

***METABOLISM of CHOLESTEROL
and
COMPLEX LIPIDS***

Lipids 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

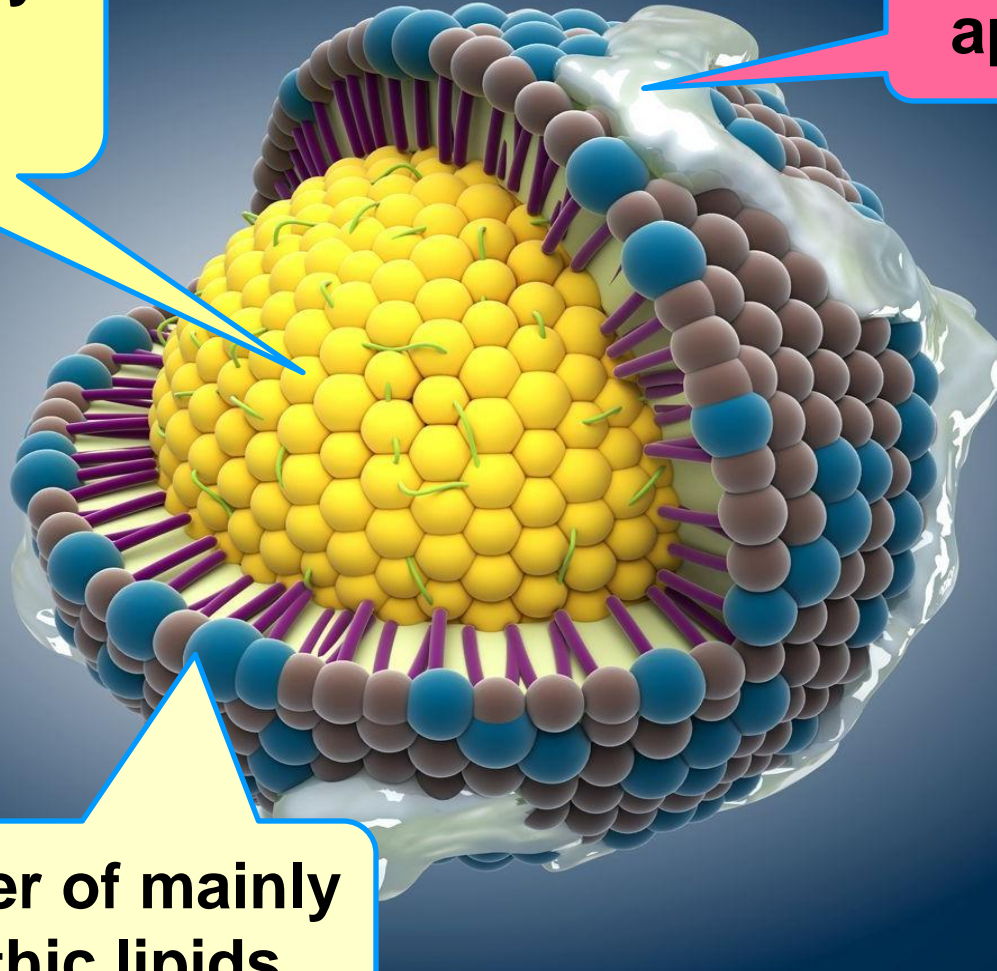
Lipids are hydrophobic compounds. Their transport in blood (in an aqueous medium) poses a problem, which is solved by associating the more insoluble lipids with more “polar” ones, such as phospholipids, cholesterol and combining with a specific, protein molecule (called as ‘apoproteins’). Thus, the hydrophobic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

Generalized structure of plasma lipoprotein

core of mainly nonpolar lipids

apoprotein

monolayer of mainly amphipathic lipids



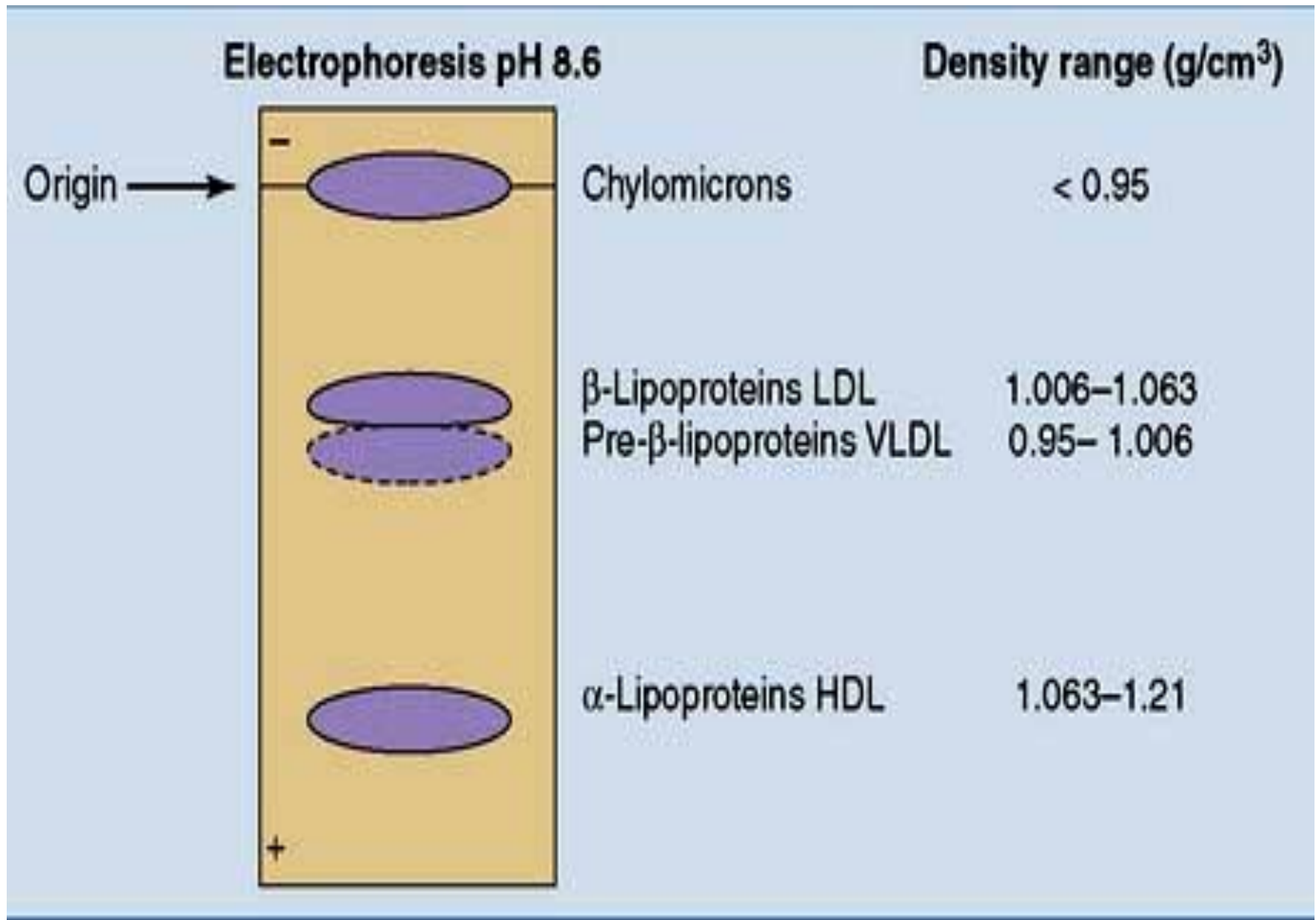
FUNCTIONS OF APOLIPOPROTEINS

- 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.

