions separated according to their electrophoretic properties
HDL high density lipoproteins	α-lipoproteins
VLDL very low density lipoproteins	pre-β lipoproteins
IDL intermediate density lipoproteins	
LDL: low density lipoproteins	β-lipoproteins
Chylomicrons	Chylomicrons


Electrophoresis pH 8.6
Density range (g/cm3)
Origin
−
+
Chylomicrons
< 0.95
β-Lipoproteins LDL
1.006–1.063
Pre-β-lipoproteins VLDL
0.95– 1.006
α-Lipoproteins HDL
1.063–1.21


LDL
HDL
IDL
Chylomicron

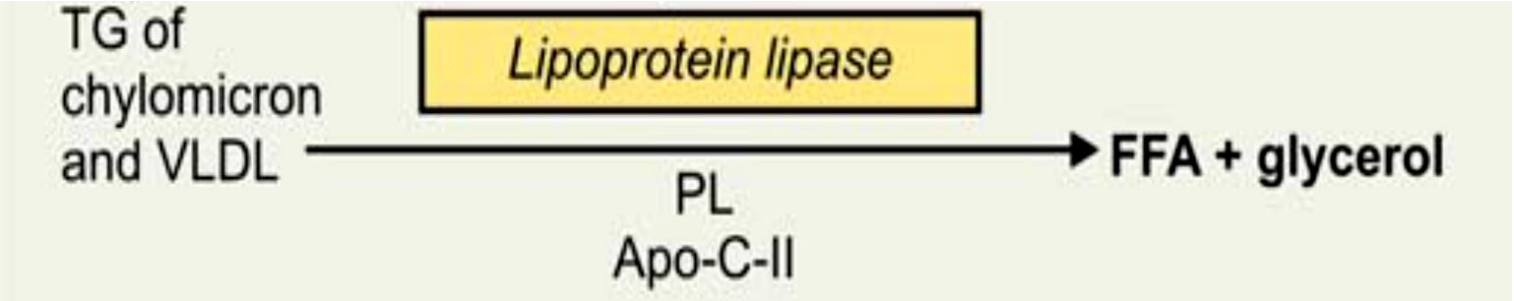
Lipoprotein	Source	Diameter (nm)	Density (g/mL)	Composition		Main Lipid Components	Apolipoproteins
				Protein (%)	Lipid (%)		
Chylomicrons	Intestine	90–1000	< 0.95	1–2	98–99	Triacylglycerol	A-I, A-II, A-IV,[1] B-48, C-I, C-II, C-III, E
Chylomicron remnants	Chylomicrons	45–150	< 1.006	6–8	92–94	Triacylglycerol, phospholipids, cholesterol	B-48, E
VLDL	Liver (intestine)	30–90	0.95–1.006	7–10	90–93	Triacylglycerol	B-100, C-I, C-II, C-III
IDL	VLDL	25–35	1.006–1.019	11	89	Triacylglycerol, cholesterol	B-100, E
LDL	VLDL	20–25	1.019–1.063	21	79	Cholesterol	B-100
HDL	Liver, intestine, VLDL, chylomicrons					Phospholipids, cholesterol	A-I, A-II, A-IV, C-I, C-II, C-III, D,[2] E
HDL_1		20–25	1.019–1.063	32	68		
HDL_2		10–20	1.063–1.125	33	67		
HDL_3		5–10	1.125–1.210	57	43		


liver
HDL
excess cholesterol
from cells
*
*
LDL
*
cholesterol
to cells
VLDL
(lipoprotein lipase)
chylomicrons
TAG to cells
(from enterocytes)
* uptake via receptor-
mediated endocytosis

The enzyme lipoproteinlipase is located in walls of blood capillaries.

The enzyme remains bound to wall

by proteoglycan chains of heparan-SO_4.

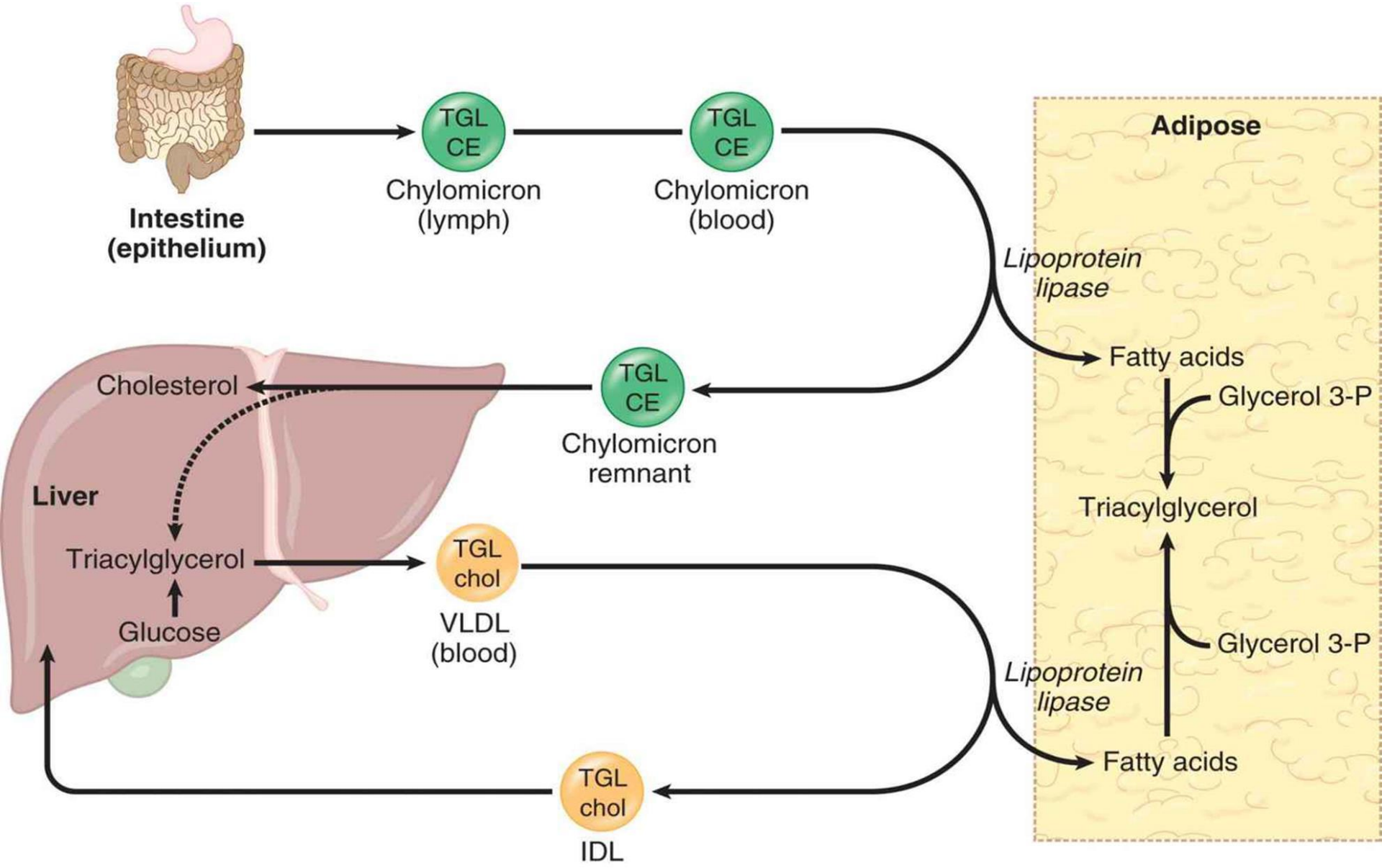


Lipoprotein lipase **activity declines in adipocytes on starvation and rises after feeding.**

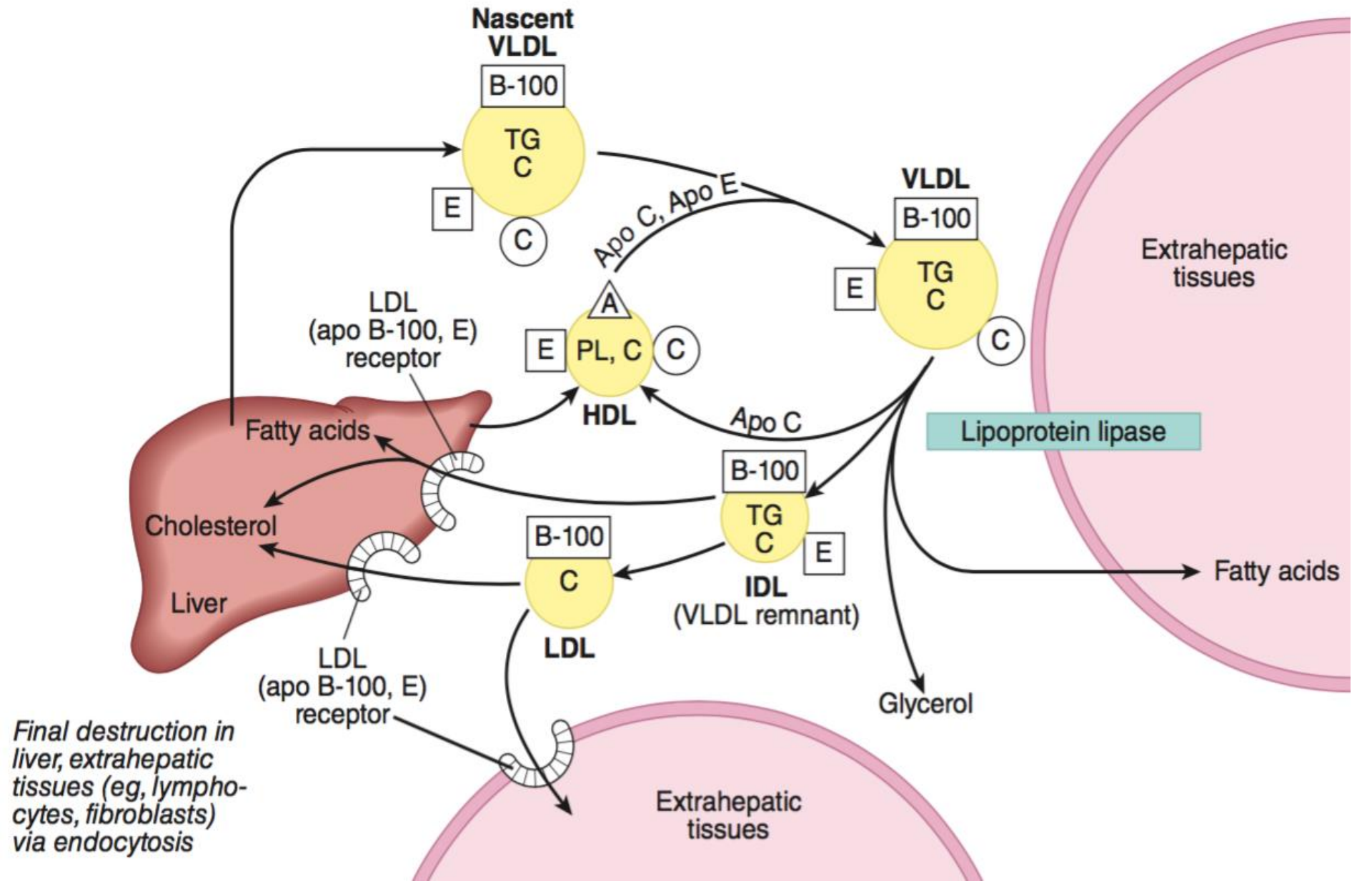
Hence starvation

reduces and feeding enhances the uptake and storage of fat by adipose tissue.

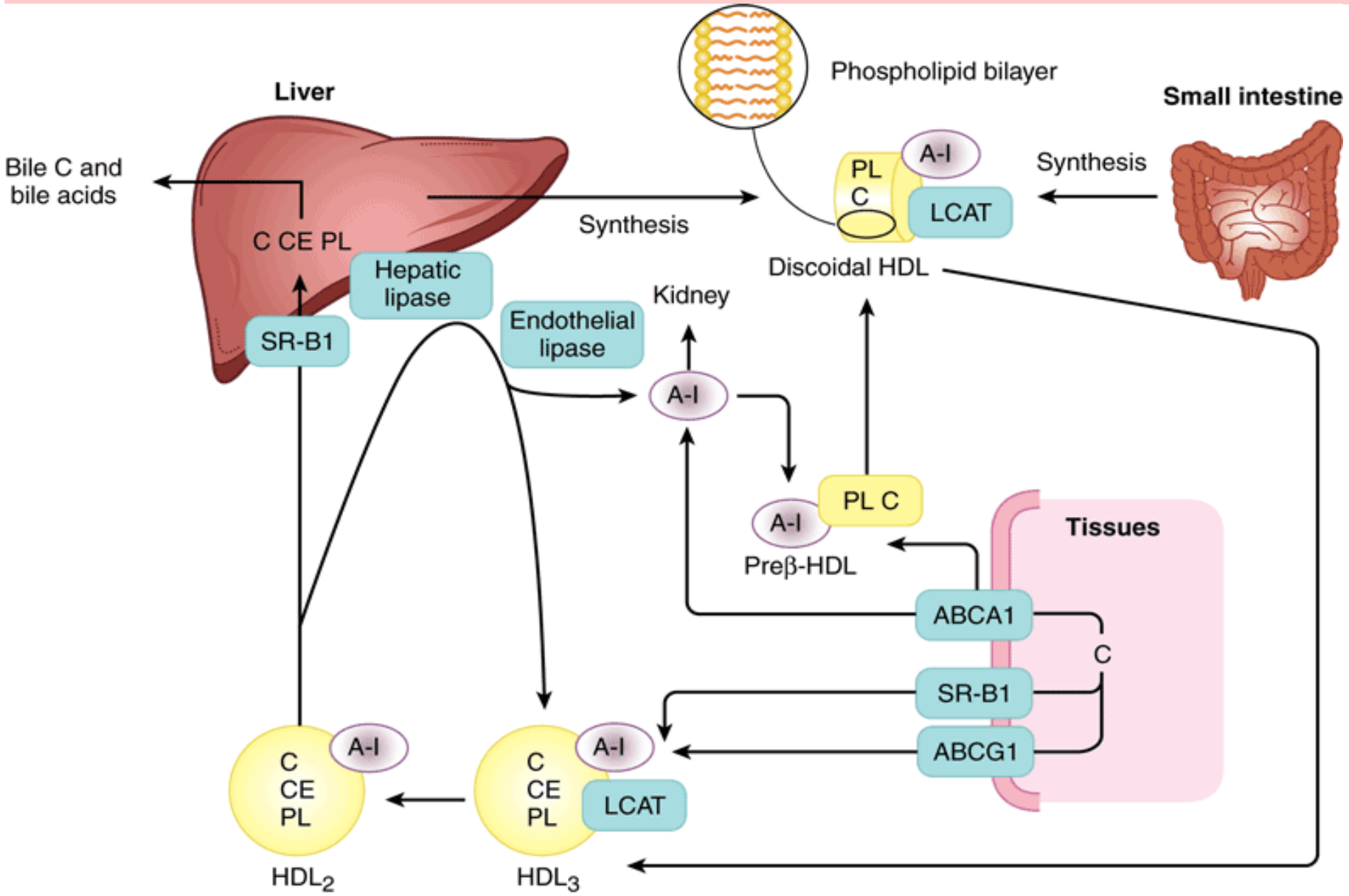
Metabolism of Chylomicrons



Metabolic fate of very low density lipoproteins (VLDL) and production of low density lipoproteins (LDL)



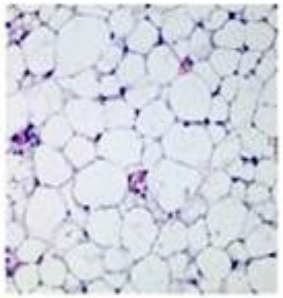
Metabolism of HDL



Source: Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA: *Harper's Illustrated Biochemistry, 29th Edition*: www.accessmedicine.com

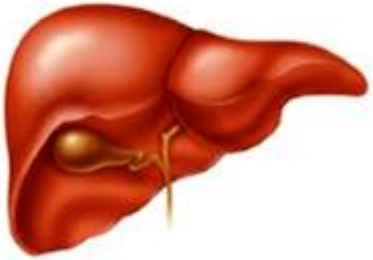
Overview of Lipid Transport in Animals

Dietary triacylglycerols



Triacylglycerols stored in adipose tissue and released in response to hormones

Glucagon
Epinephrine



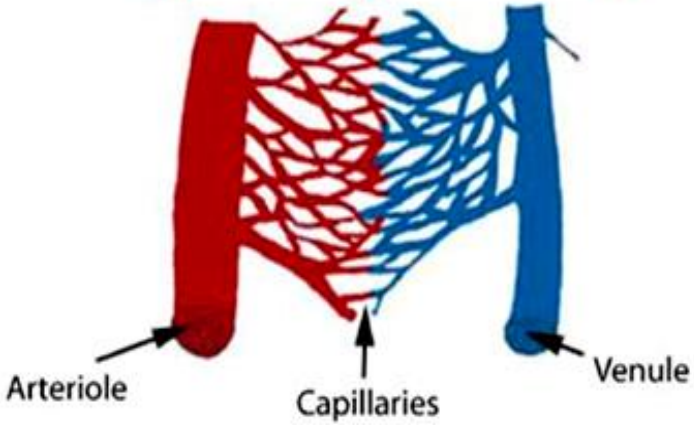
Triacylglycerols synthesized in the liver from carbohydrates and exported