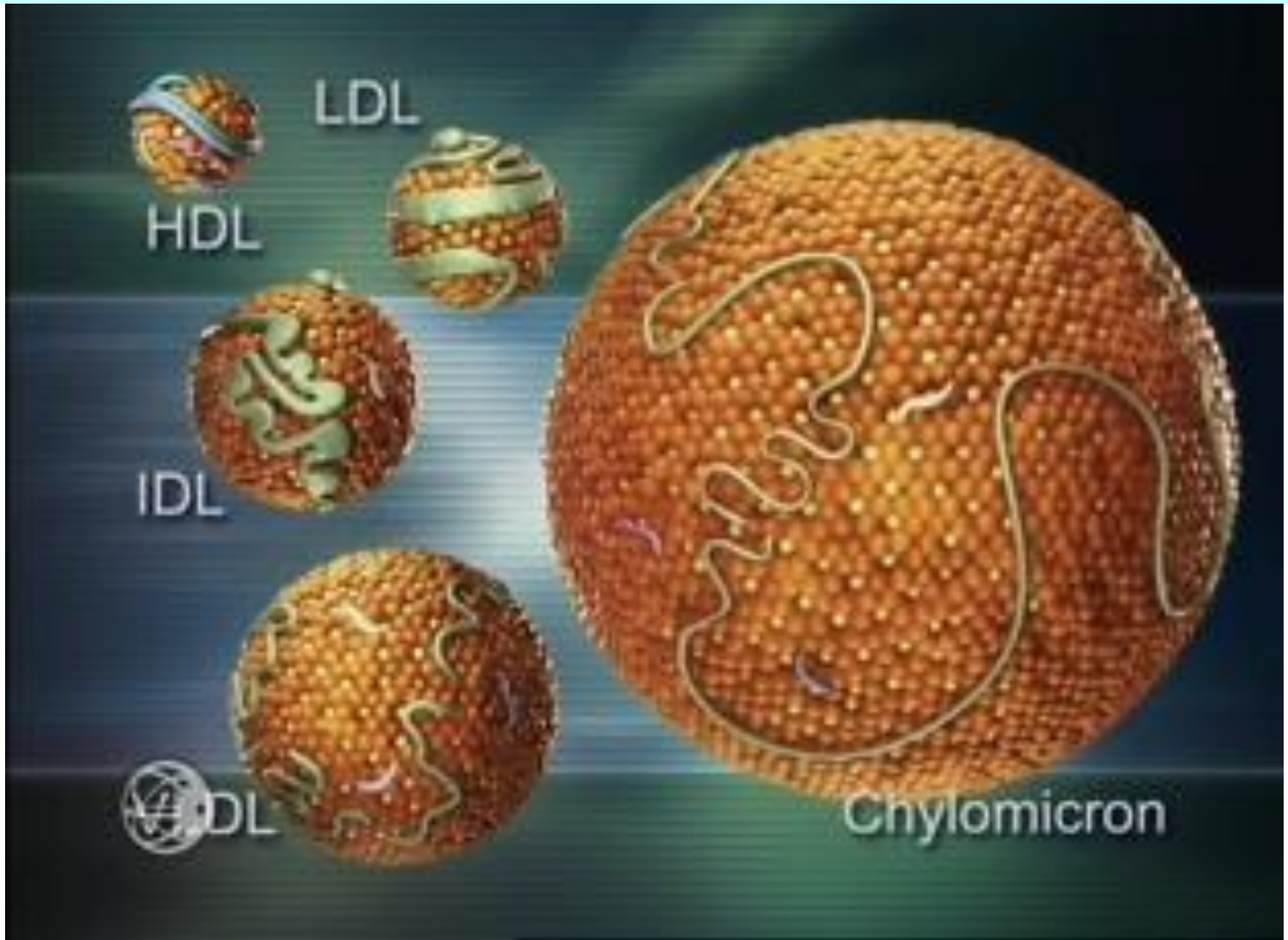
Classification of plasma lipoproteins

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

Plasma lipoproteins



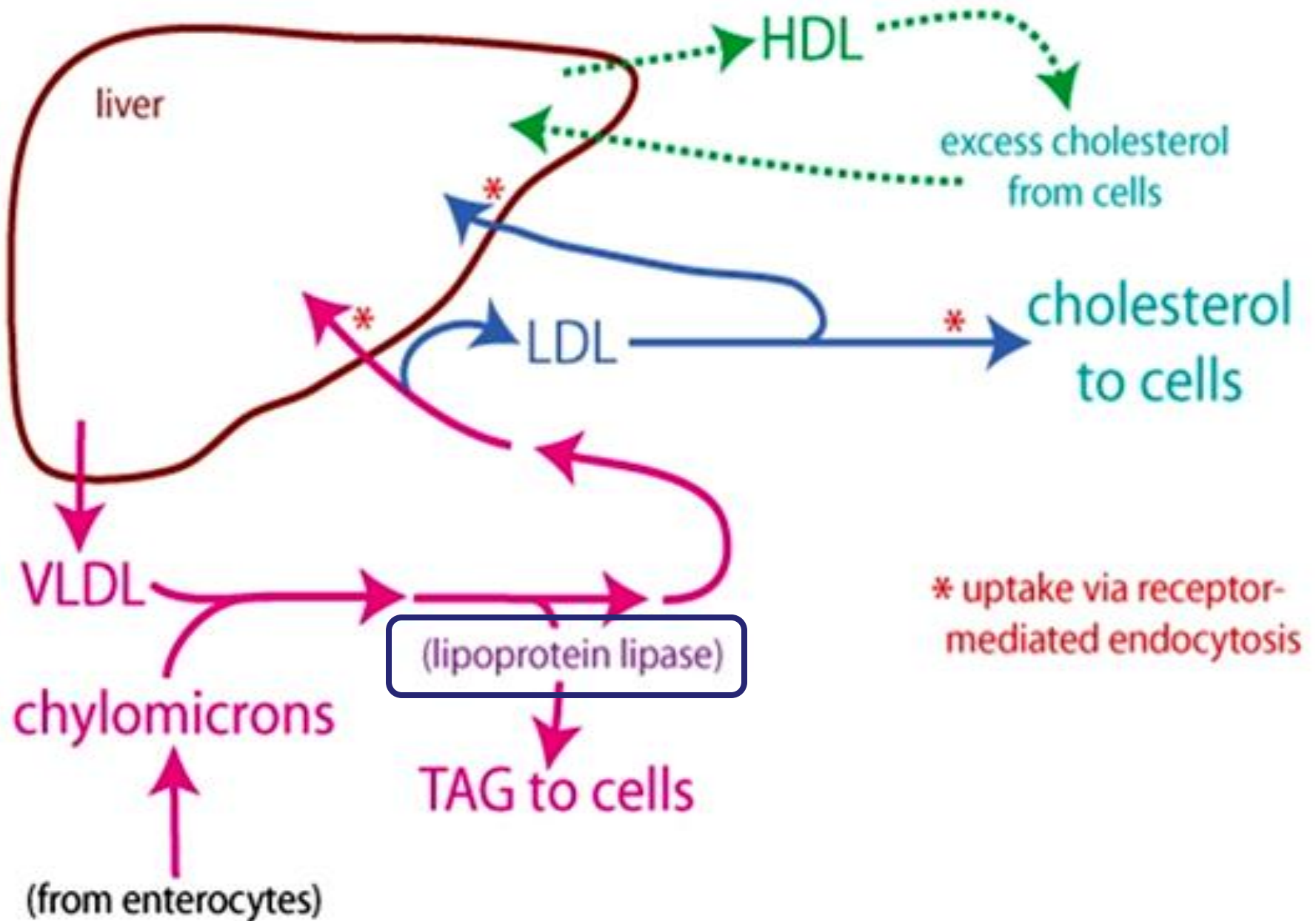
Plasma lipoproteins



Plasma lipoproteins

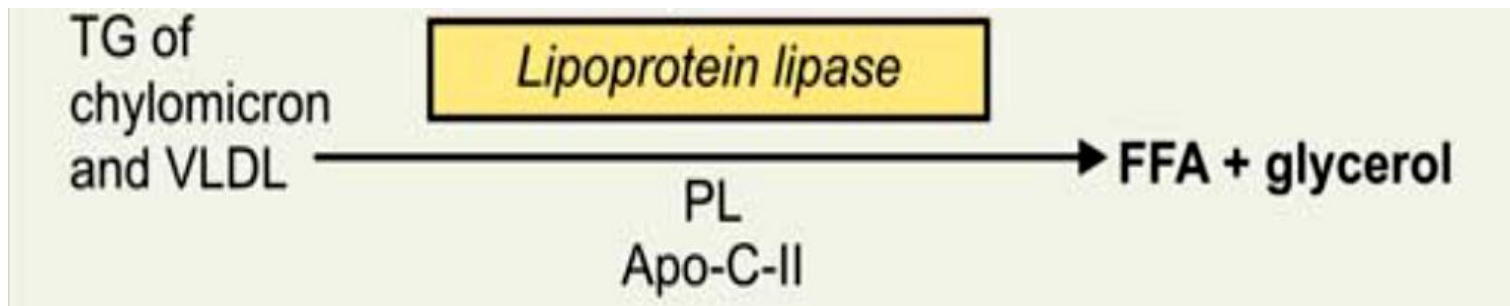
Lipoprotein	Source	Diameter (nm)	Density (g/mL)	Composition		Main Lipid Components	Apolipoproteins
				Protein (%)	Lipid (%)		
Chylomicrons	Intestine	90–1000	< 0.95	1–2	98–99	Triacylglycerol	A-I, A-II, A-IV, ¹ B-48, C-I, C-II, C-III, E
Chylomicron remnants	Chylomicrons	45–150	< 1.006	6–8	92–94	Triacylglycerol, 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	20–25	1.019–1.063	32	68	Phospholipids, cholesterol	A-I, A-II, A-IV, C-I, C-II, C-III, D, ² E
HDL ₁							
HDL ₂							
HDL ₃		5–10	1.125–1.210	57	43		

Plasma lipoproteins



The enzyme lipoprotein lipase is located in walls of blood capillaries.

The enzyme remains bound to wall by proteoglycan chains of heparan-SO₄.

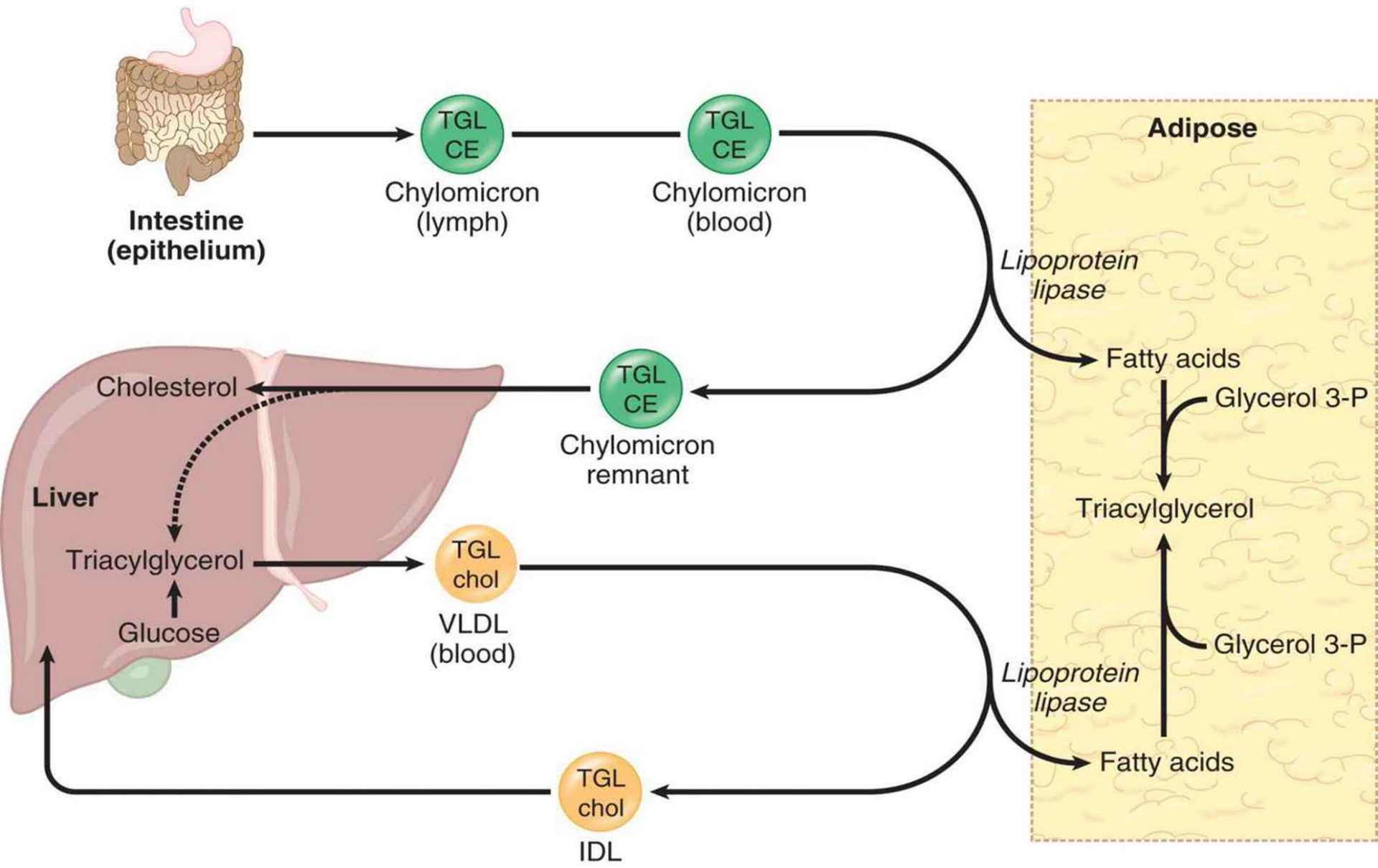


Lipoprotein lipase activity declines in adipocytes on starvation and rises after feeding.

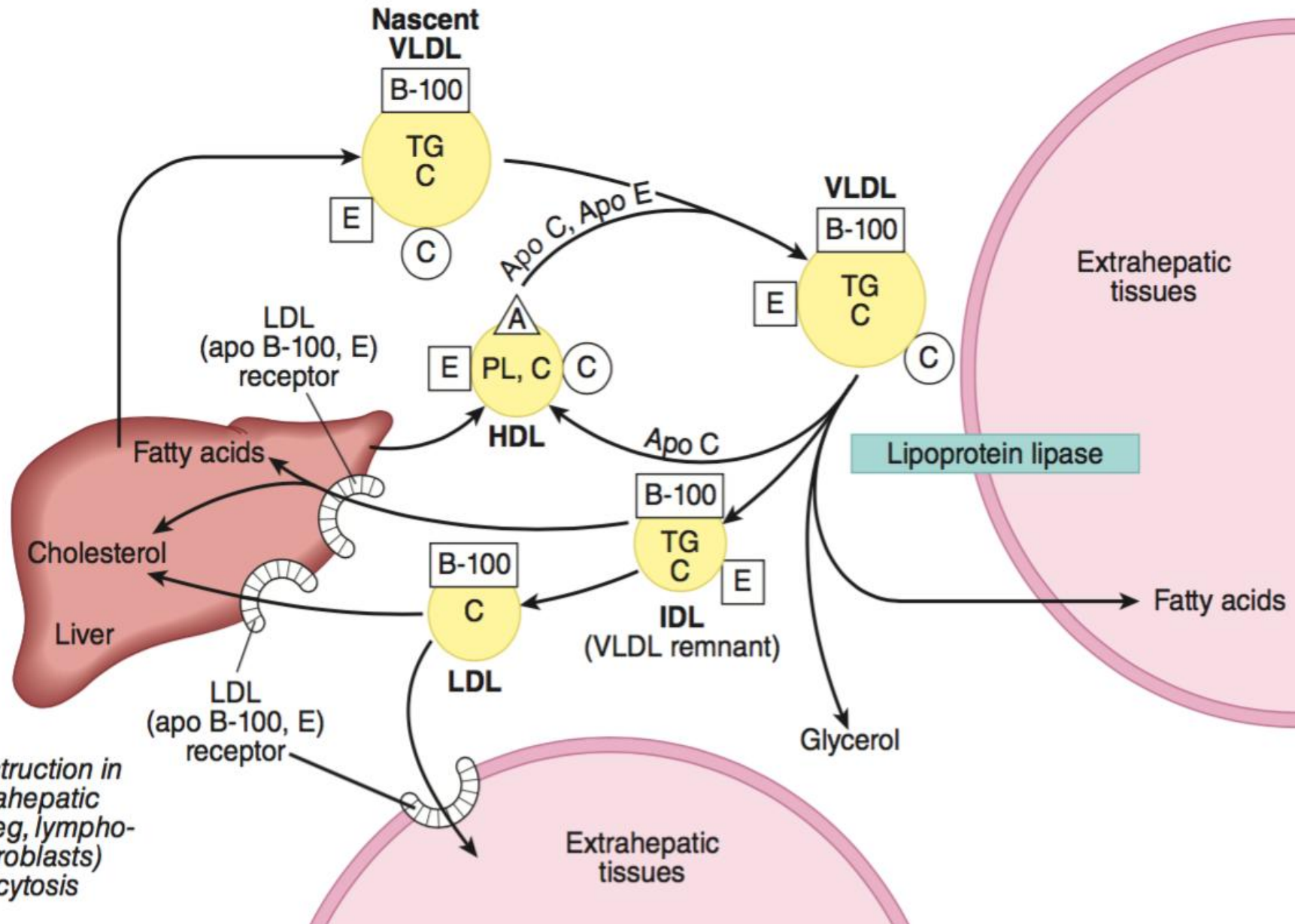
Hence starvation

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

Metabolism of Chylomicrons



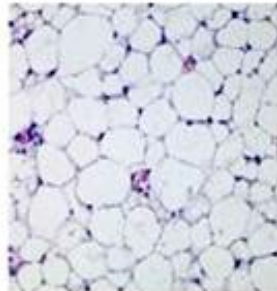
Metabolic fate of very low density lipoproteins (VLDL) and production of low density lipoproteins (LDL)