Chylomicrons

Fatty acids

Albumin

VLDL particles

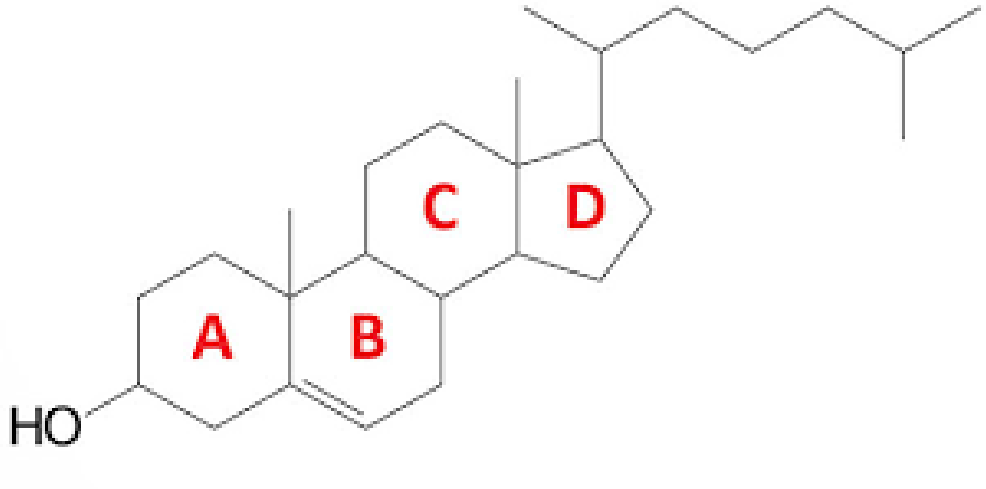


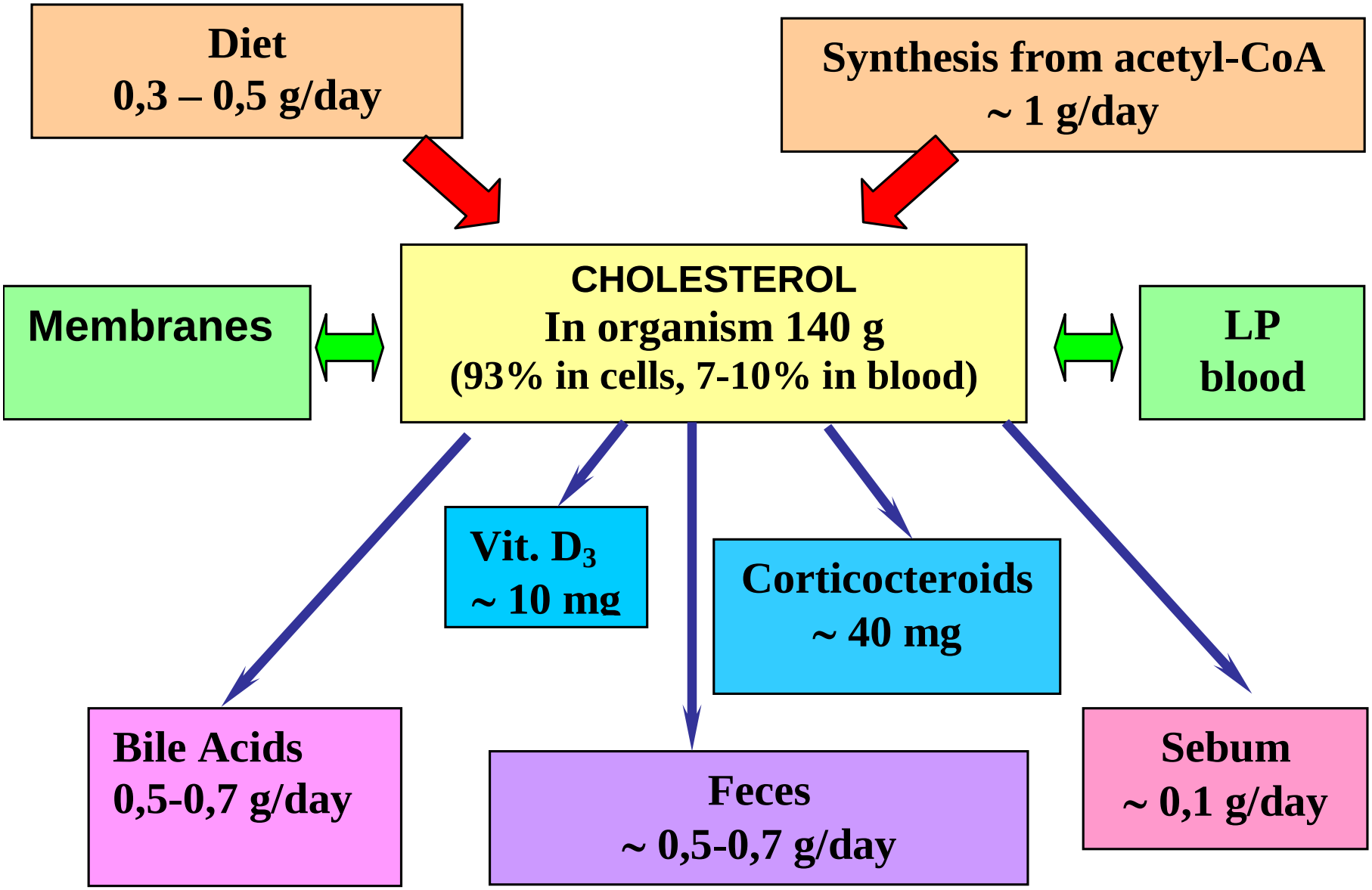
Disorders of Plasma Lipoproteins (Dyslipoproteinemias)

Harper's Illustrated Biochemistry

(Chapter Cholesterol Synthesis, Transport,& Excretion)

Metabolism of cholesterol in the body




Diet
0,3 – 0,5 g/day
Synthesis from acetyl-CoA
~ 1 g/day
Membranes
CHOLESTEROL
In organism 140 g
(93% in cells, 7-10% in blood)
LP
blood
Vit. D3
~ 10 mg
Corticocteroids
~ 40 mg
Bile Acids
0,5-0,7 g/day
Feces
~ 0,5-0,7 g/day
Sebum
~ 0,1 g/day

Synthesis of cholesterol

Step I: biosynthesis of mevalonate

Step II: formation of isoprenoid units
Step III: formation of squalene

II

Step IV: formation of lanosterol
Step V: formation of cholesterol

III

Synthesis of cholesterol

2 acetyl-CoA

↓

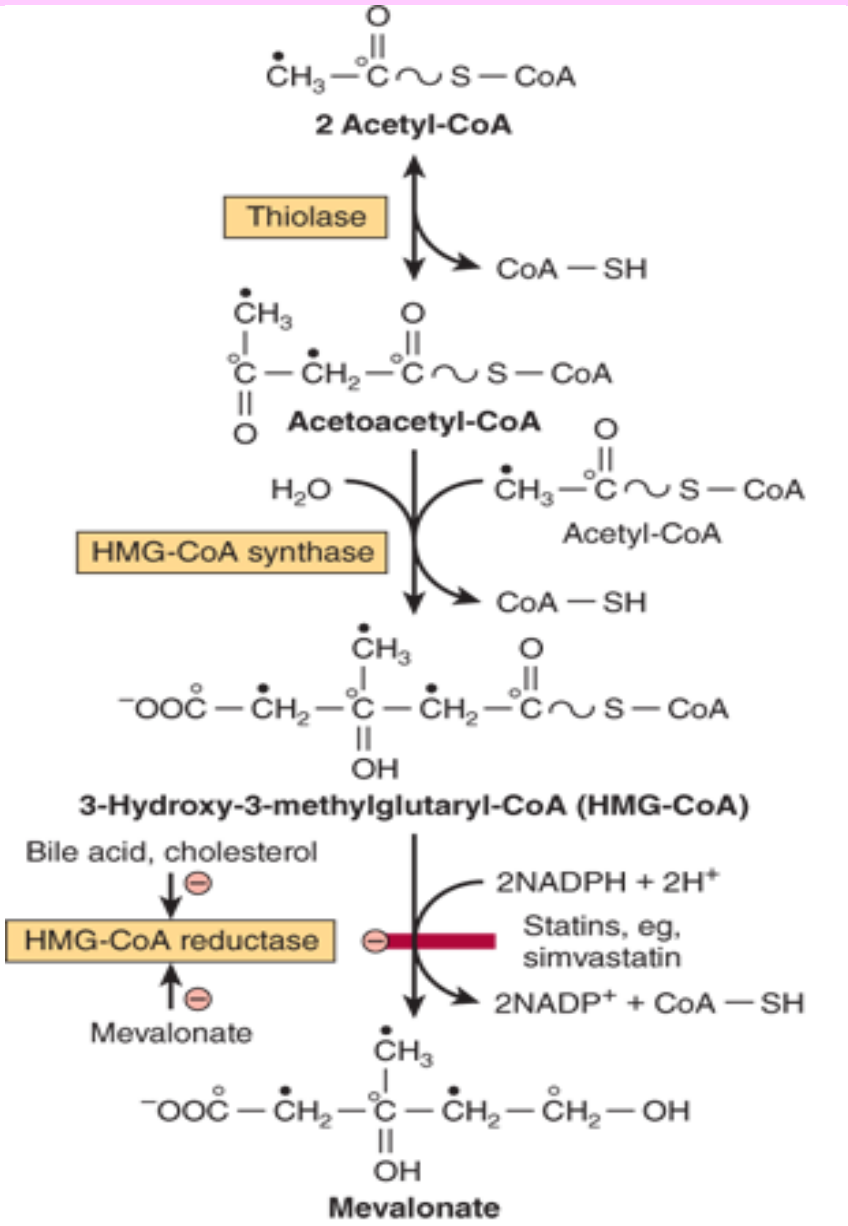
Acetoacetyl-CoA

↓

HMG-CoA

↓

Mevalonate

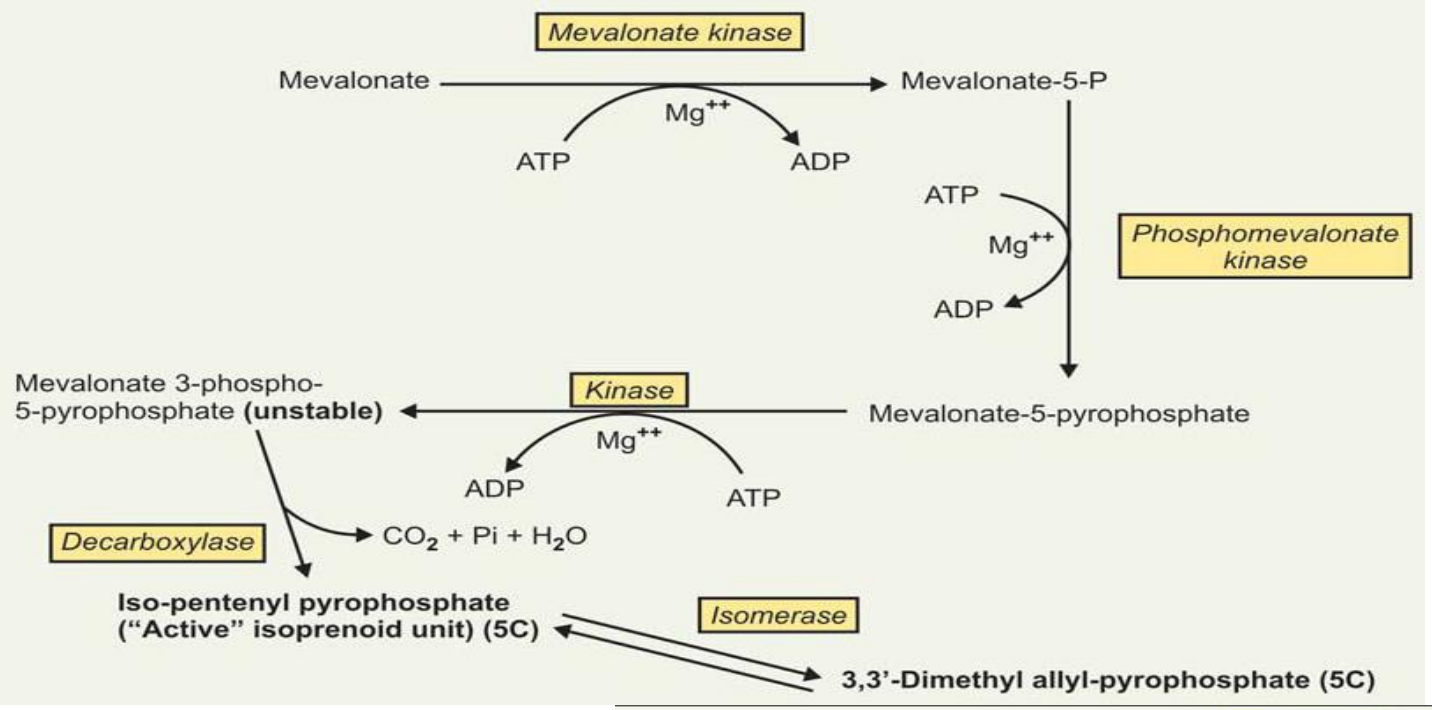


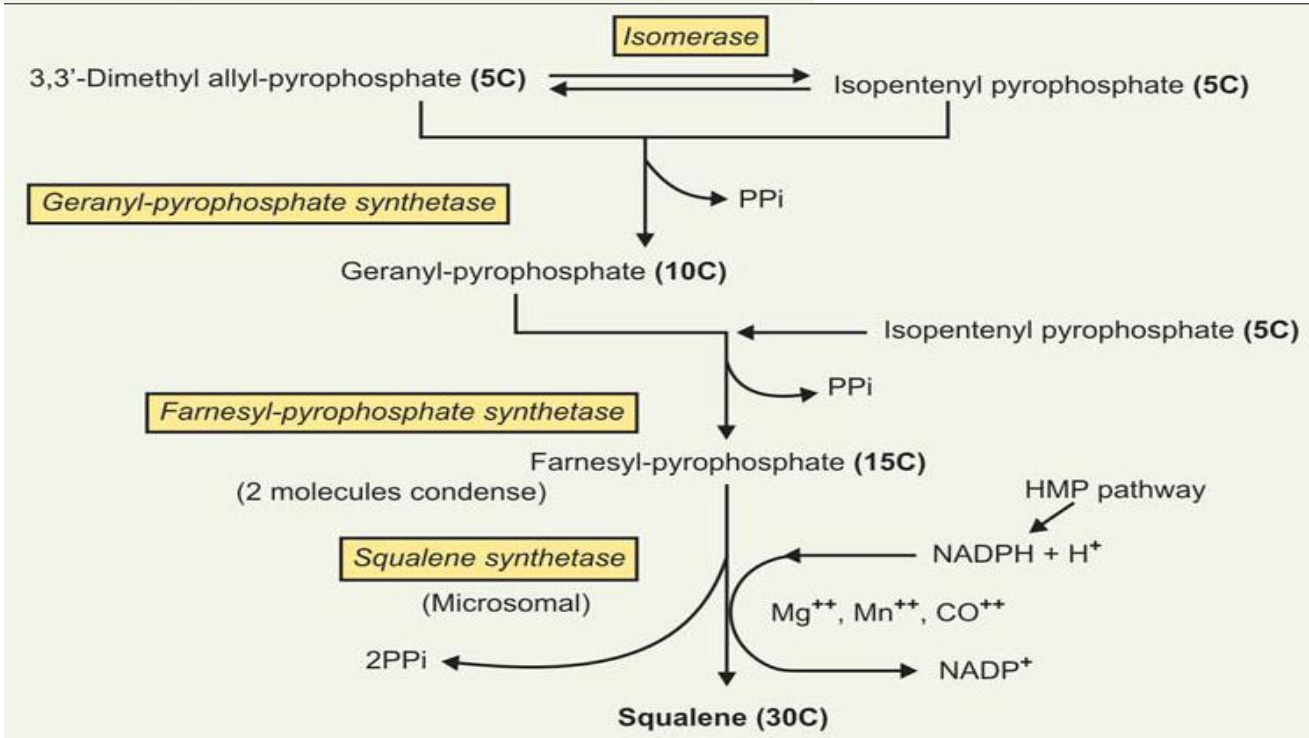
Source: V. W. Rodwell, D. A. Bender, K. M. Botham, P.
www.accessmedicine.com

Synthesis of cholesterol

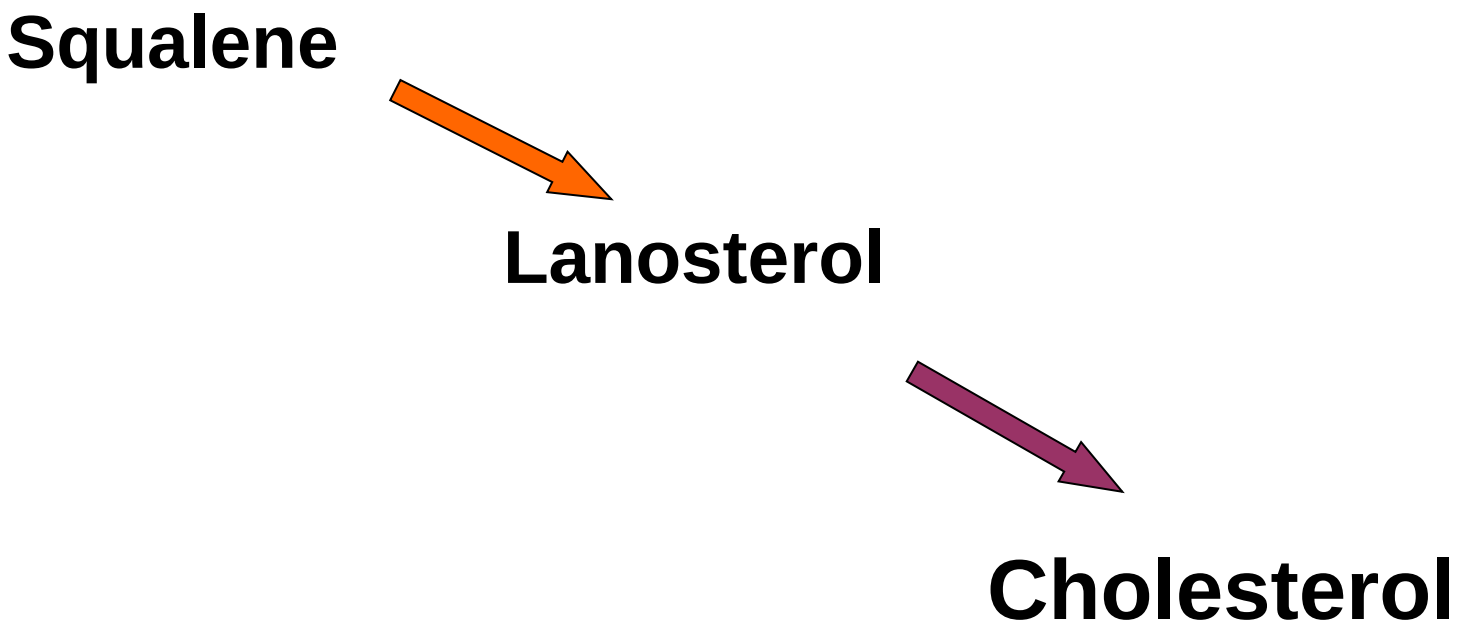
Mevalonate → Mevalonate 5-phosphate → Mevalonate 5-diphosphate → Mevalonate 3-pospho-5-diphosphate → Isopenttenyl diphosphate → Dimethylallyl diphosphate → … → ….