Overview of Lipid Transport in Animals



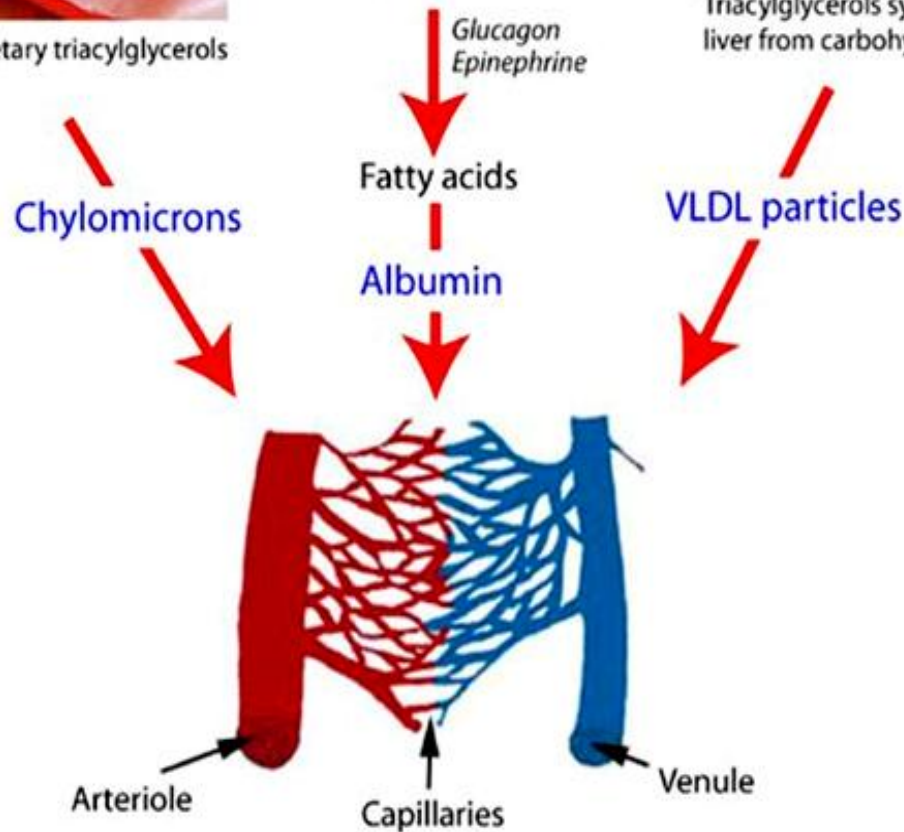
Dietary triacylglycerols



Triacylglycerols stored in adipose tissue and released in response to hormones



Triacylglycerols synthesized in the liver from carbohydrates and exported

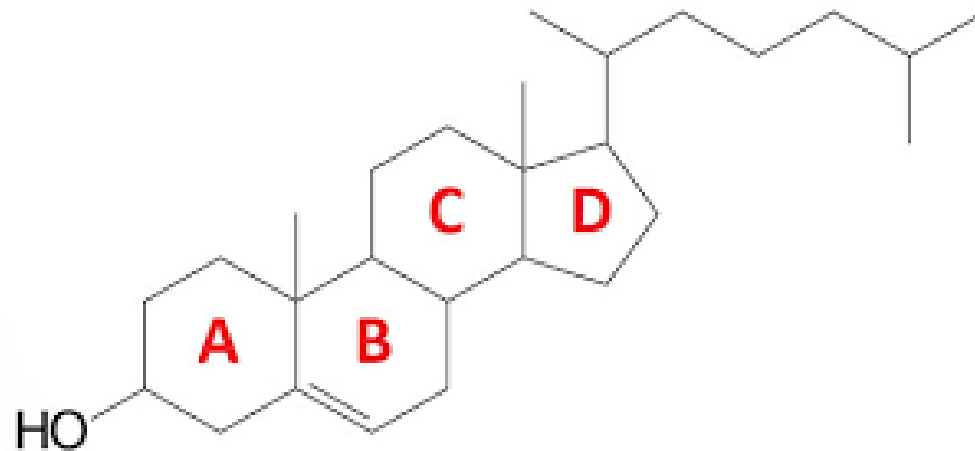


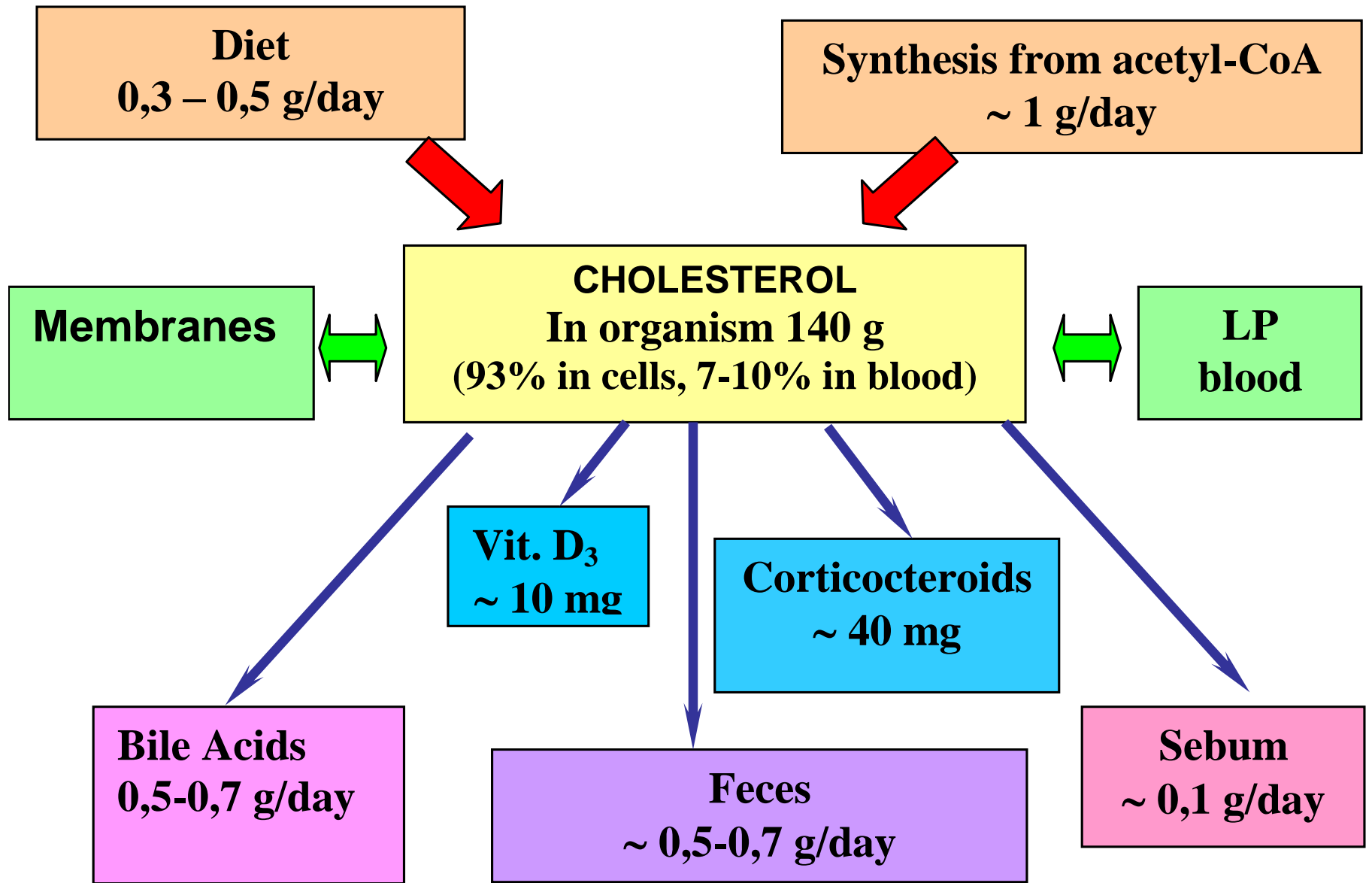
Disorders of Plasma Lipoproteins (Dyslipoproteinemias)

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

Corticosteroids
~ 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

Step IV: formation of lanosterol

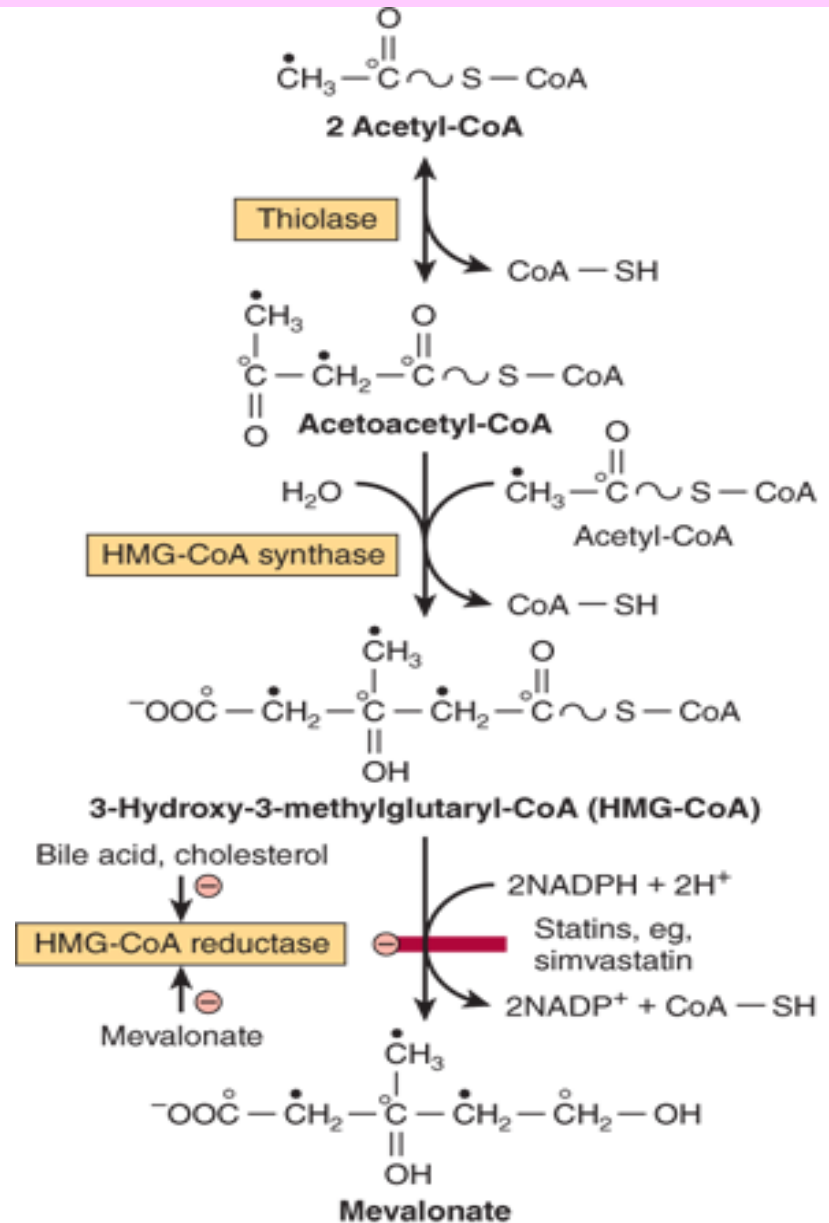
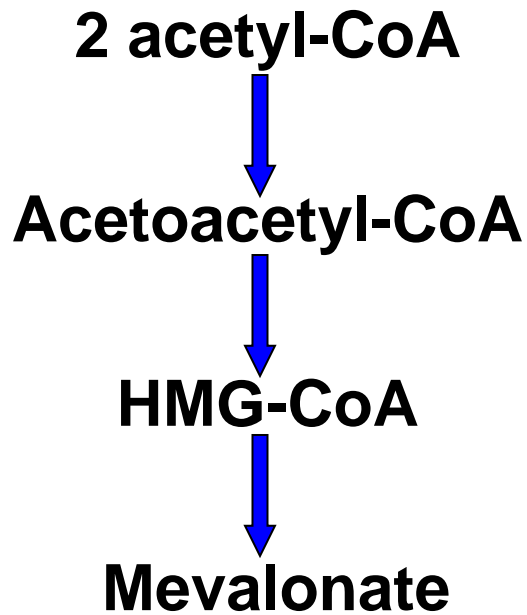
Step V: formation of cholesterol



II

III

Synthesis of cholesterol

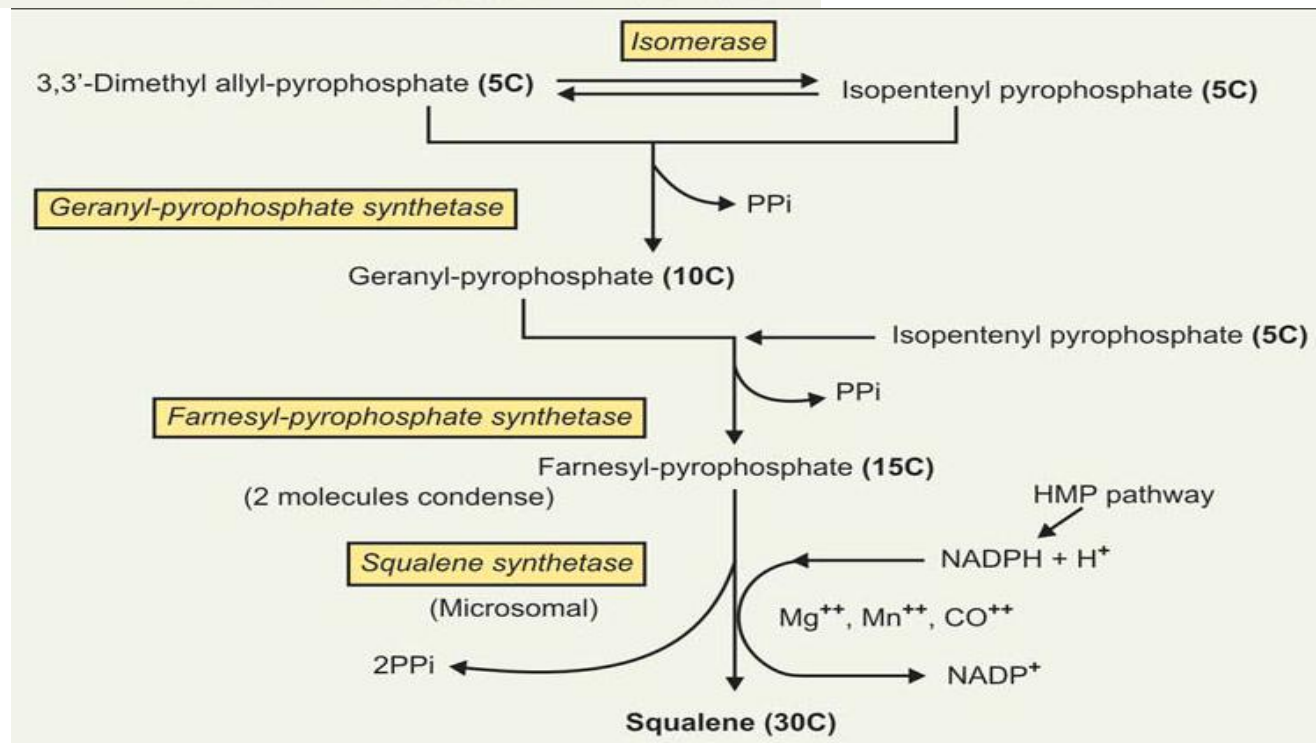
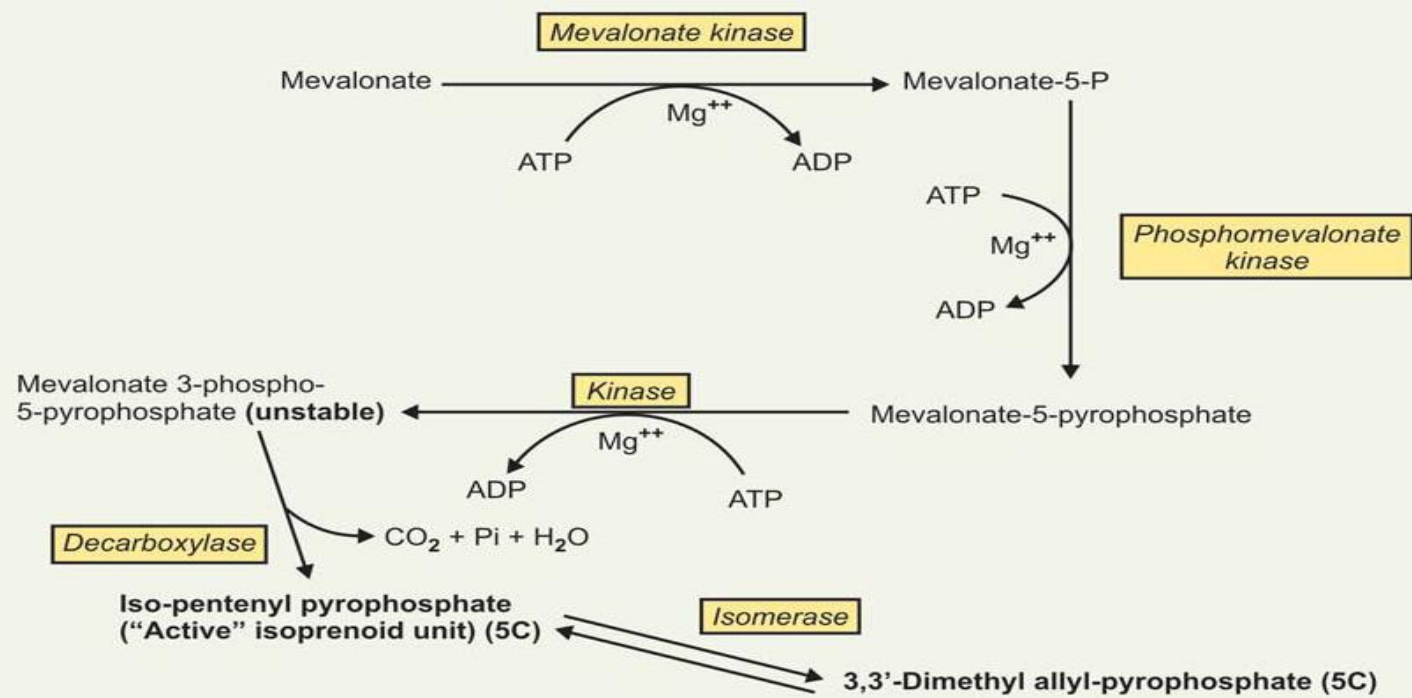