Squalene


Mevalonate kinase
Mevalonate
Mevalonate-5-P
Mg++
ATP
ADP
ATP
Mg++
ADP
Phosphomevalonate kinase
Mevalonate 3-phospho-5-pyrophosphate (unstable)
Kinase
Mevalonate-5-pyrophosphate
Mg++
ADP
ATP
Decarboxylase
CO2 + Pi + H2O
Iso-pentenyl pyrophosphate ("Active" isoprenoid unit) (5C)
Isomerase
3,3'-Dimethyl allyl-pyrophosphate (5C)


Isomerase
3,3'-Dimethyl allyl-pyrophosphate (5C)
Isopentenyl pyrophosphate (5C)
Geranyl-pyrophosphate synthetase
PPi
Geranyl-pyrophosphate (10C)
Isopentenyl pyrophosphate (5C)
PPi
Farnesyl-pyrophosphate synthetase
Farnesyl-pyrophosphate (15C)
(2 molecules condense)
HMP pathway
NADPH + H+
Squalene synthetase
(Microsomal)
Mg++, Mn++, CO++
2PPi
NADP+
Squalene (30C)

Synthesis of cholesterol



Regulation of cholesterol synthesis

The rate limiting step: HMG-CoA reductase step.

I: mevalonate, cholesterol, bile acids

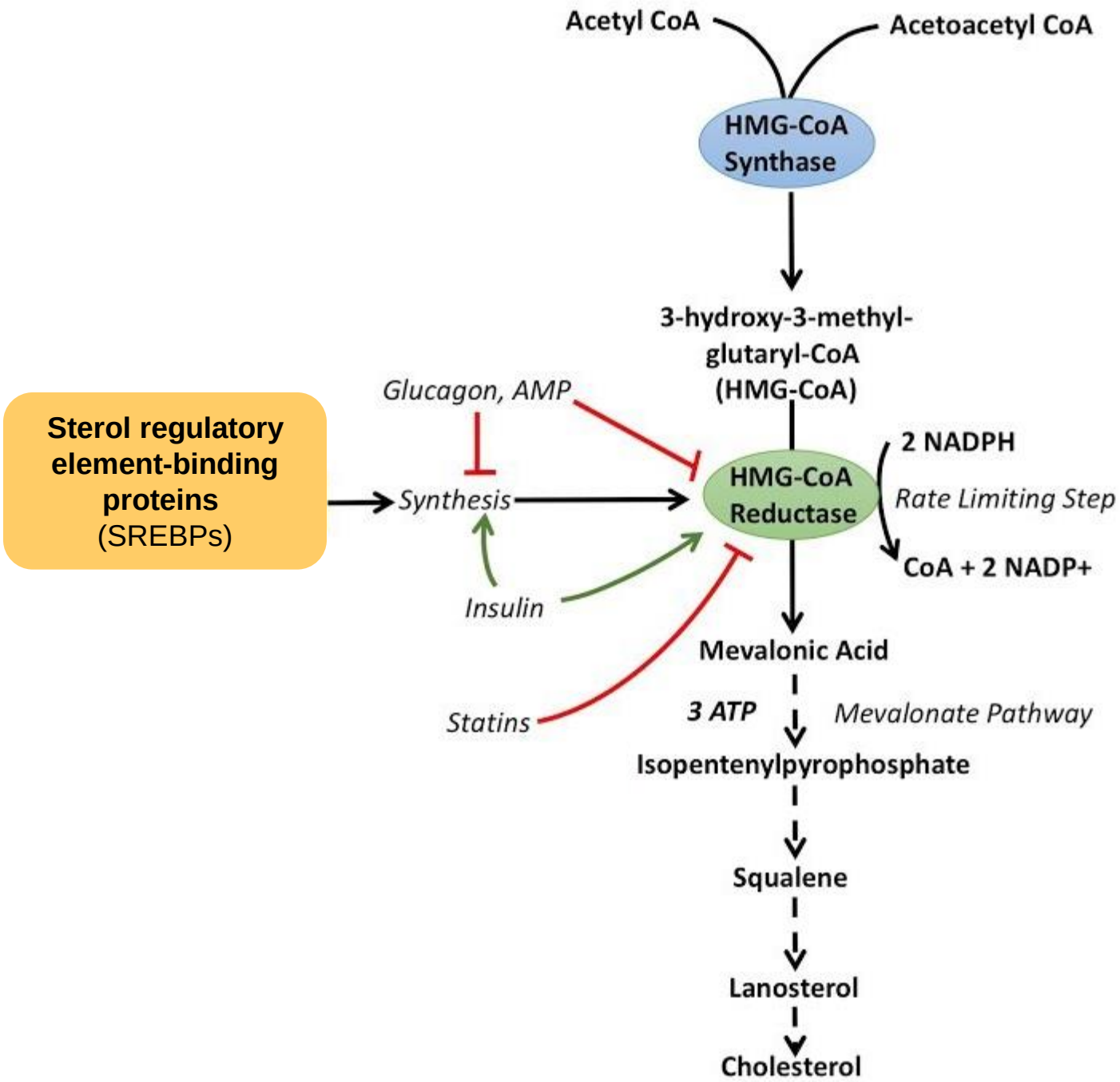
Cholesterol and metabolites repress transcription of the HMG-CoA reductase gene

Fasting and/starvation also inhibit the enzyme and activate HMG-Co lyase to form ketone bodies.

Feeding cholesterol reduces the hepatic biosynthesis of cholesterol by reducing the activity of HMG-CoA reductase.

Intestinal cholesterol biosynthesis does not respond to the feeding of high cholesterol diets.

A **second control point** appears to be at the cyclisation of squalene and conversion to lanosterol, but details of the regulation at this step is not clear.


Acetyl CoA
Acetoacetyl CoA
HMG-CoA Synthase
3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA)
Glucagon, AMP
Sterol regulatory element-binding proteins (SREBPs)
Synthesis
HMG-CoA Reductase
2 NADPH
Rate Limiting Step
CoA + 2 NADP+
Insulin
Mevalonic Acid
Statins
3 ATP
Mevalonate Pathway
Isopentenylpyrophosphate
Squalene
Lanosterol
Cholesterol

ROLE OF HORMONES

Insulin increases HMG-CoA reductase activity.

Thyroid hormones stimulate HMG-CoA reductase activity.

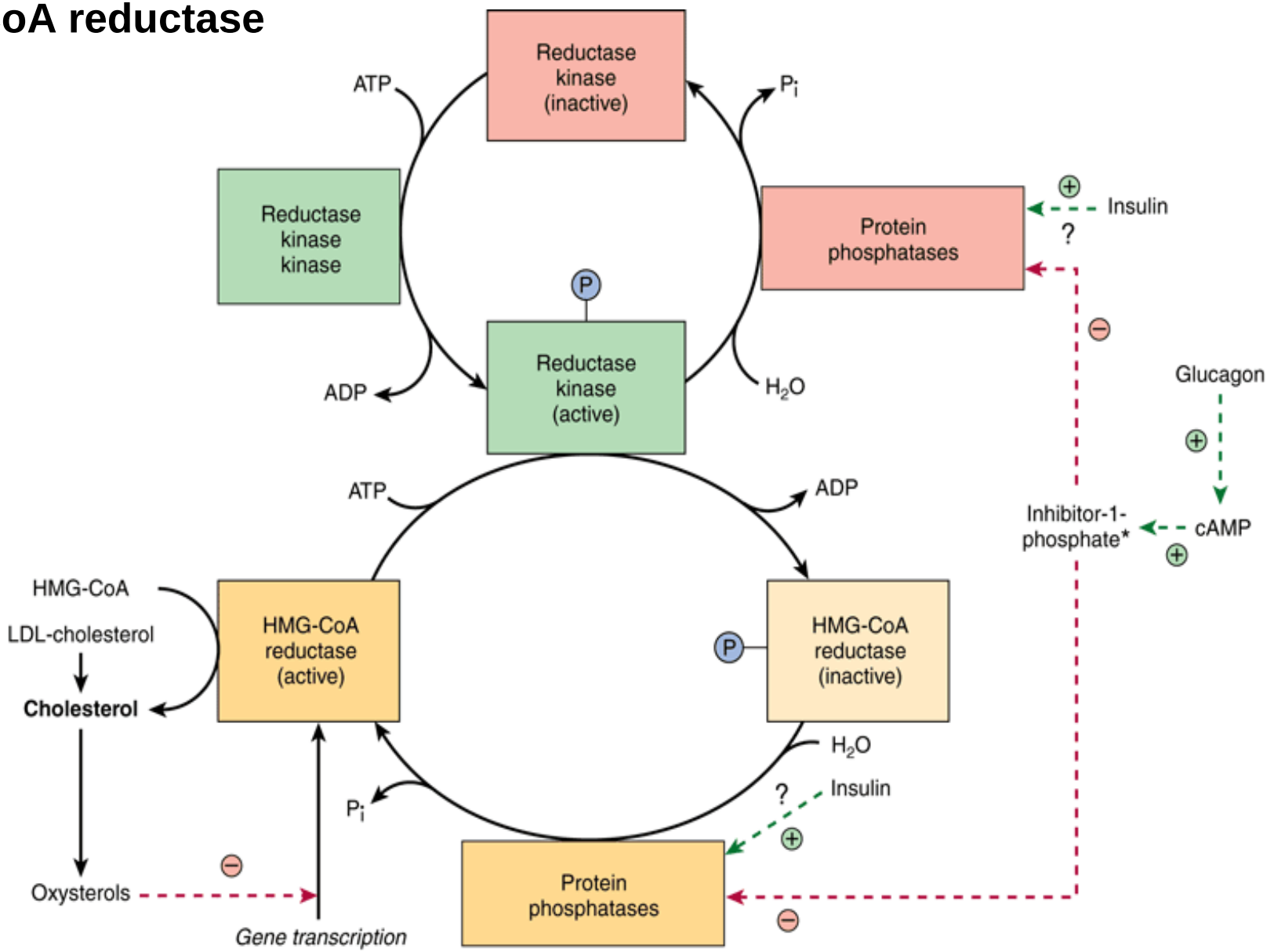
Glucagon and/glucocorticoids: decreases the activity of HMG-CoA reductase and reduces the cholesterol biosynthesis.

Role of cAMP:

HMG-CoA reductase may exist in active/inactive forms, which is reversibly modified by phosphorylation/and dephosphorylation mechanisms, which may be mediated by cAMP-dependent protein kinases.

cAMP inhibits cholesterol biosynthesis by converting HMG-CoA reductase to inactive form.

Possible mechanisms in the regulation of cholesterol synthesis by HMG-CoA reductase



Source: Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA: *Harper's Illustrated Biochemistry, 29th Edition*: www.accessmedicine.com

TRANSPORT OF CHOLESTEROL

Cholesterol in the diet is absorbed from the intestine, and are incorporated into chylomicrons and also to some extent VLDL.

The greater part of cholesterol is found in the esterified form and is transported as lipoproteins in plasma.

Highest proportion of circulating cholesterol is found in LDL **which carry cholesterol to tissues and also in HDL, which takes cholesterol to liver from tissues for degradation *(scavenging action)*.**

Free cholesterol exchanges readily between tissues and lipoproteins, whereas cholesterol esters do not exchange freely.

Some plasma cholesterol ester may be formed in HDL as a result of transesterification reaction in plasma between cholesterol and FA in position-2 of lecithin which is catalysed by the enzyme *lecithincholesterol acyl transferase* (LCAT)

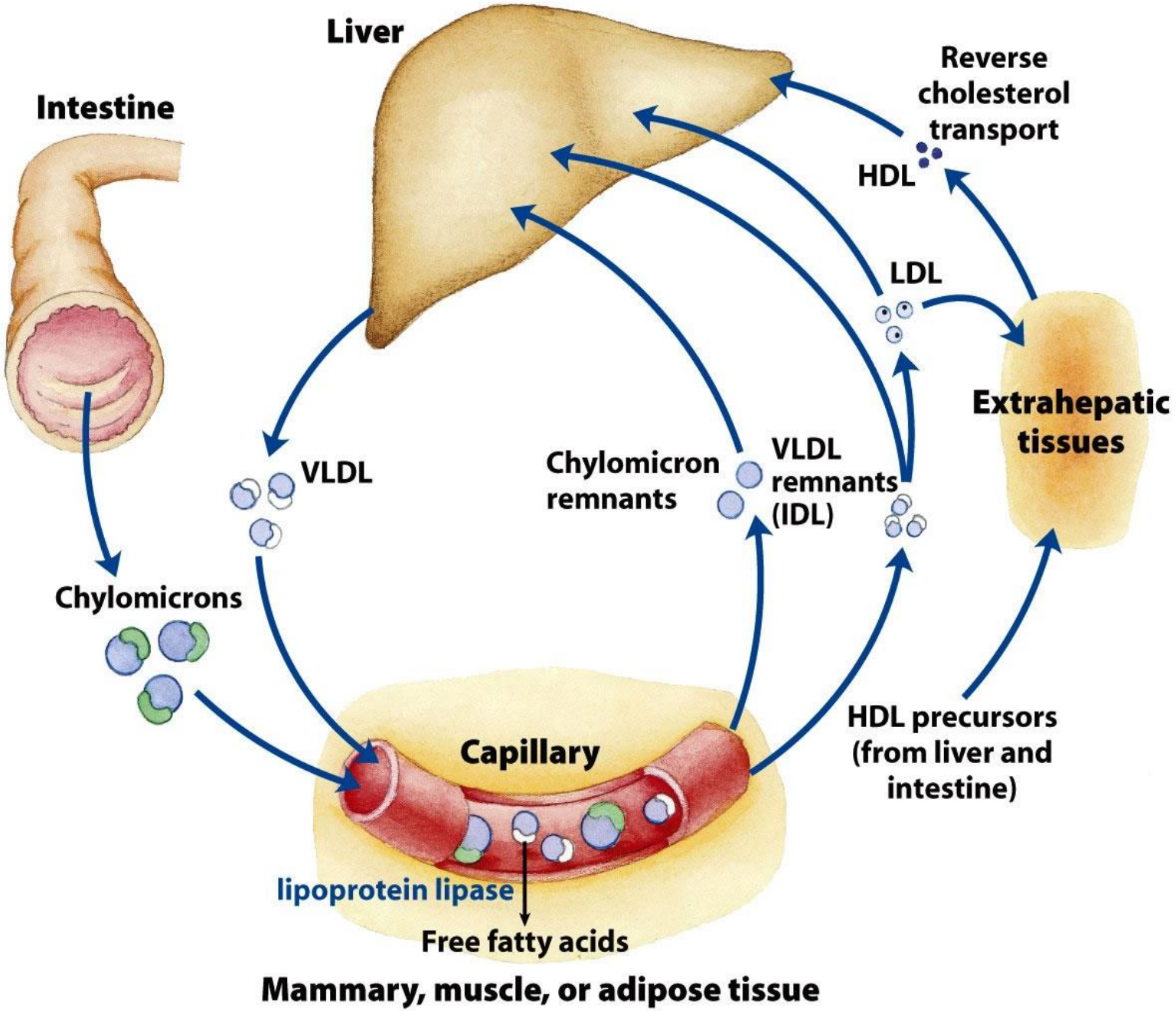
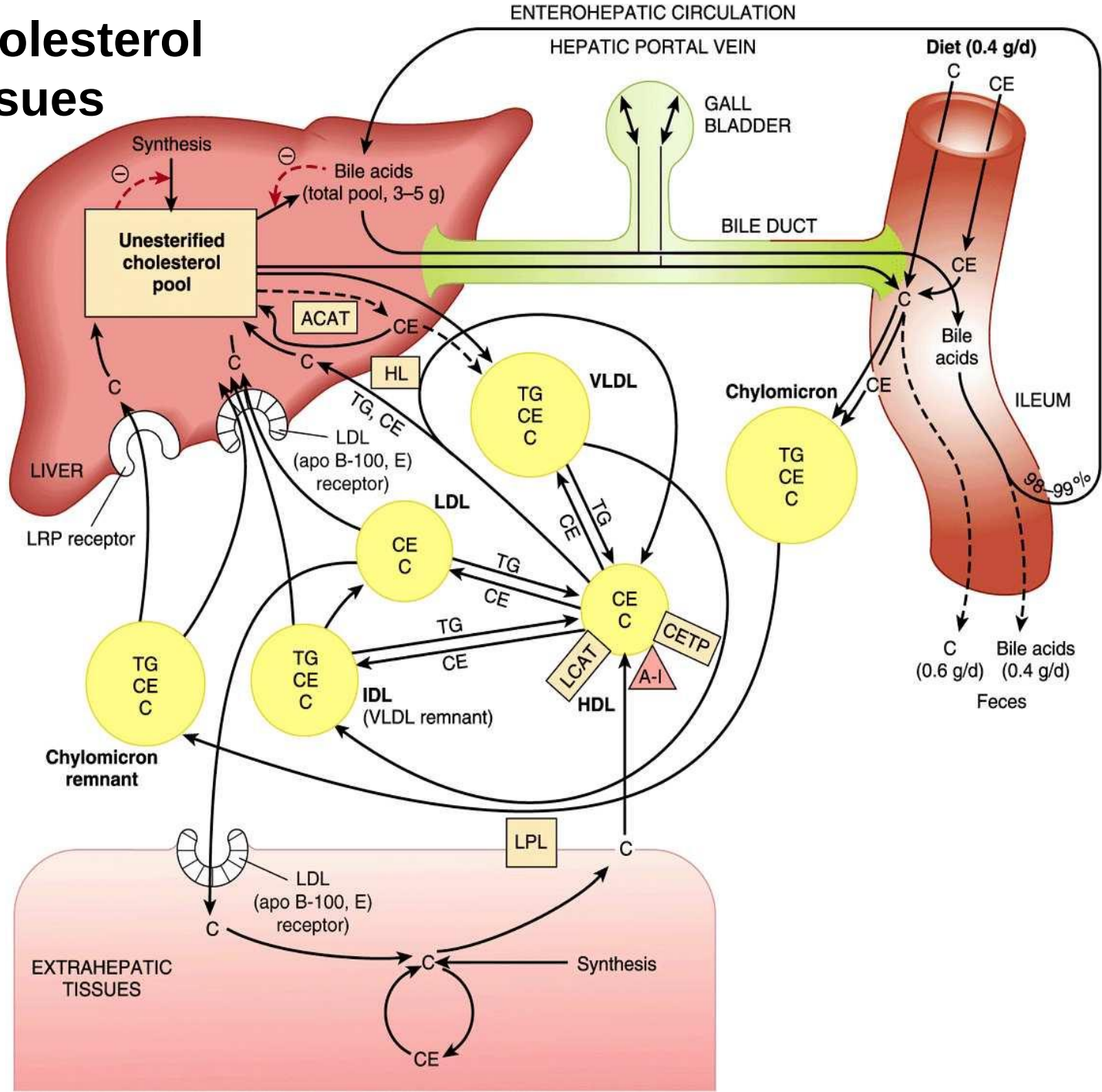


Figure 21-40a

Lehninger Principles of Biochemistry, Fifth Edition

Transport of cholesterol between the tissues in humans



Cholesterol balance in tissues:

- Increased synthesis of cholesterol.
- Hydrolysis of cholesterol ester by *cholesterol esterase*
- Uptake and delivery of cholesterol in cells by circulating LDL (by specific receptors).
- Uptake of cholesterol containing lipoproteins by 'non-receptor' mediated pathway.
- Uptake of free cholesterol by cell membranes.