Source: V. W. Rodwell, D. A. Bender, K. M. Botham, P. www.accessmedicine.com

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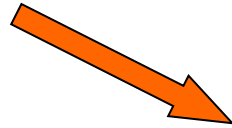
Synthesis of cholesterol

**Mevalonate → Mevalonate 5-phosphate
→ Mevalonate 5-diphosphate →
Mevalonate 3-phospho-5-diphosphate →
Isopentenyl diphosphate →
Dimethylallyl diphosphate →
... → ...
Squalene**

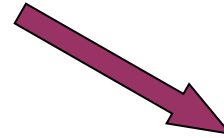


Synthesis of cholesterol

Squalene



Lanosterol



Cholesterol

Regulation of cholesterol synthesis

The rate limiting step: **HMG-CoA reductase** step.

I: mevalonate, cholesterol, bile acids

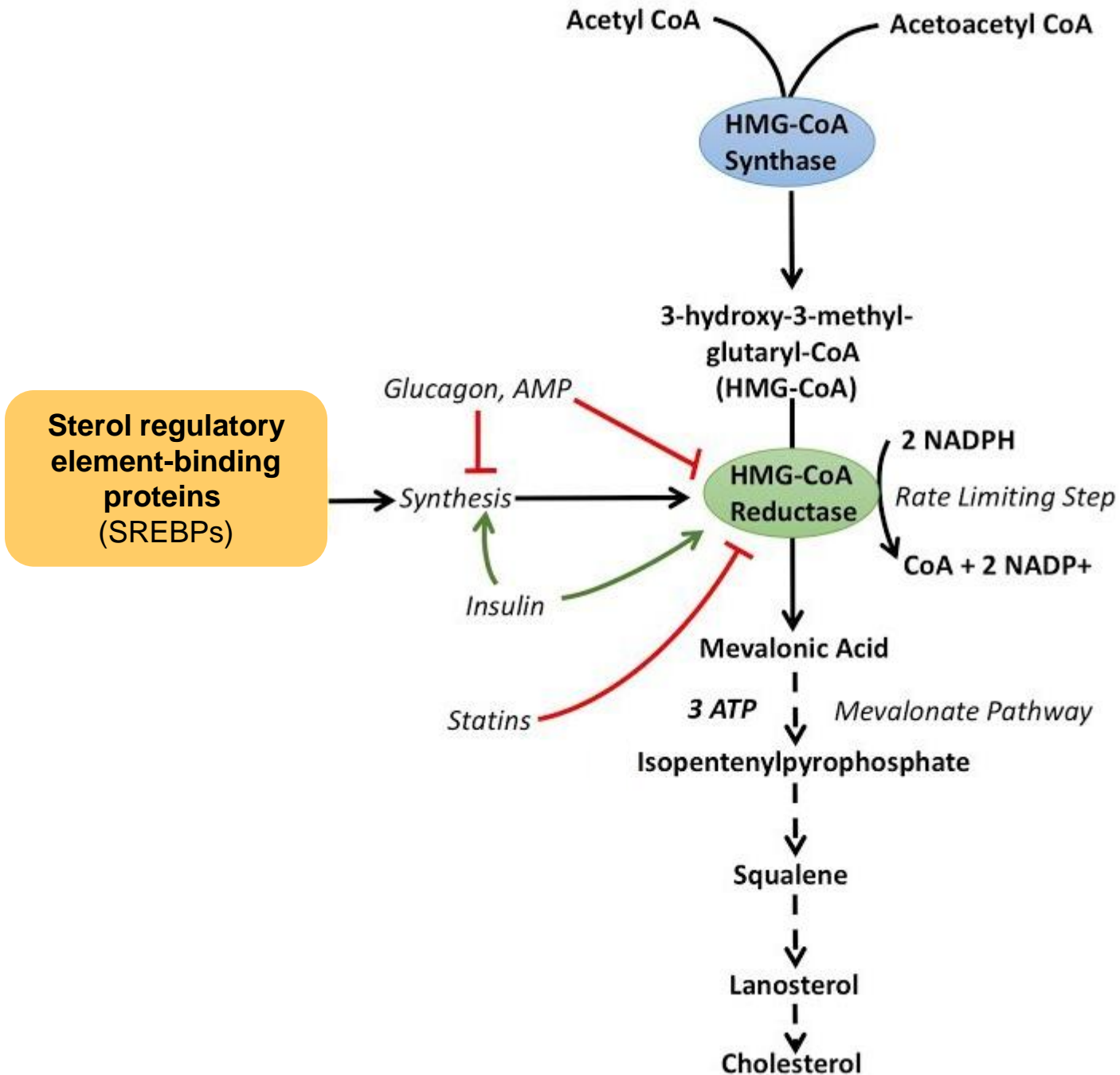
Cholesterol and metabolites repress transcription of the HMG-CoA reductase gene

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.



ROLE OF HORMONES

Insulin increases HMG-CoA reductase activity.

Thyroid hormones stimulate HMG-CoA reductase activity.

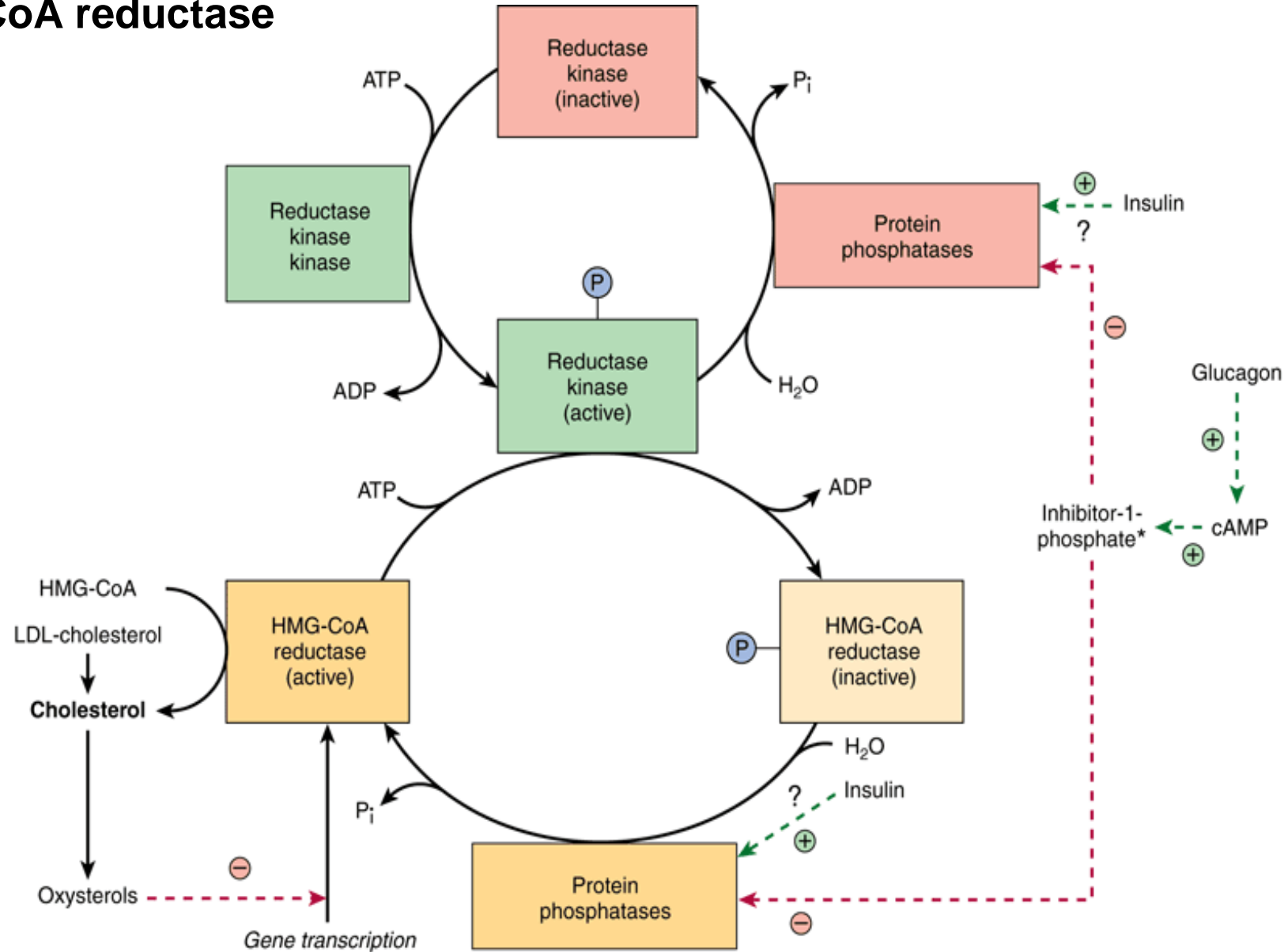
Glucagon and/glucocorticoids: decreases the activity of HMG-CoA reductase and reduces the cholesterol biosynthesis.