- Efflux of cholesterol from cells to HDL *(scavenging action).*
- Esterification of cholesterol by the enzyme *Acyl-CoA-cholesterol acyl transferase* (ACAT).
- Utilisation of cholesterol for synthesis of steroid hormones,.
- In liver cells: formation of cholic acid.
- Formation of vit D_3.

FACTORS THAT INFLUENCE CHOLESTEROL LEVEL and SYNTHESIS

Increase	Decrease
A reduction in dietary cholesterol	Cholesterol feeding Inhibits HMG-CoA reductase
Feeding of more saturated fatty acids	Fastings/starvation inhibits HMG-CoA reductase activity
High carbohydrate diet	Administration of analogues of mevalonate or squalene
Loss of bile	Administration of cholates
Administration of plant sterols	Presence of fats and bile acids in intestinal lumen
Lack of dietary fibres	Feeding of polyunsaturated fatty acid
Pyridoxal deficiency	Increased cAMP inhibits synthesis
Insulin , thyroid hormones	Glucagon and glucocorticoids
	Hypolipidaemic drugs

PATHOLOGICAL VARIATIONS OF SERUM CHOLESTEROL

- ***Normal value:*** ***3.6-5.2 mmol/L***

- **Hypercholesterolemia:** ***in nephrotic syndrome, diabetes mellitus, obstructive jaundice, myxoedema, xanthomatous biliary cirrhosis***, ***hypopituitarism***, ***xanthomatosis, coronary thrombosis and in angina pectoris.***
- **Hypocholesterolemia**: ***in thyrotoxicosis, anaemias, haemolytic jaundice, malabsorption syndrome, wasting diseases, acute infections and in a number of terminal states.***

BILE ACIDS

- **Primary bile acids:** synthesised in the liver from cholesterol.

  They are: ***Cholic acid***

  Chenodeoxycholic acid.

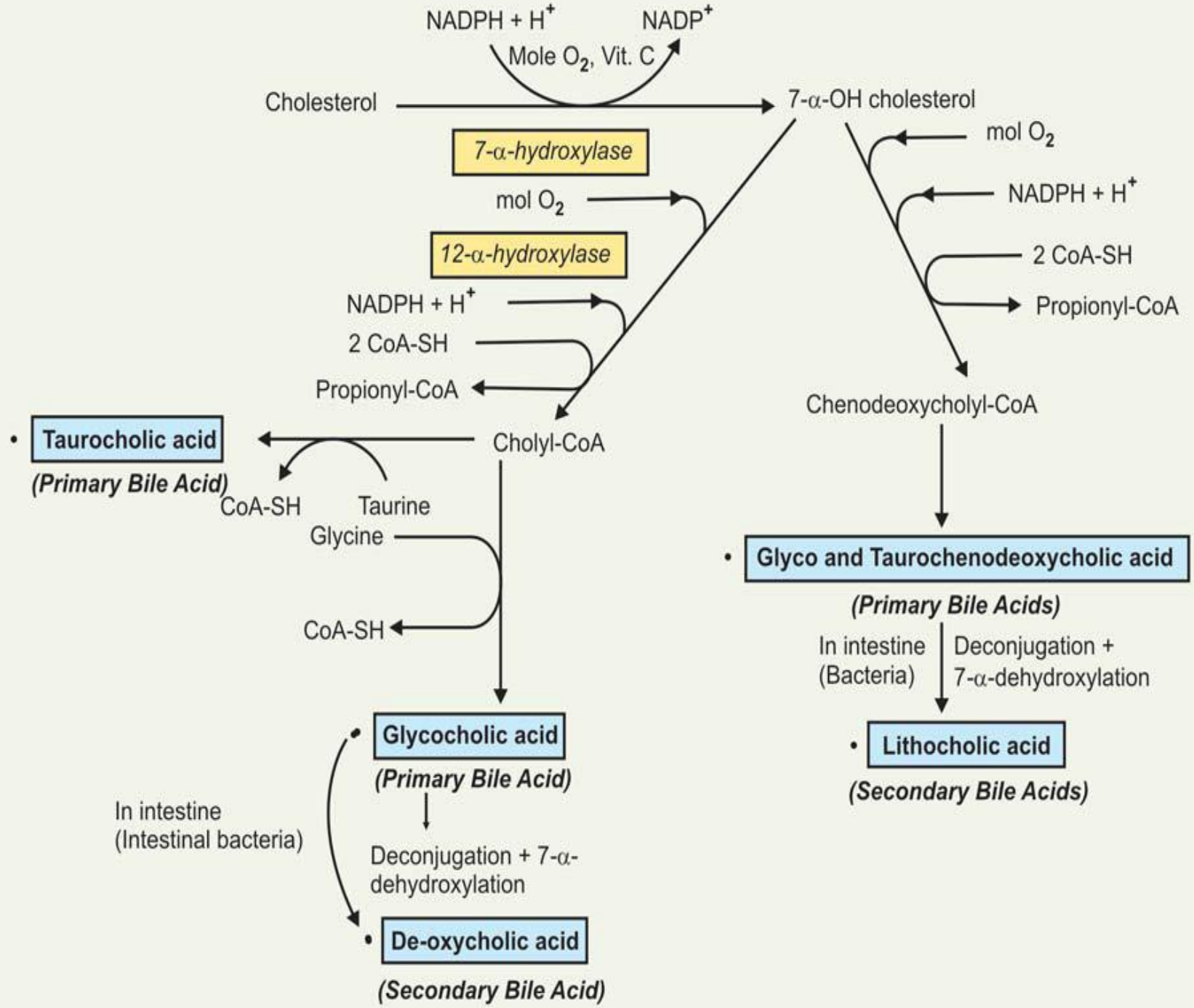
- **Secondary bile acids:** are produced in intestine from the primary bile acids by the action of intestinal bacteria.

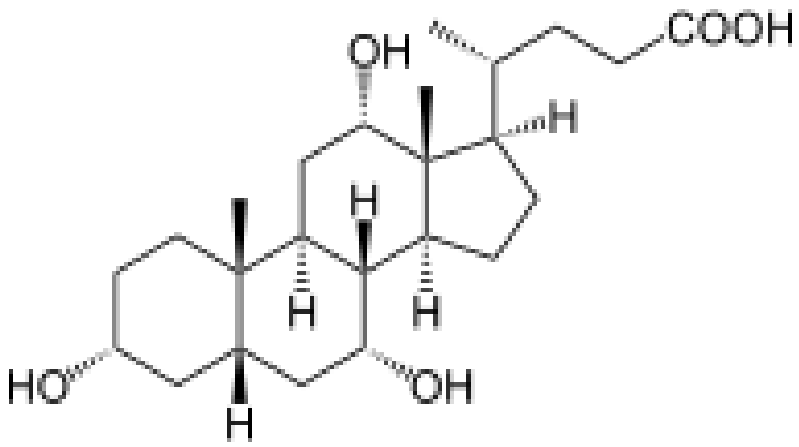
  They are: ***Deoxycholic acid***

  Lithocholic acid

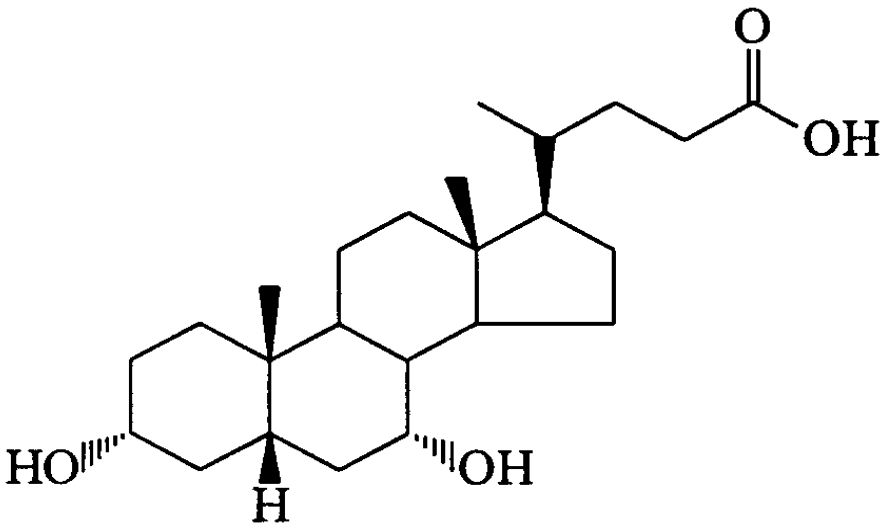
Functions of Bile Acids (Bile Salts)

- **Emulsification of fats**
- ***Accelerate the action of pancreatic lipase***
- ***Bile salts form 'micelles'* with fatty acids, mono- and diacyl glycerols and also TAG which are made water soluble and helps absorption.**
- **They aid in the absorption of fat soluble vitamins.**
- **They stimulate intestinal motility.**
- **•Bile salts keep cholesterol in solution.**

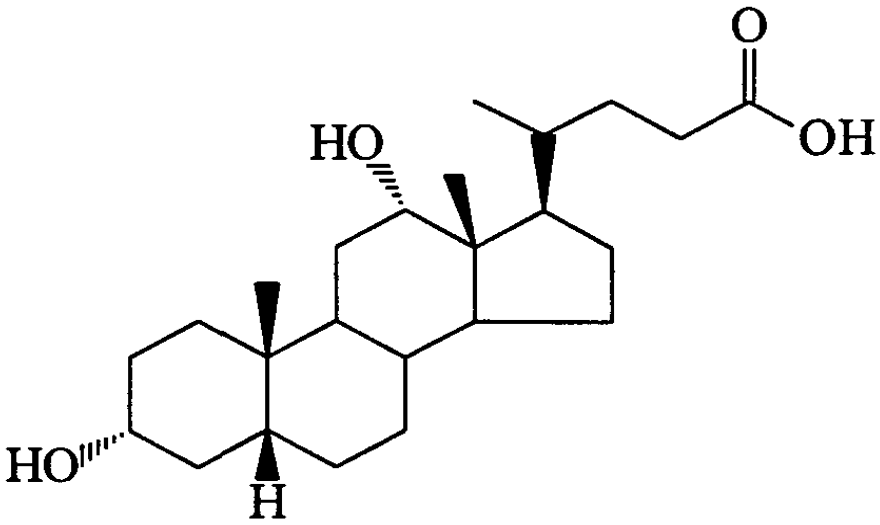

NADPH + H+
NADP+
Mole O2, Vit. C
Cholesterol
7-α-OH cholesterol
7-α-hydroxylase
mol O2
12-α-hydroxylase
NADPH + H+
2 CoA-SH
Propionyl-CoA
mol O2
NADPH + H+
2 CoA-SH
Propionyl-CoA
Chenodeoxycholyl-CoA
Cholyl-CoA
• Taurocholic acid
(Primary Bile Acid)
CoA-SH
Taurine
Glycine
CoA-SH
• Glyco and Taurochenodeoxycholic acid
(Primary Bile Acids)
In intestine (Bacteria)
Deconjugation + 7-α-dehydroxylation
• Lithocholic acid
(Secondary Bile Acids)
• Glycocholic acid
(Primary Bile Acid)
In intestine (Intestinal bacteria)
Deconjugation + 7-α-dehydroxylation
• De-oxycholic acid
(Secondary Bile Acid)



Cholic acid



Chenodeoxycholic Acid

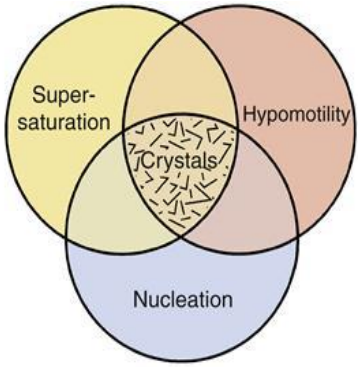


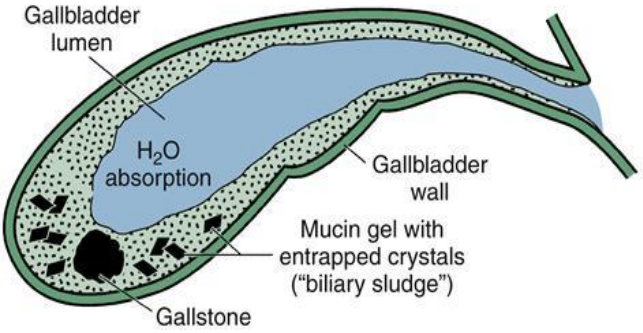
Deoxycholic Acid

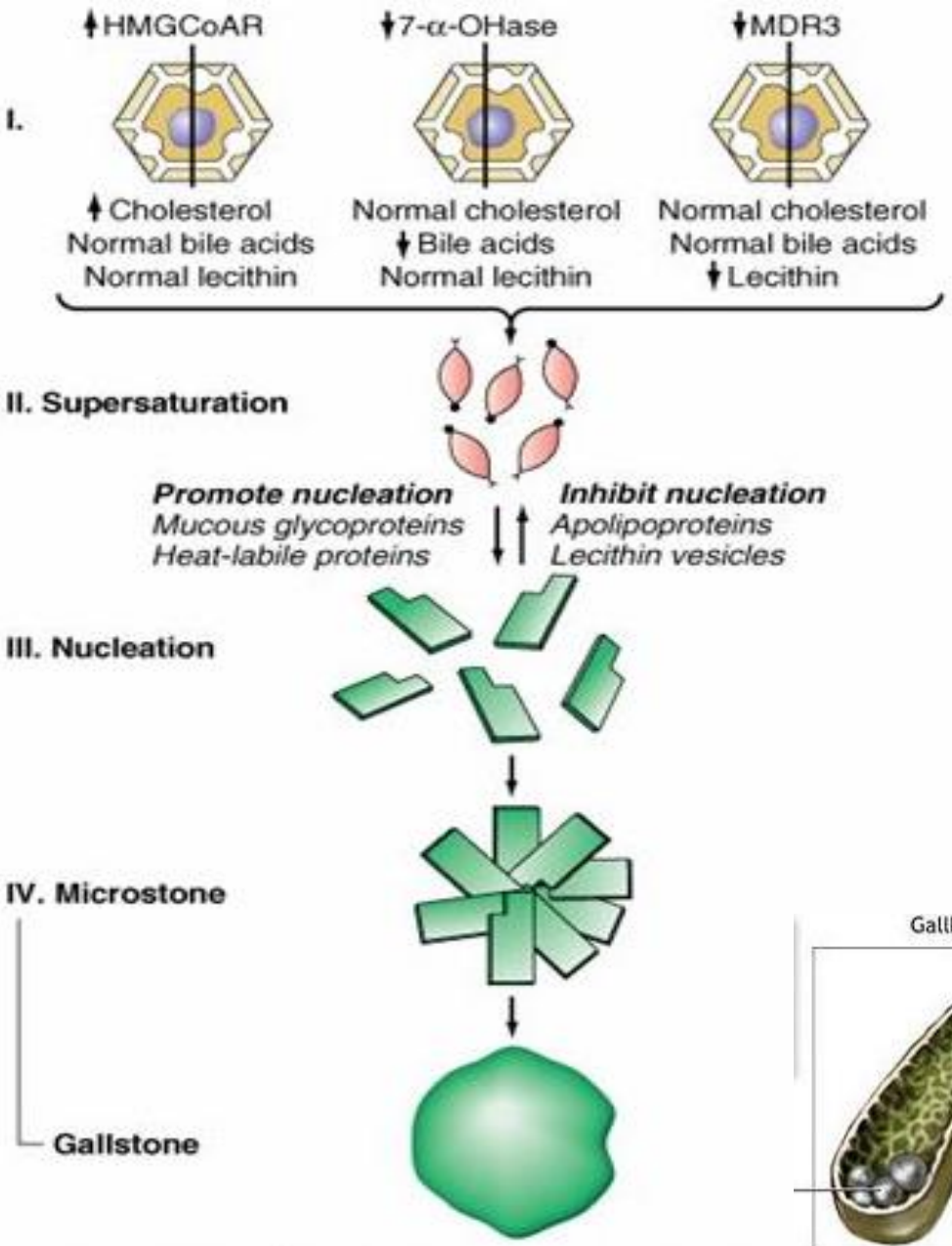
Bile salts keep cholesterol in solution in gallbladder bile.

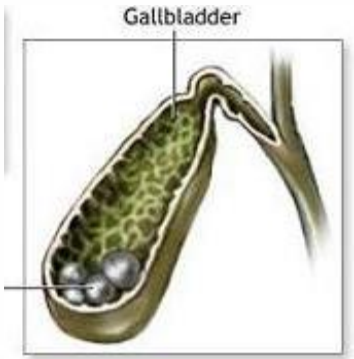
In the absence of bile salts, cholesterol may get precipitated producing **gallstones**.

Cholelithiasis









Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J:
Harrison's Principles of Internal Medicine, 17th Edition: http://www.accessmedicine.com

Conditions which Favour Stone Formation

1. Infection favours stone formation.

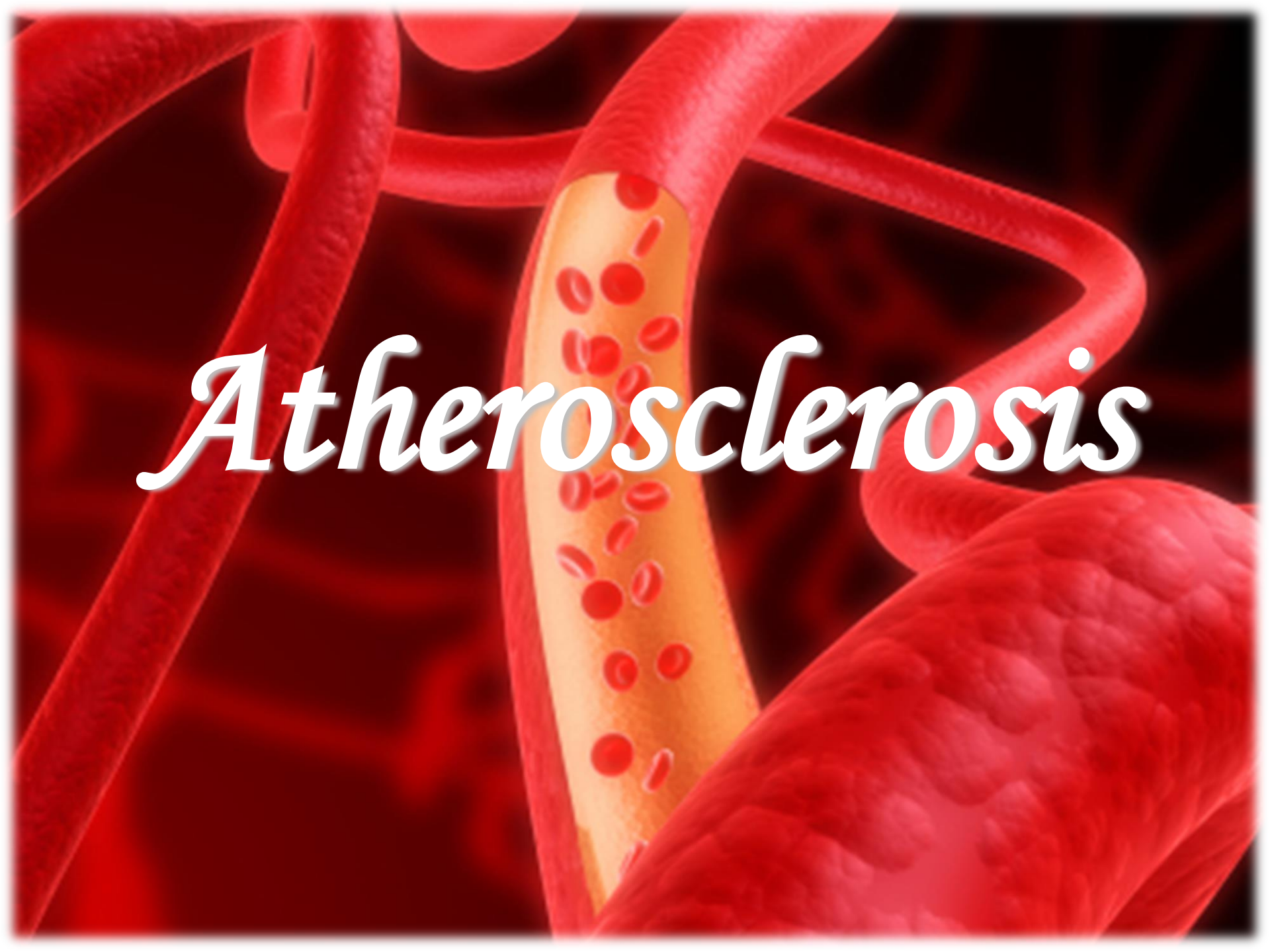
Infection causes:

- Deconjugation of bile acids leading to decrease in solubility.
- Production of phospholipase, which converts lecithin to lysolecithin.

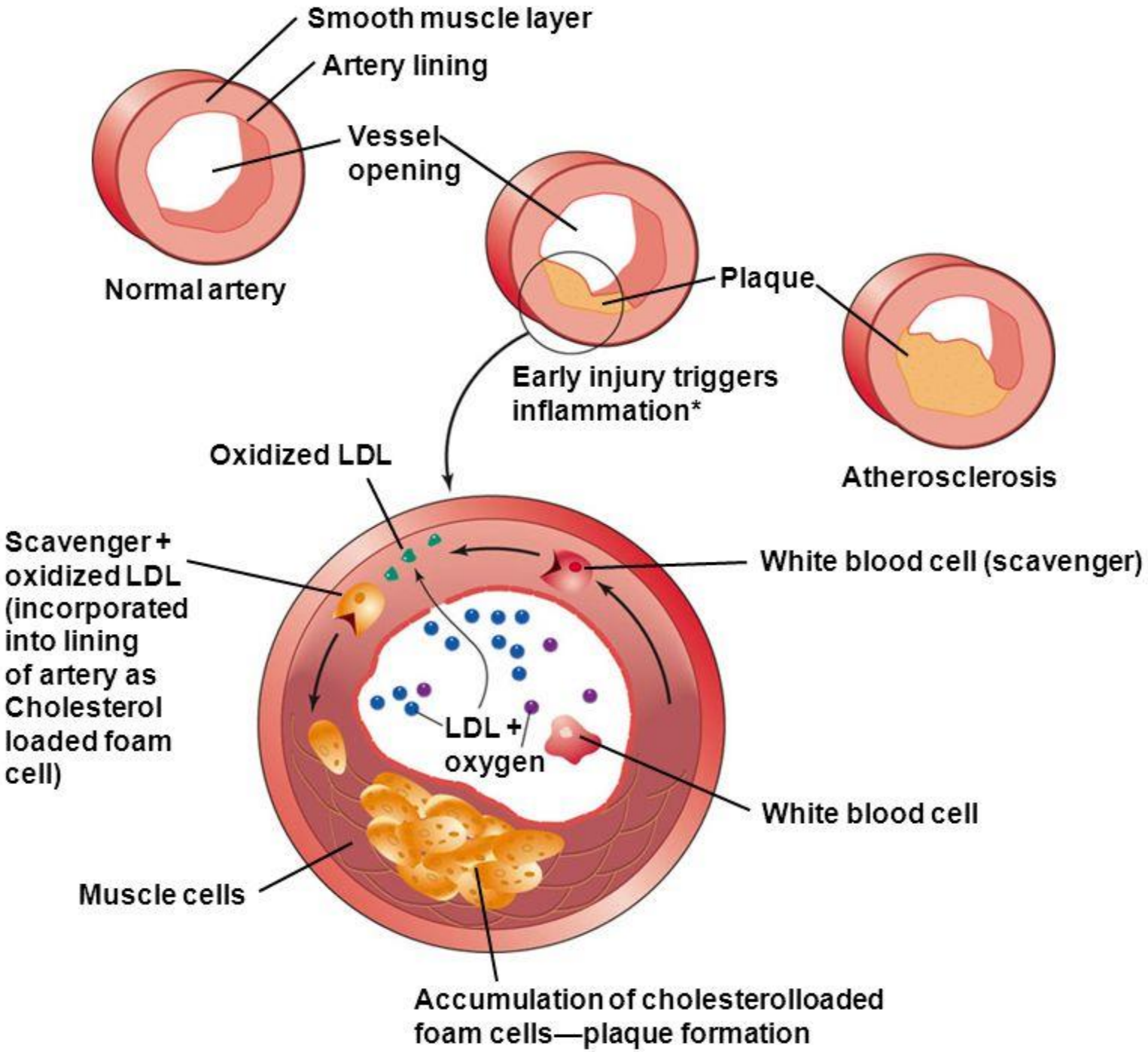
Thus, the ratio cholesterol/bile acids is disturbed leading to precipitation of cholesterol.

2. Reduction in bile salt pool:

- Defect in enterohepatic circulation.
- Disease of terminal ileum.
- In patients with cirrhosis liver


Atherosclerosis

Atherosclerosis is characterized by the deposition of cholesterol and cholesteryl esters from the plasma into the artery wall


Smooth muscle layer
Artery lining
Vessel opening
Normal artery
Plaque
Early injury triggers inflammation*
Atherosclerosis
Oxidized LDL
Scavenger + oxidized LDL (incorporated into lining of artery as Cholesterol loaded foam cell)
White blood cell (scavenger)
LDL + oxygen
White blood cell
Muscle cells
Accumulation of cholesterolloaded foam cells—plaque formation

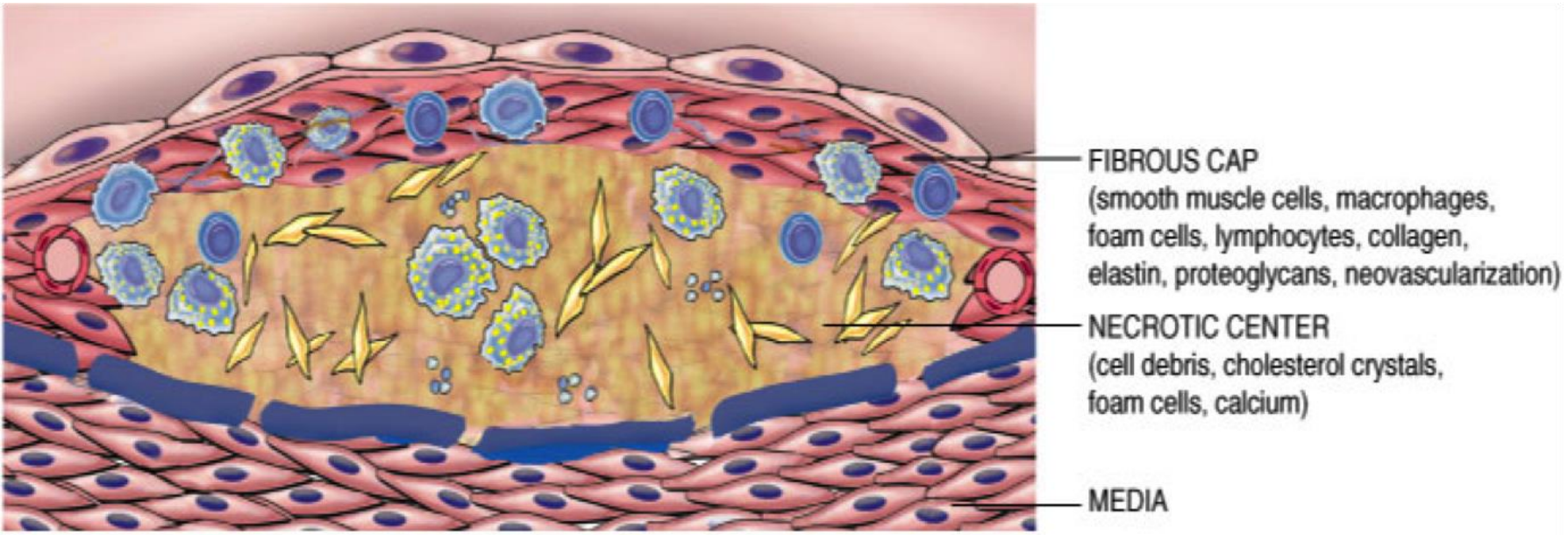
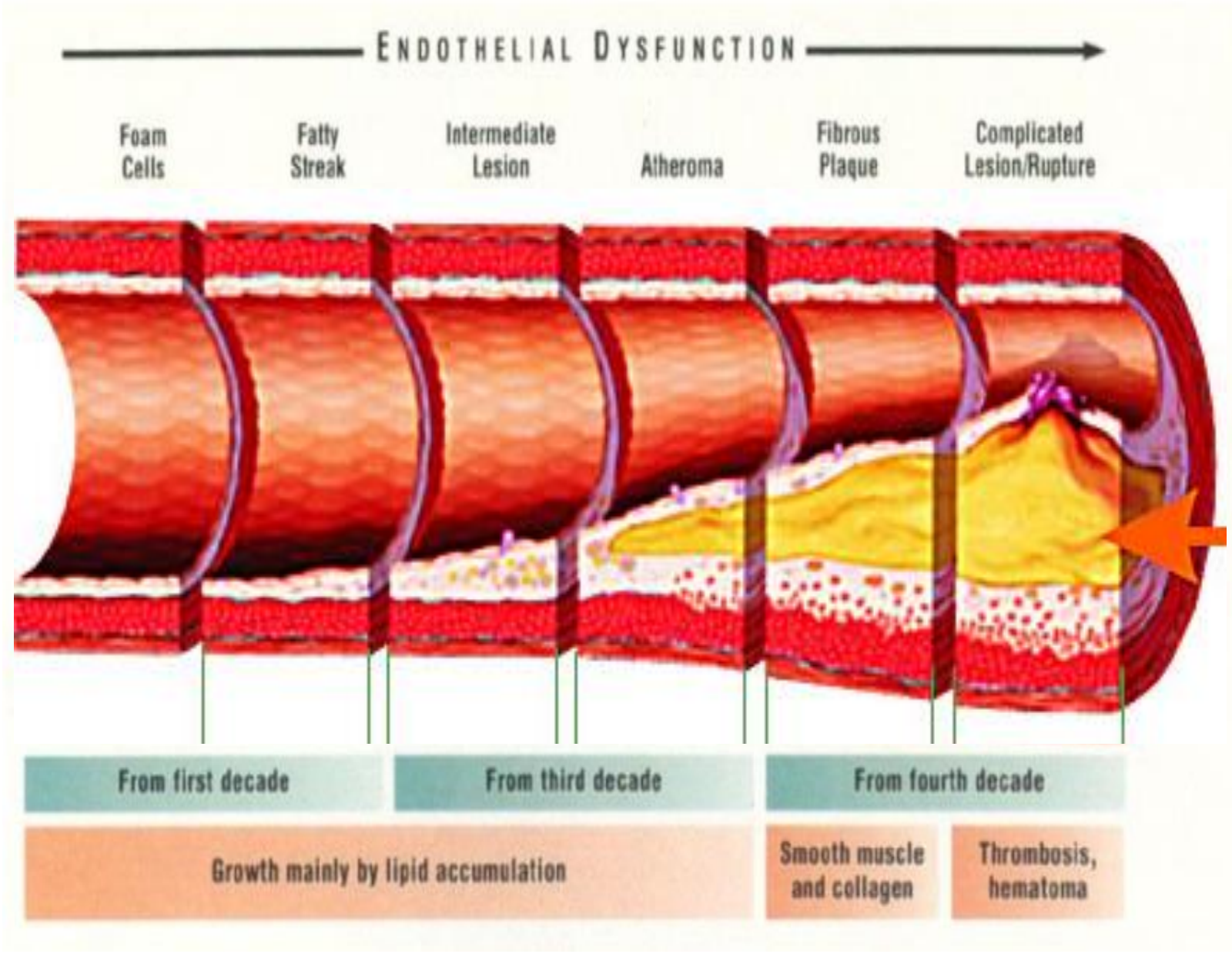
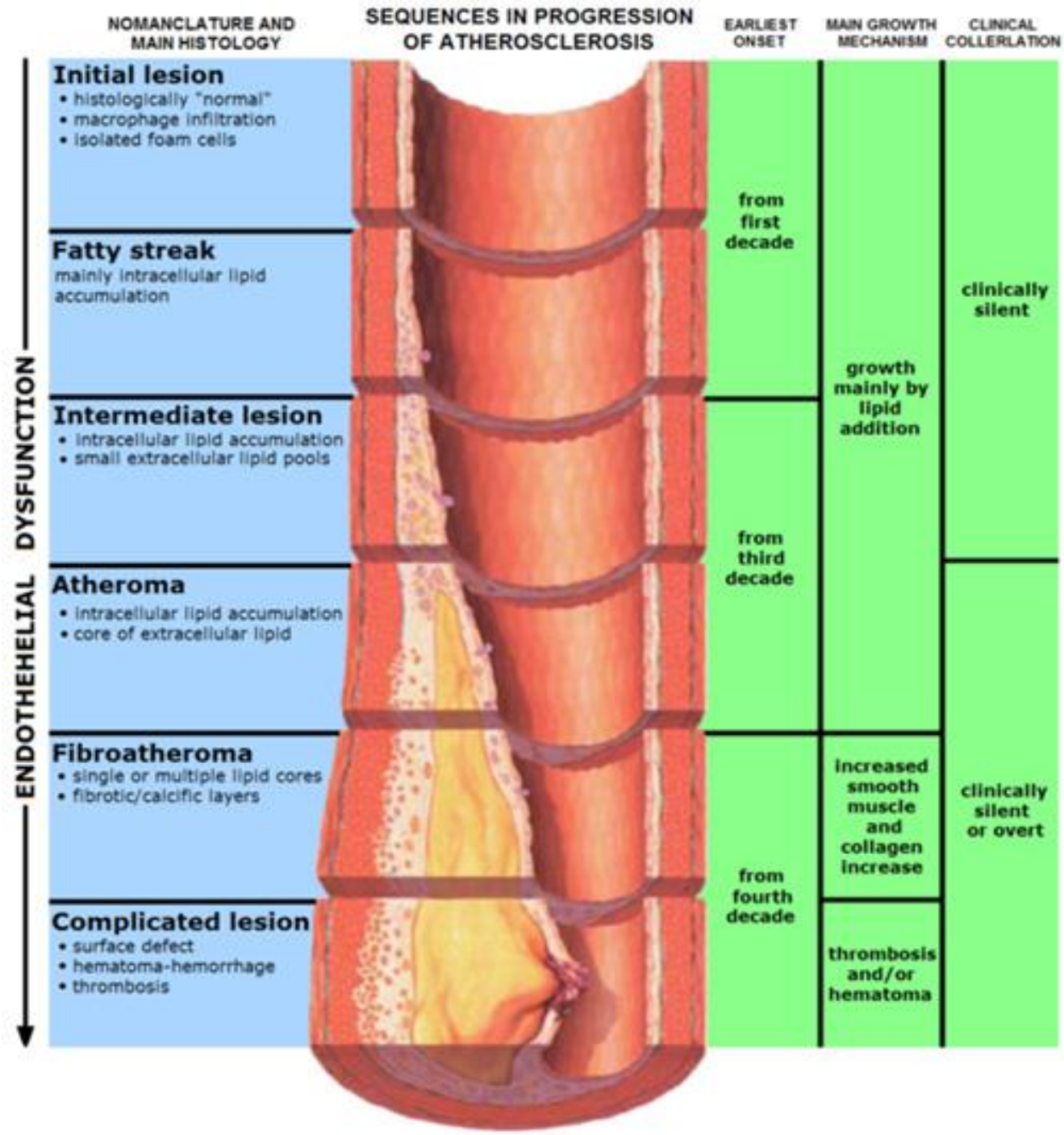
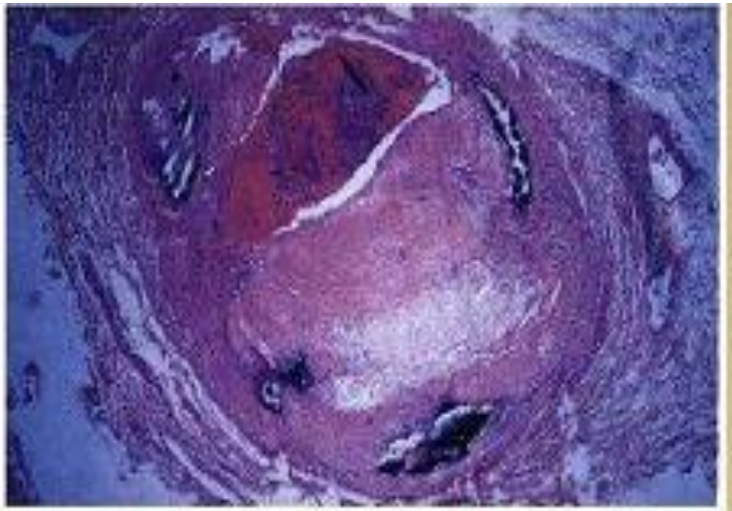
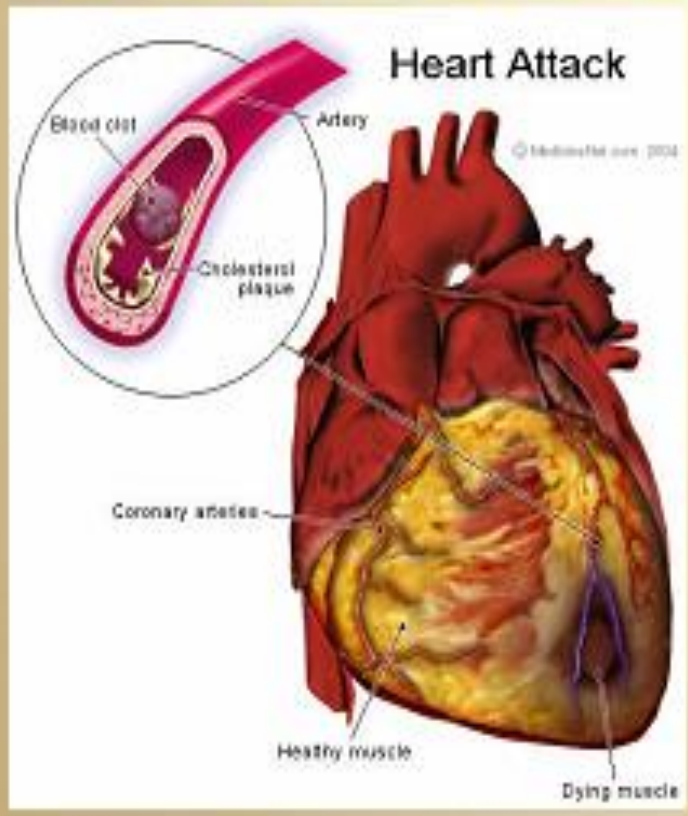