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)

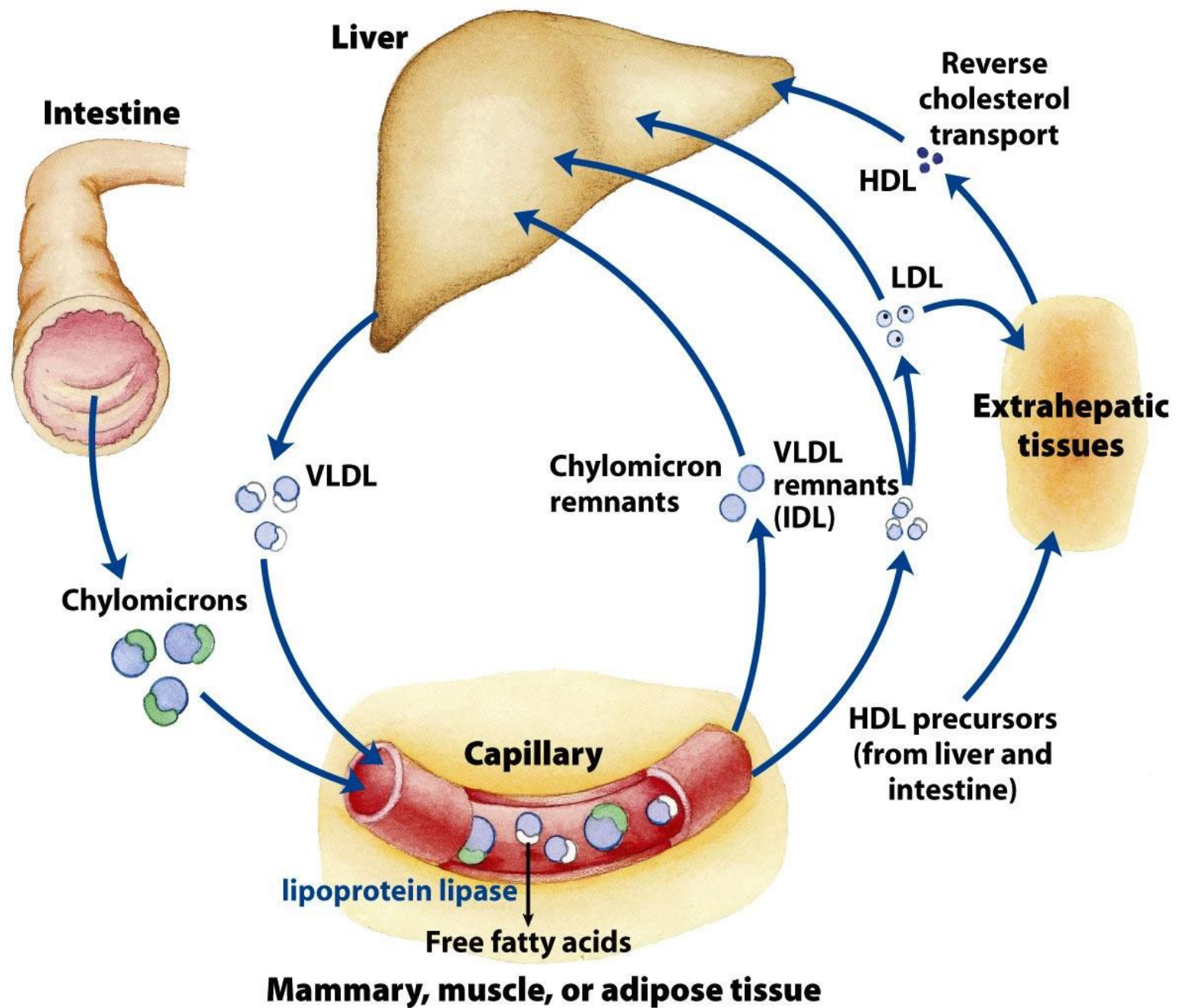
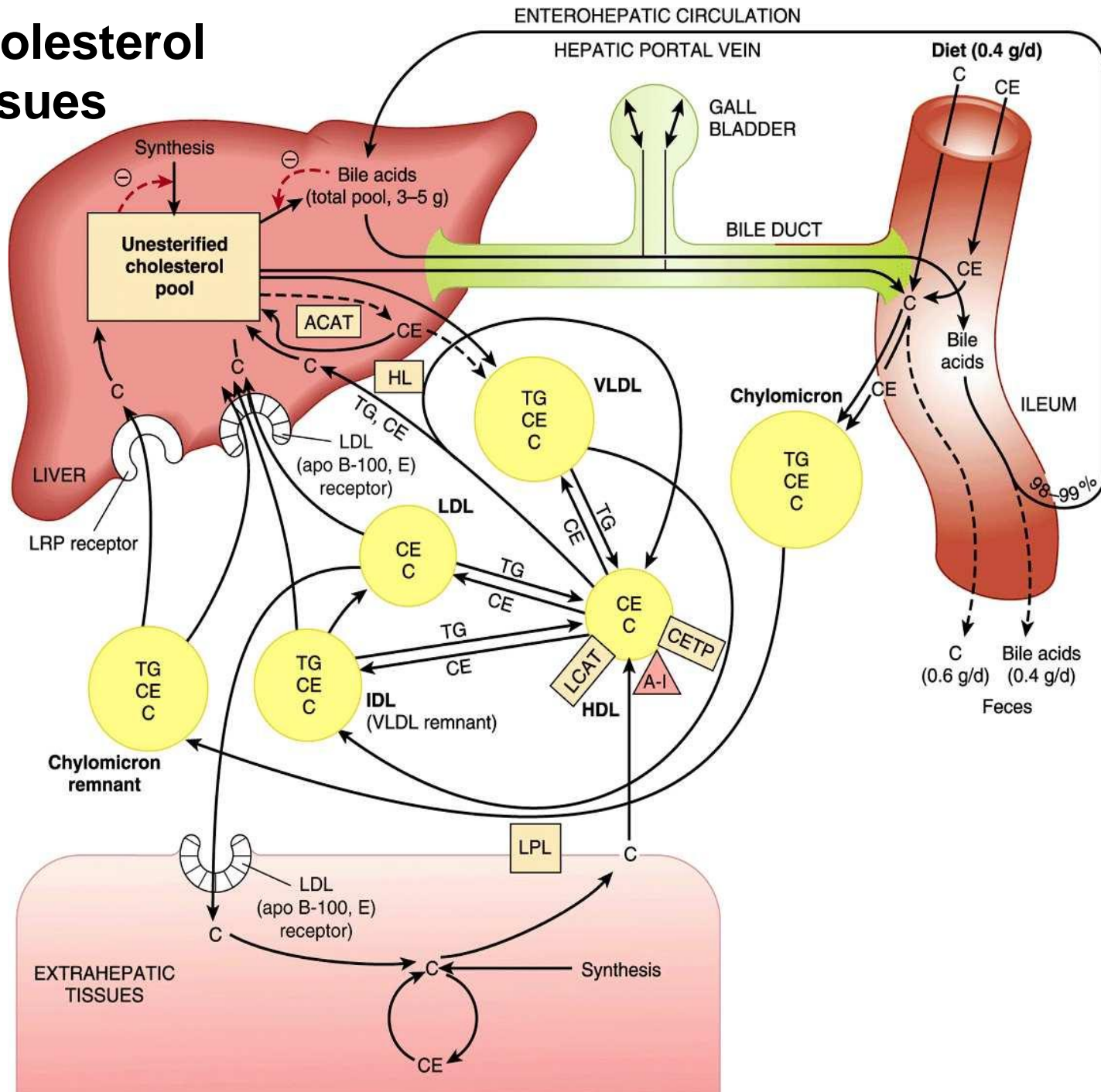


Figure 21-40a

Lehninger Principles of Biochemistry, Fifth Edition

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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 D₃.

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.

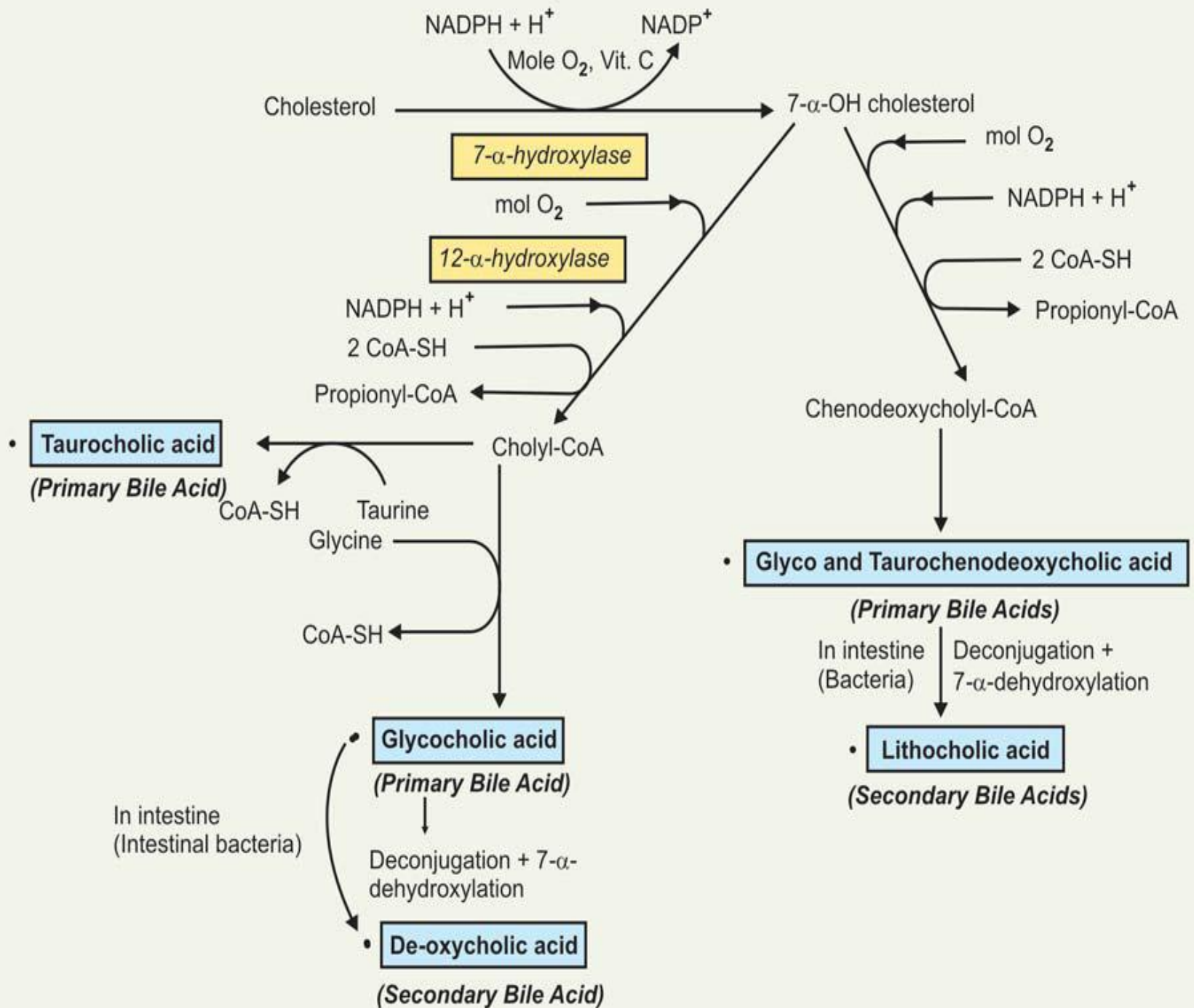
- **Secondary bile acids:** are produced in intestine from the primary bile acids by the action of intestinal bacteria.