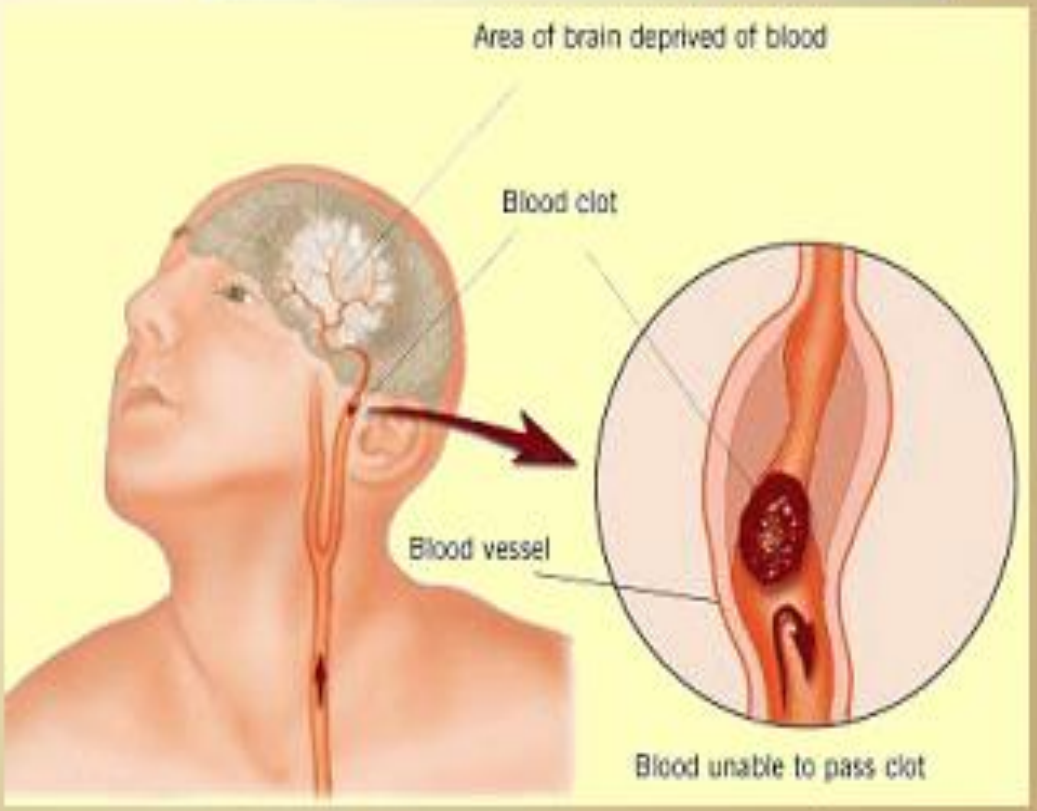
Fig. 10–3. The major components of a well-developed intimal atheromatous plaque overlying an intact media.


ENDOTHELIAL DYSFUNCTION
Foam Cells
Fatty Streak
Intermediate Lesion
Atheroma
Fibrous Plaque
Complicated Lesion/Rupture
From first decade
From third decade
From fourth decade
Growth mainly by lipid accumulation
Smooth muscle and collagen
Thrombosis, hematoma


NOMANCLATURE AND MAIN HISTOLOGY
SEQUENCES IN PROGRESSION OF ATHEROSCLEROSIS
EARLIEST ONSET
MAIN GROWTH MECHANISM
CLINICAL COLLERLATION
ENDOTHEHELIAL DYSFUNCTION
Initial lesion
• histologically "normal"
• macrophage infiltration
• isolated foam cells
Fatty streak
mainly intracellular lipid accumulation
Intermediate lesion
• intracellular lipid accumulation
• small extracellular lipid pools
Atheroma
• intracellular lipid accumulation
• core of extracellular lipid
Fibroatheroma
• single or multiple lipid cores
• fibrotic/calcific layers
Complicated lesion
• surface defect
• hematoma-hemorrhage
• thrombosis
from first decade
from third decade
from fourth decade
growth mainly by lipid addition
increased smooth muscle and collagen increase
thrombosis and/or hematoma
clinically silent
clinically silent or overt




Heart Attack
Blood clot
Artery
Cholesterol plaque
Coronary arteries
Healthy muscle
Dying muscle


Area of brain deprived of blood
Blood clot
Blood vessel
Blood unable to pass clot

Atherosclerosis

Men more suffer a atherosclerosis than women

Complications

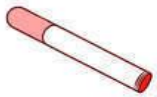
Stroke

Heart attack

Gangrene

Risk

Diabetes



Smoking

Vitamin B6 deficiency

Advanced age

Obesity

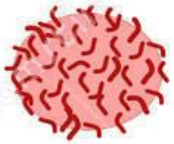
Male sex

Genetic abnormalities

Sedentary lifestyle

Unhealthy food

Hypertension

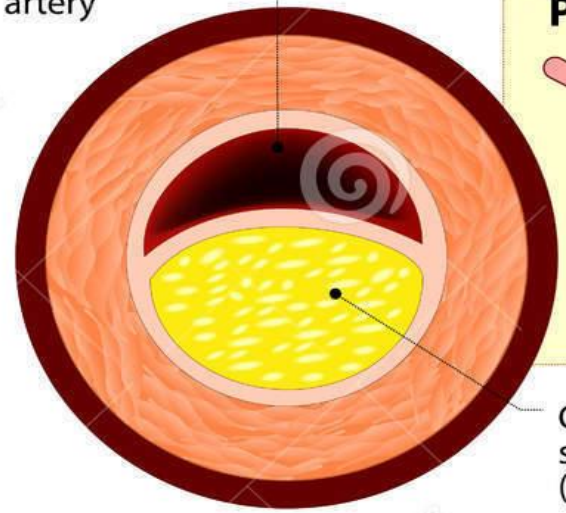


White blood cells

Postmenopausal estrogen deficiency

Chlamydia pneumoniae

Narrowed artery



Cholesterol substances (plaques)

Prevention & Treatment

Weight loss

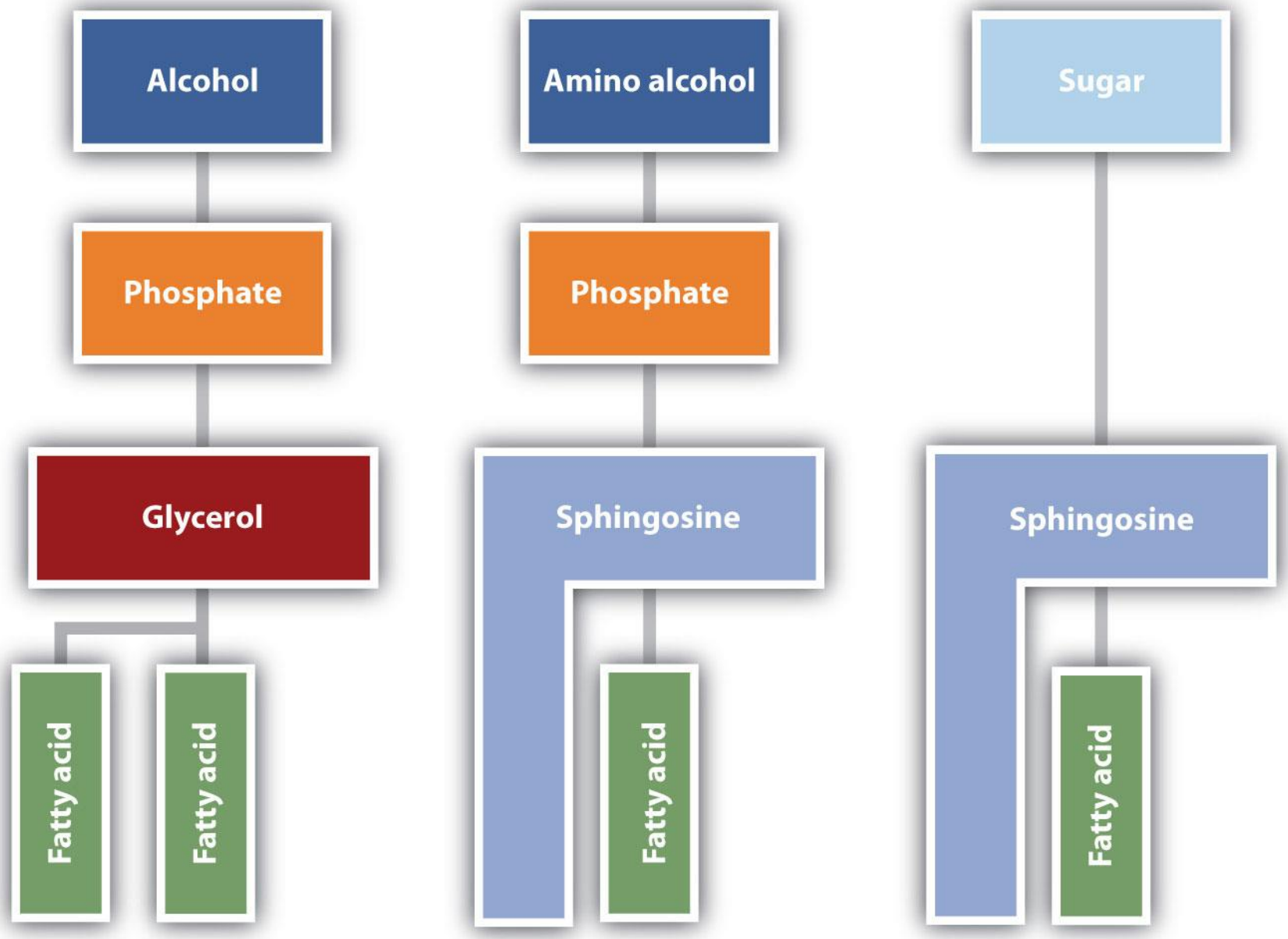
Exercise

Diet

Fat

Metabolism

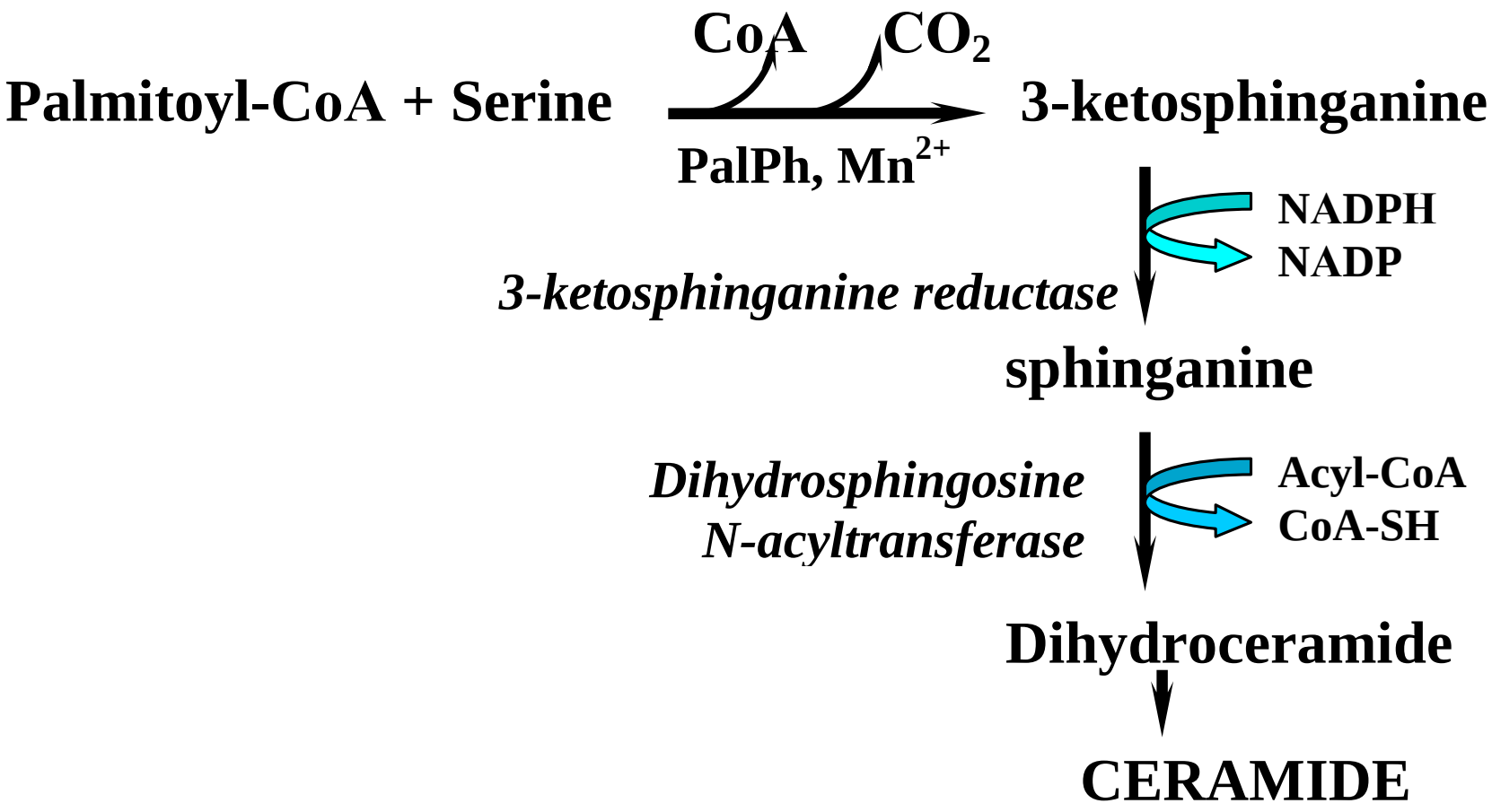
of sphingolipids



Phosphoglyceride (a phospholipid)