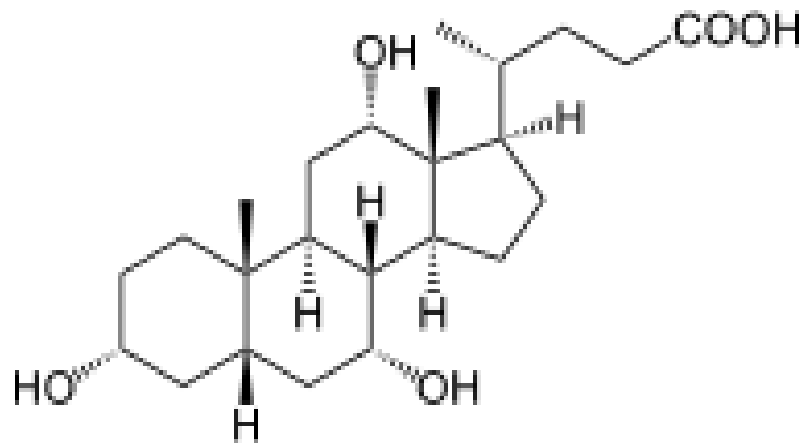
They are: ***Deoxycholic acid***

Lithocholic acid

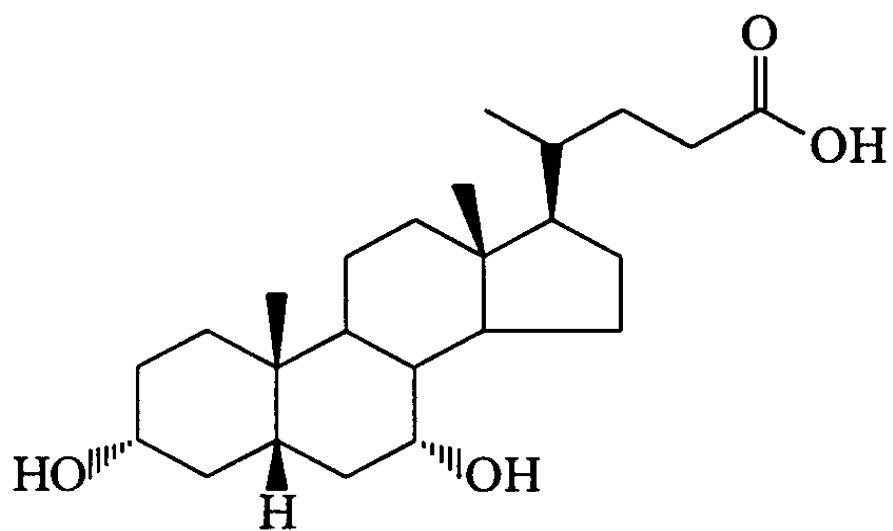
Functions of Bile Acids (Bile Salts)

- 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.

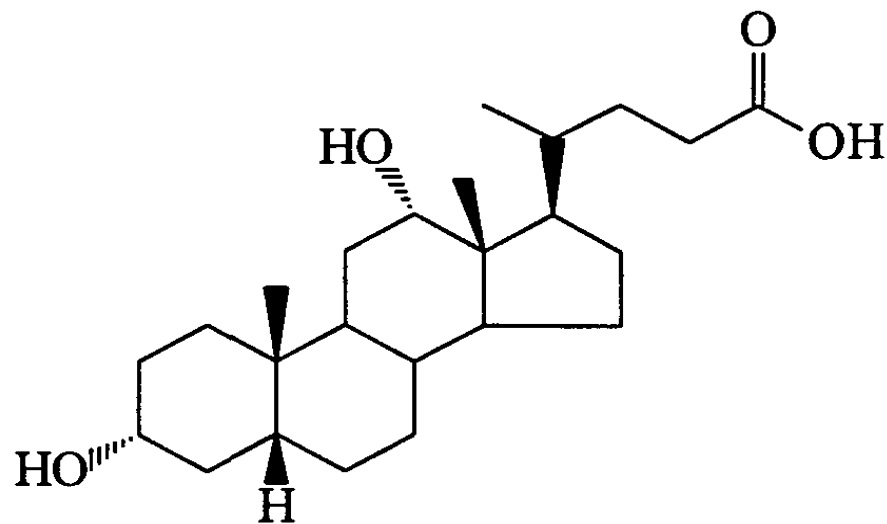




Cholic acid



Chenodeoxycholic Acid

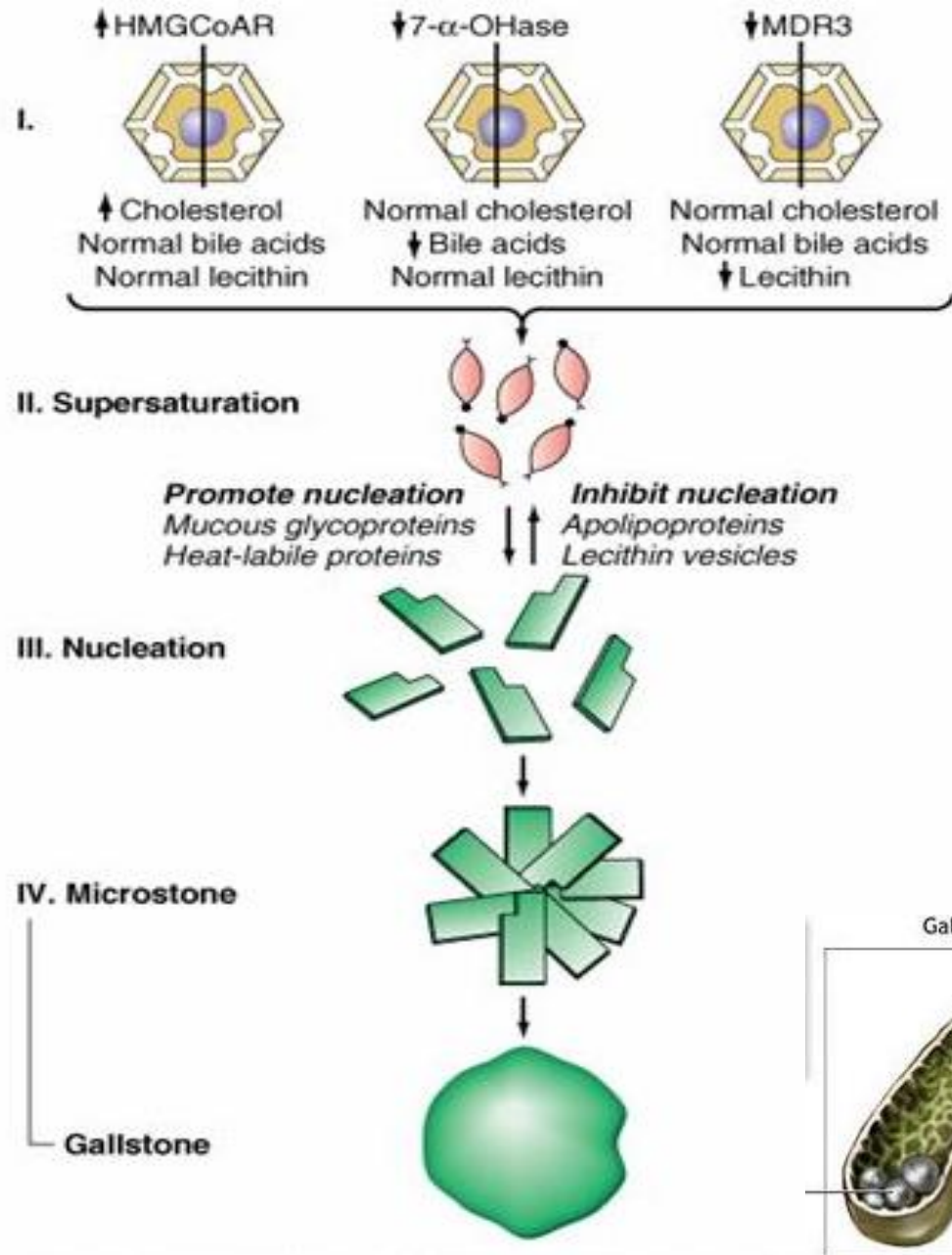
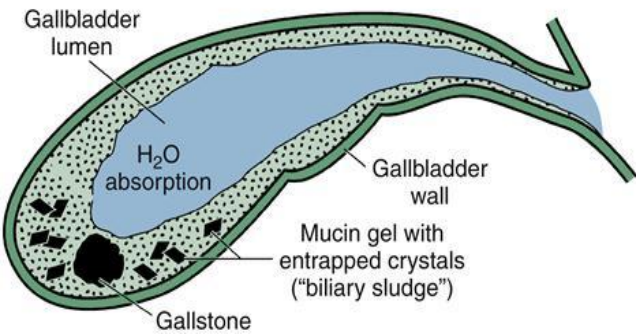
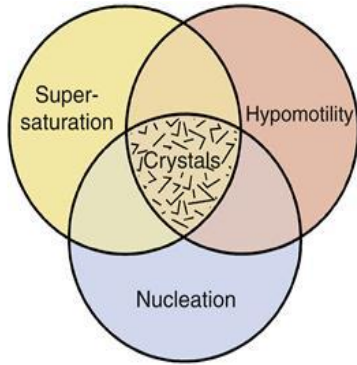


Deoxycholic Acid

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>

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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.