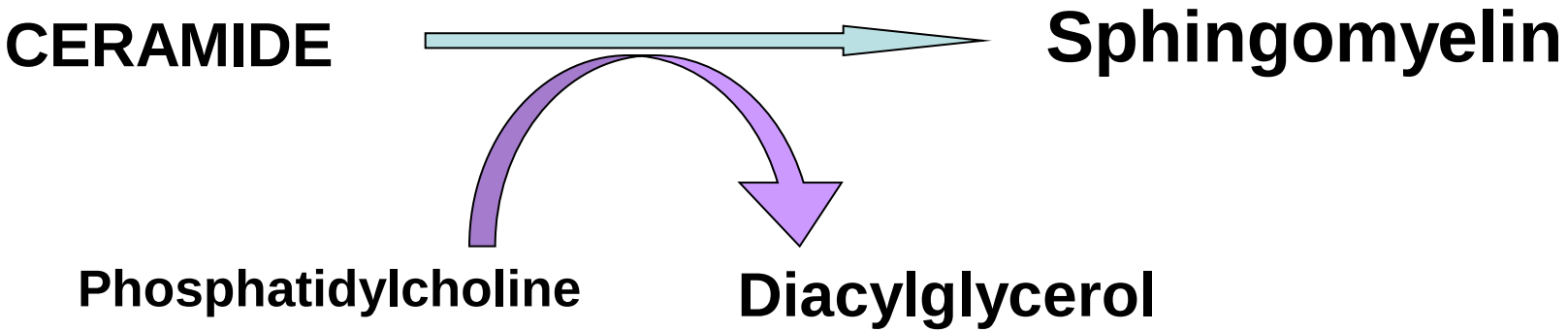
Sphingomyelin (both a phospholipid and a sphingolipid)

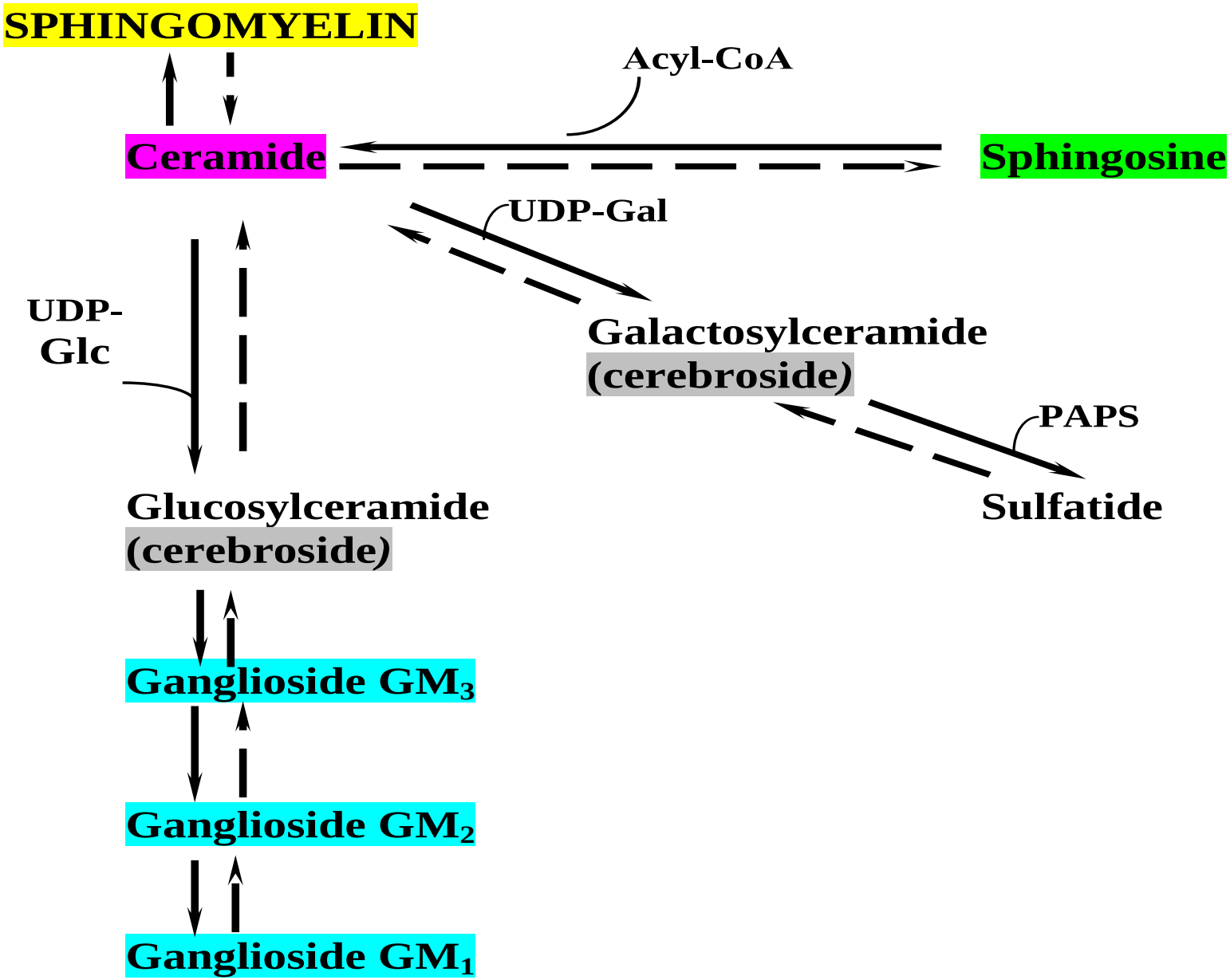
Cerebroside (both a sphingolipid and a glycolipid)



Biosynthesis of ceramide

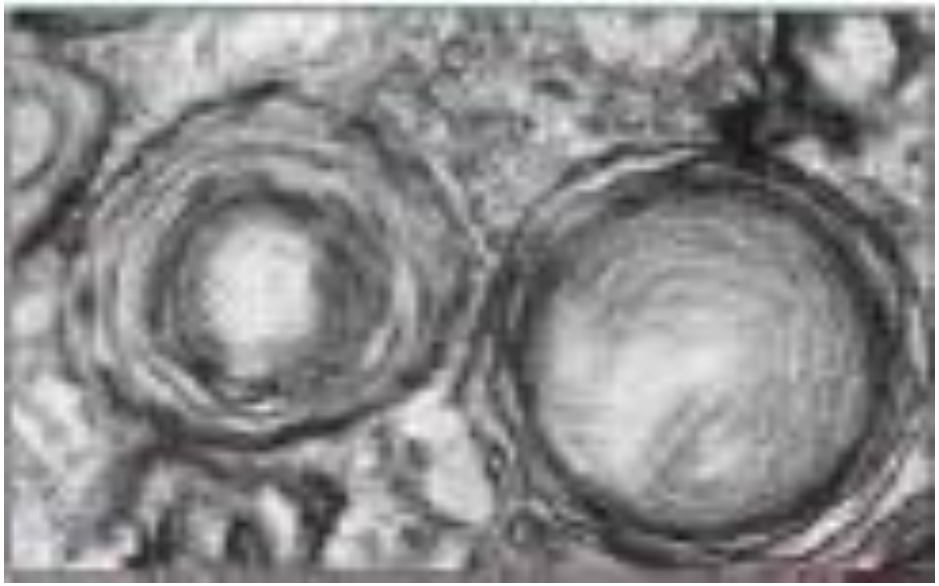
Biosynthesis of sphingomyelin

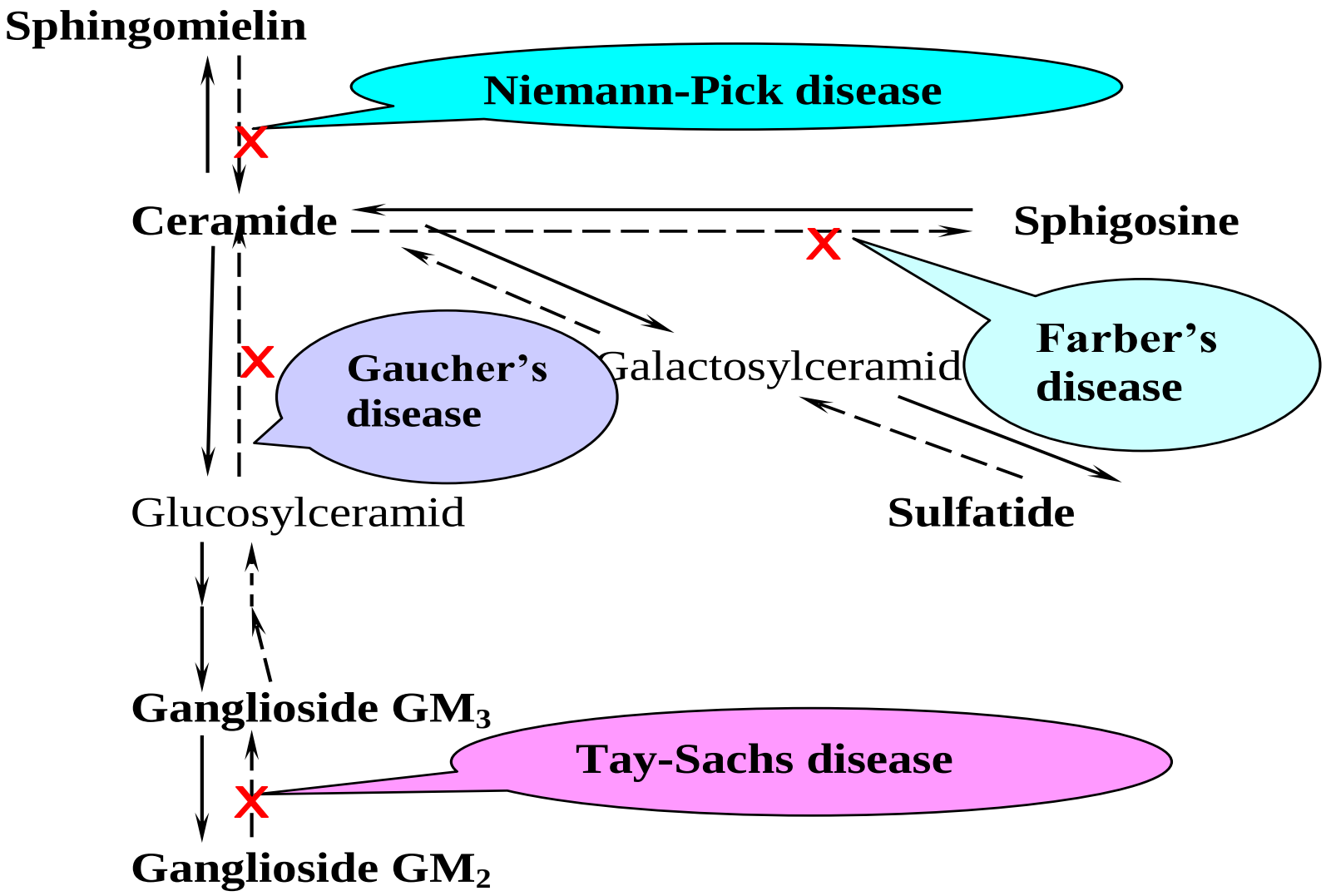



SPHINGOMYELIN
Acyl-CoA
Ceramide
Sphingosine
UDP-Gal
UDP-
Glc
Galactosylceramide
(cerebroside)
PAPS
Sulfatide
Glucosylceramide
(cerebroside)
Ganglioside GM3
Ganglioside GM2
Ganglioside GM1

Sphingolipidoses
(Lipid storage diseases)

A group of inherited diseases that are often manifested in childhood.




Sphingomielin
Niemann-Pick disease
Ceramide
Sphigosine
Gaucher's disease
Galactosylceramid
Farber's disease
Glucosylceramid
Sulfatide
Ganglioside GM3
Tay-Sachs disease
Ganglioside GM2

Treatment

There is no effective treatment for many of these diseases.

Recently some success has been achieved with enzymes that have been chemically modified to ensure binding to receptors of target cells, e.g. to macrophages in the liver in order to deliver β-glucosidase (glucocerebrosidase) in the treatment of Gaucher's disease.

A recent promising approach is substrate reduction therapy to inhibit the synthesis of sphingolipids.

Gene therapy for lysosomal disorders is currently under investigation.

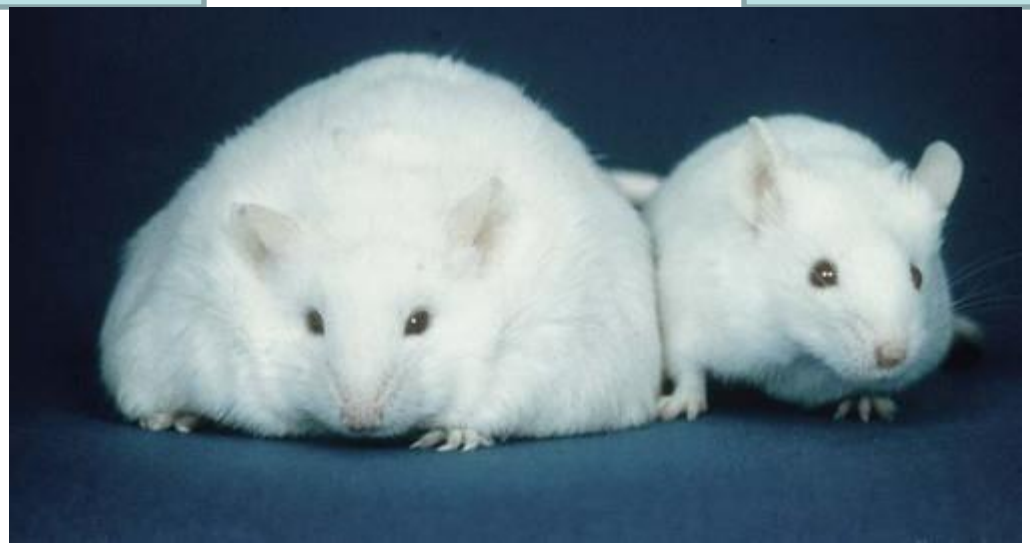
Obesity

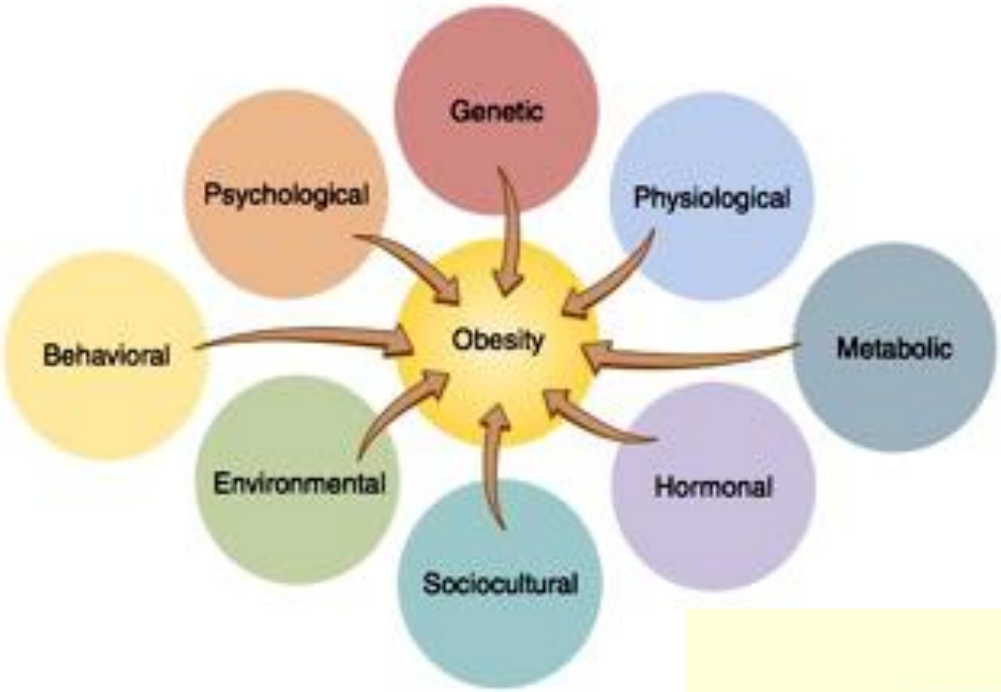
a condition where the body weight by 20 % is more than ideal for a given individual

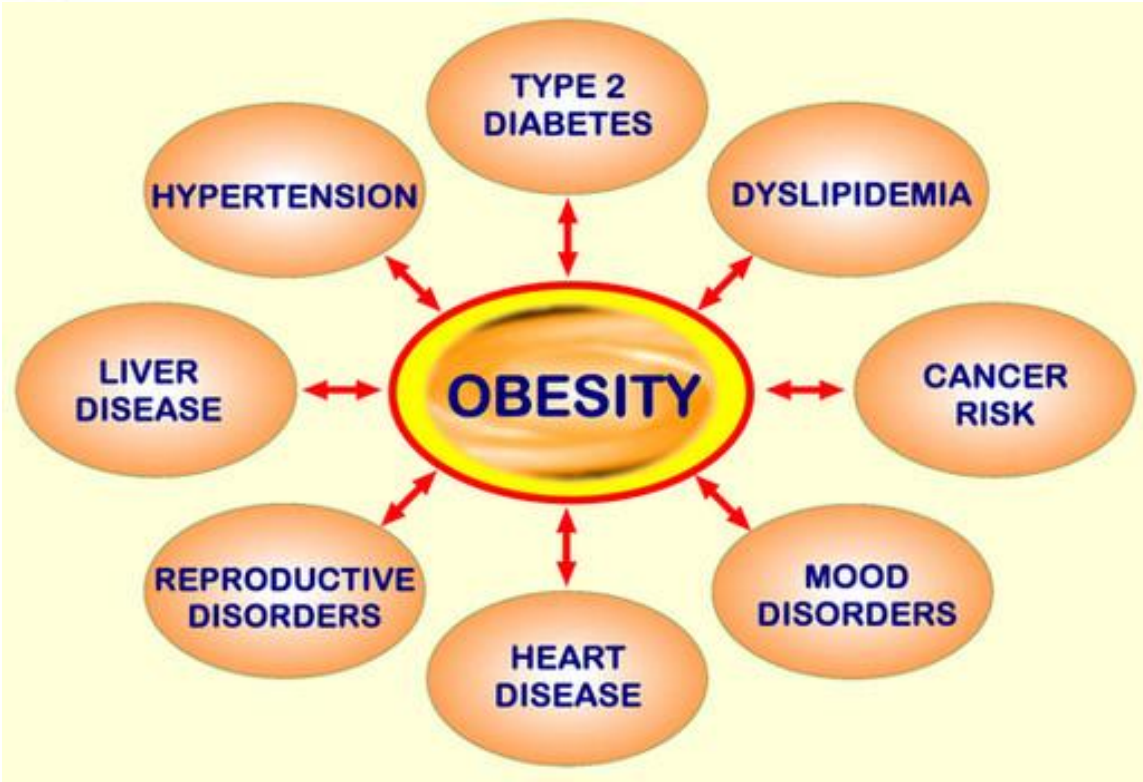
Obesity

Hyperplastic
increasing of total number of adipocytes

Hypertrophic
enlarged size of adipocytes




Genetic
Psychological
Physiological
Behavioral
Obesity
Metabolic
Environmental
Hormonal
Sociocultural


TYPE 2 DIABETES
HYPERTENSION
DYSLIPIDEMIA
LIVER DISEASE
OBESITY
CANCER RISK
REPRODUCTIVE DISORDERS
MOOD DISORDERS
HEART DISEASE

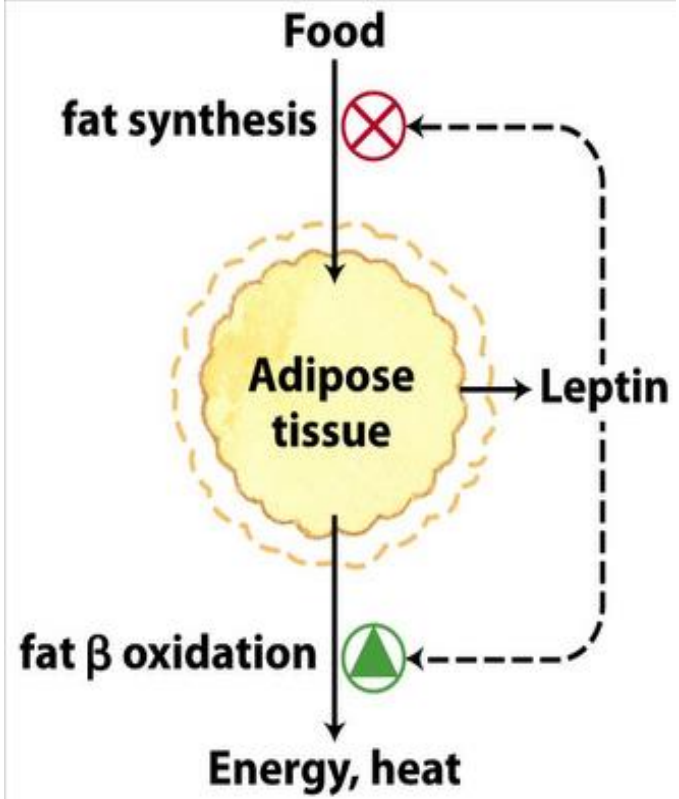
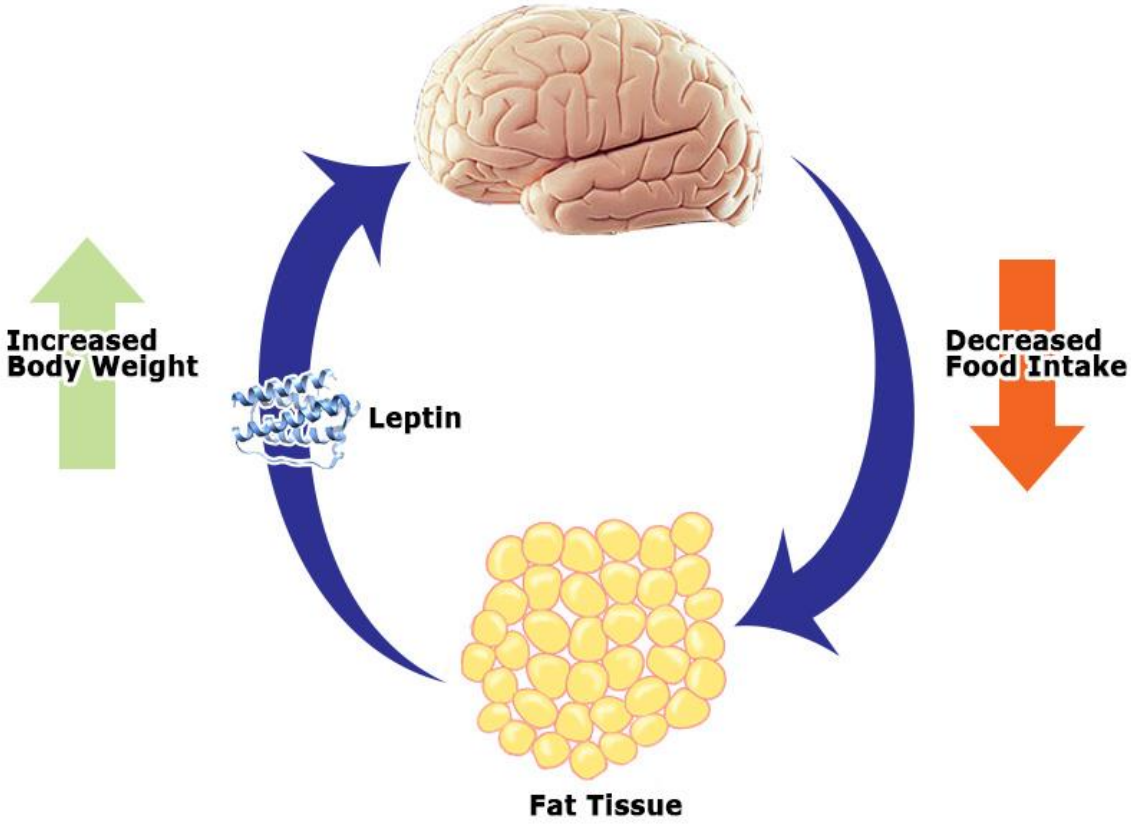
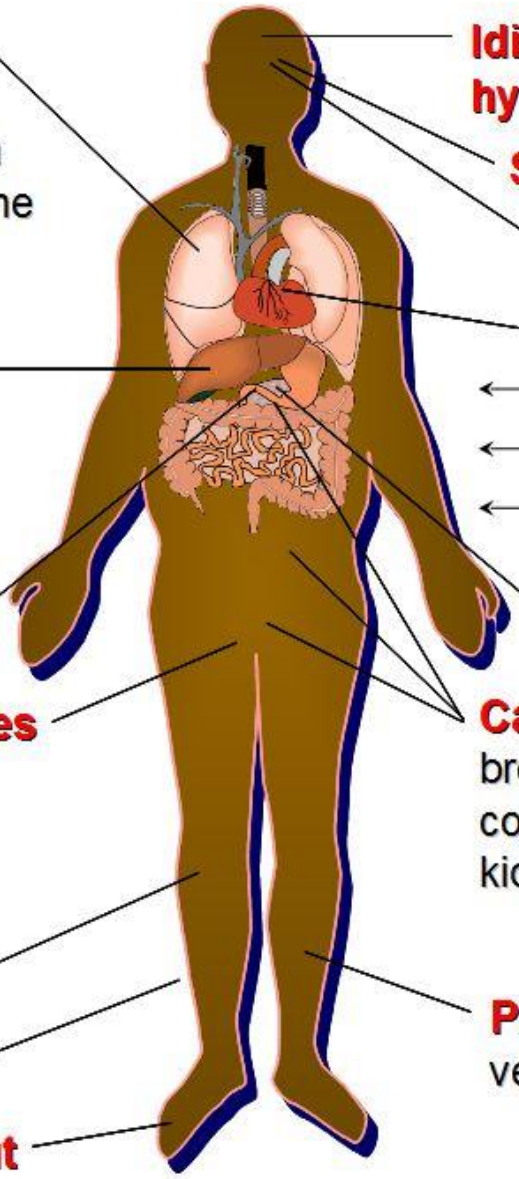


Figure 23-33
Lehninger Principles of Biochemistry, Fifth Edition



Medical Complications of Obesity



Pulmonary disease
abnormal function
obstructive sleep apnea
hypoventilation syndrome

Nonalcoholic fatty liver disease
steatosis
steatohepatitis
cirrhosis

Gall bladder disease

Gynecologic abnormalities
abnormal menses
infertility
polycystic ovarian syndrome

Osteoarthritis

Skin

Gout

Idiopathic intracranial hypertension

Stroke

Cataracts

Coronary heart disease

Diabetes

Dyslipidemia

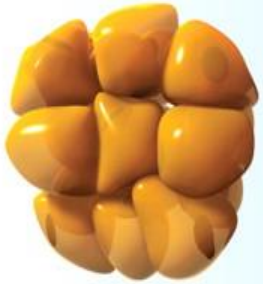
Hypertension

Severe pancreatitis

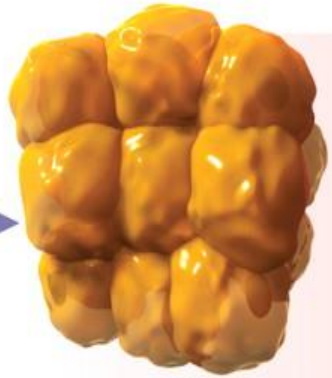
Cancer
breast, uterus, cervix
colon, esophagus, pancreas
kidney, prostate

Phlebitis
venous stasis

Positive energy balance → Subcutaneous adipose tissue expansion



- Adipogenesis intact (minimal hypertrophy)
- Sufficient storage capacity
- Functional adipose tissue
- Metabolically healthy (no inflammation)
- Insulin sensitive



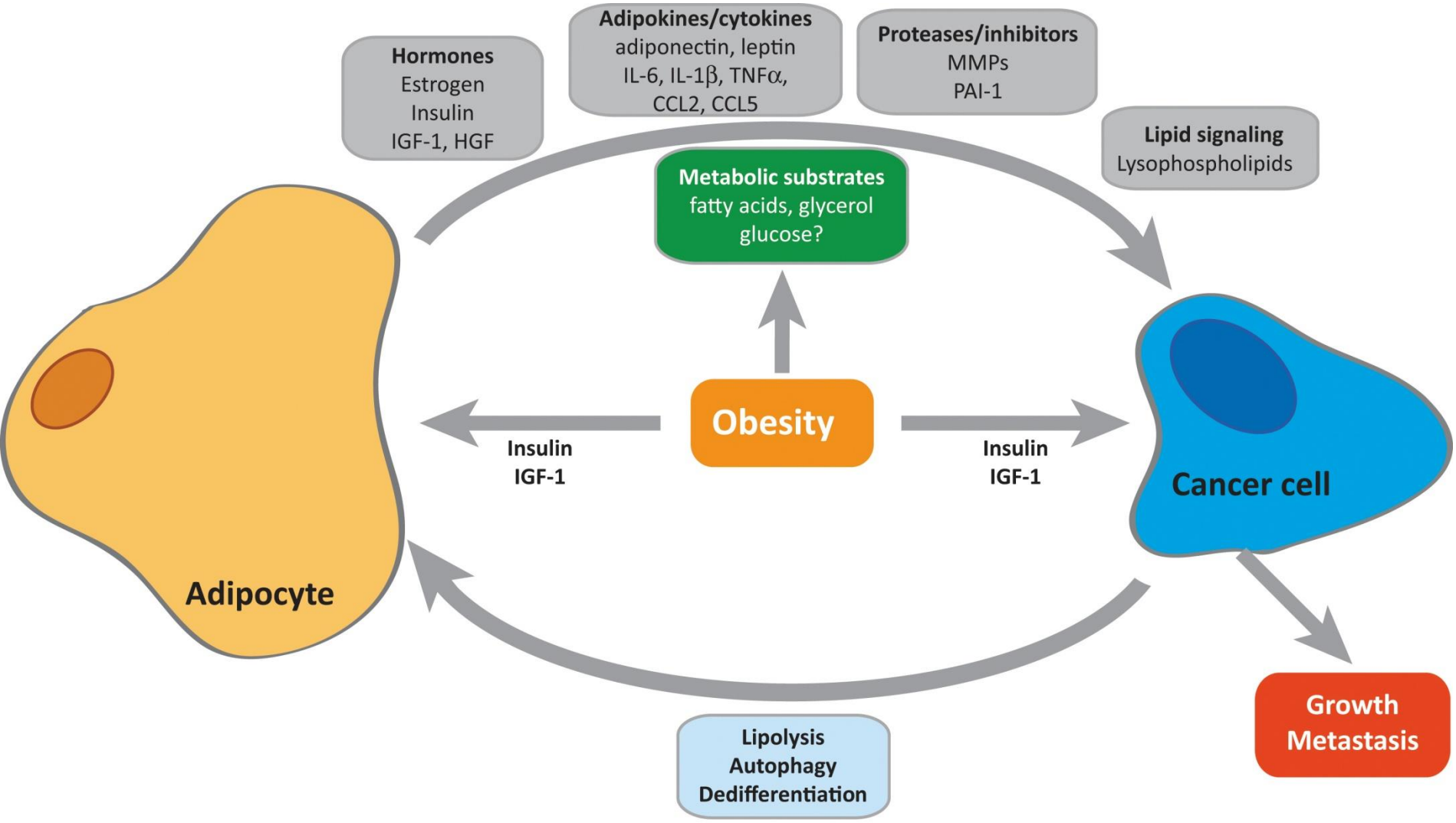
- Decreased adipogenesis; leads to adipocyte hypertrophy in the abdomen, thorax and possibly breasts
- Dysfunctional adipose tissue:
  - Storage capacity compromised
  - Increased lipolysis
  - Low-grade inflammation
  - Insulin resistance

Increased visceral adipose tissue → Free fatty acids

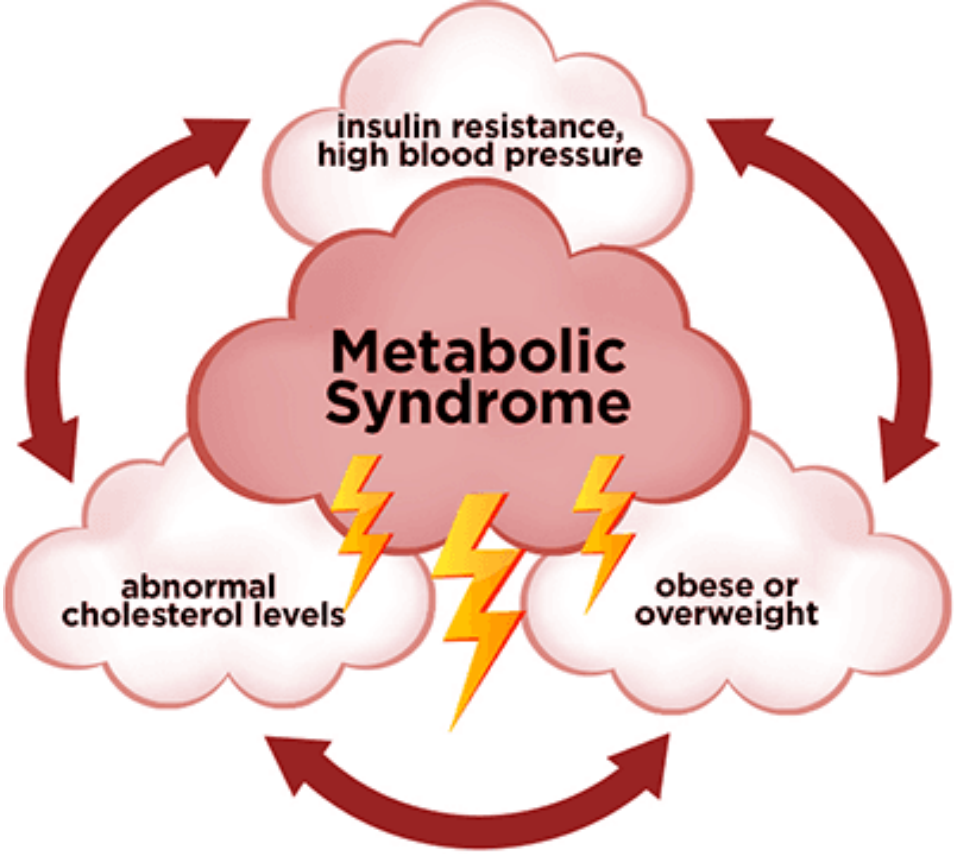
Increased visceral adipose tissue → Pro-inflammatory adipokine profile

Free fatty acids → Inflammation and malfunction of liver, skeletal muscle and islet insulin-secreting beta cells

Pro-inflammatory adipokine profile → Inflammation and malfunction of liver, skeletal muscle and islet insulin-secreting beta cells



Trends in Molecular Medicine



Metabolic syndrome is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function.

It is a risk factor for coronary heart disease, as well as diabetes, fatty liver, and several cancers.

Biomarkers for obesity

- Immunological (elevated C-reactive protein, TNF-α and IL-6)
- Biochemical (glucose, lipids, satiety-related hormones)
- Microbiological (the fecal microbial composition)
- Genetic markers: genes coding adrenergic receptors (ADBRs), uncoupling proteins (UCPs), leptin (LEP), leptin receptor (LEPR), melanocortin pathways genes (MC3R, POMC), serotonin receptor, peroxisome proliferator-activated receptor PPAR-γ-2, and genes related