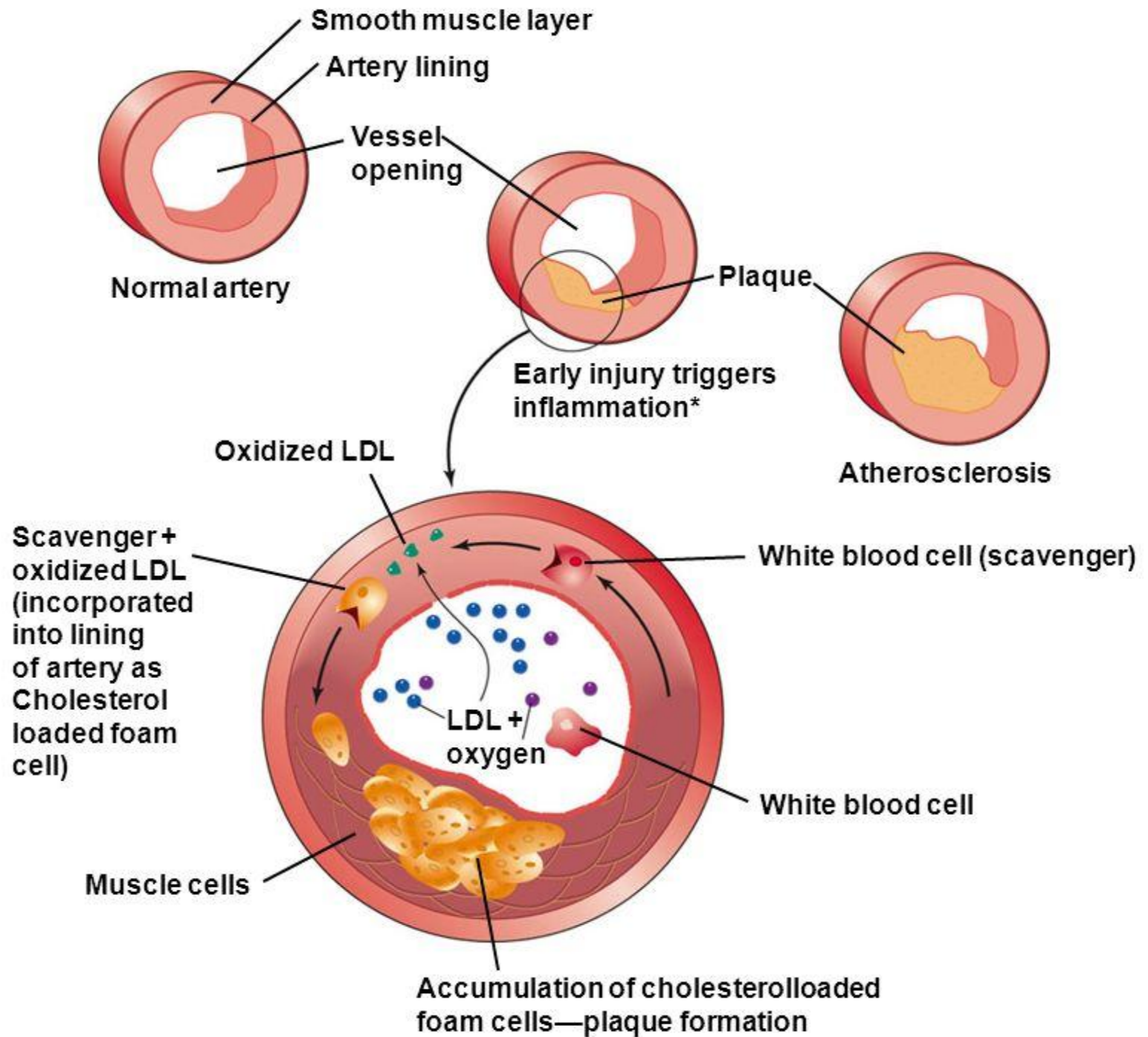
2. Reduction in bile salt pool:

- 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



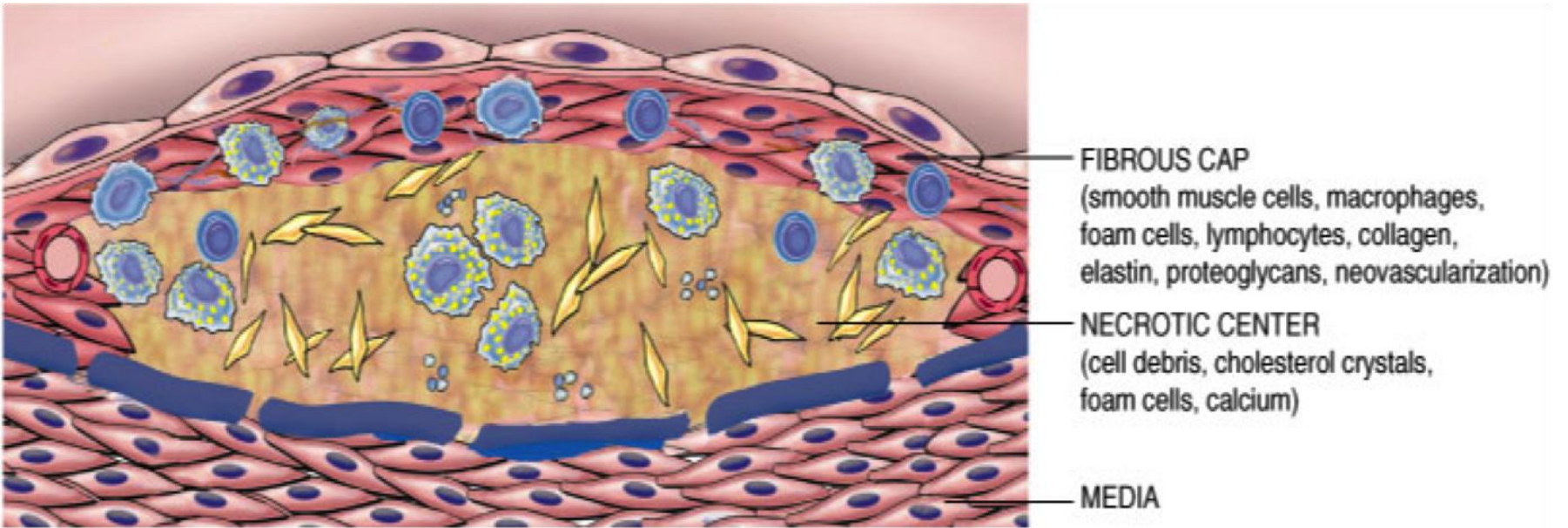


Fig. 10-3. The major components of a well-developed intimal atheromatous plaque overlying an intact media.

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ENDOTHELIAL DYSFUNCTION →

Foam Cells

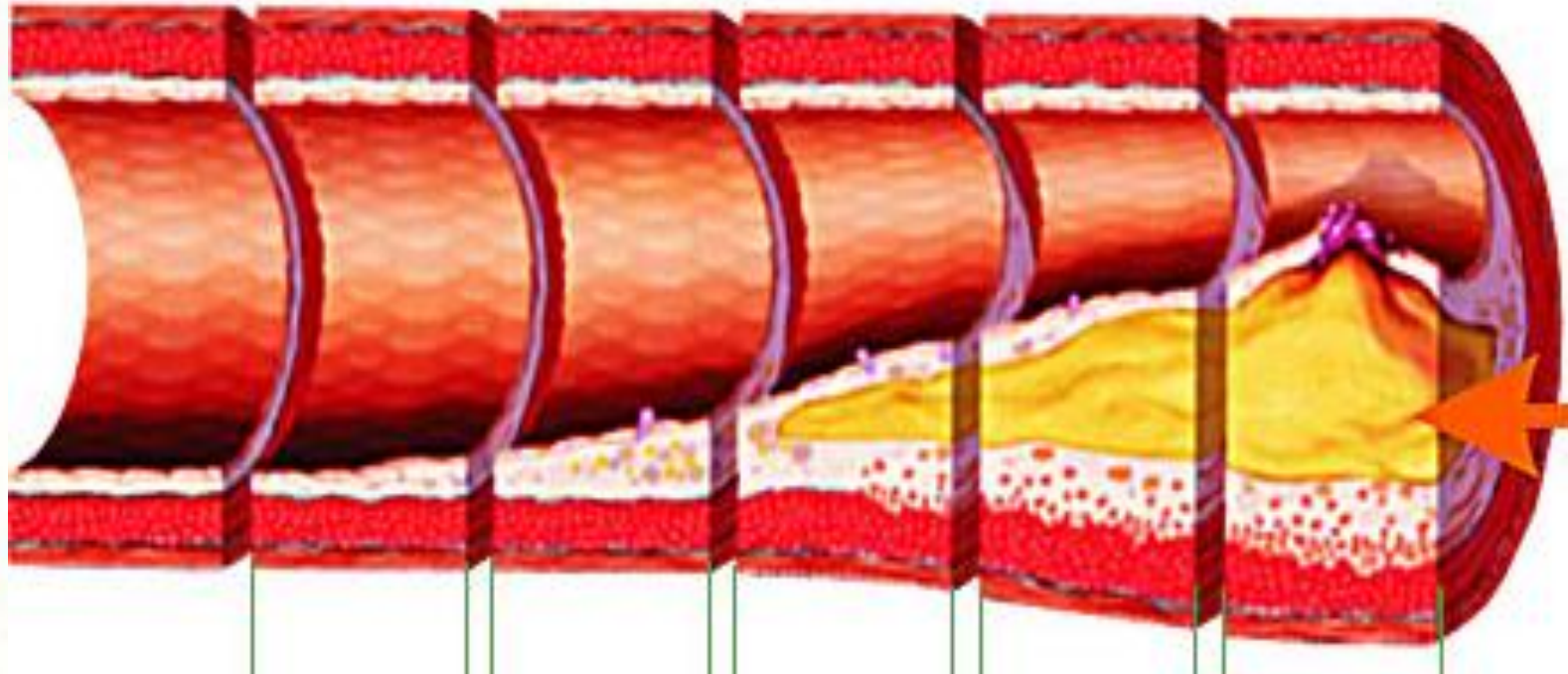
Fatty Streak

Intermediate Lesion

Atheroma

Fibrous Plaque

Complicated Lesion/Rupture



From first decade

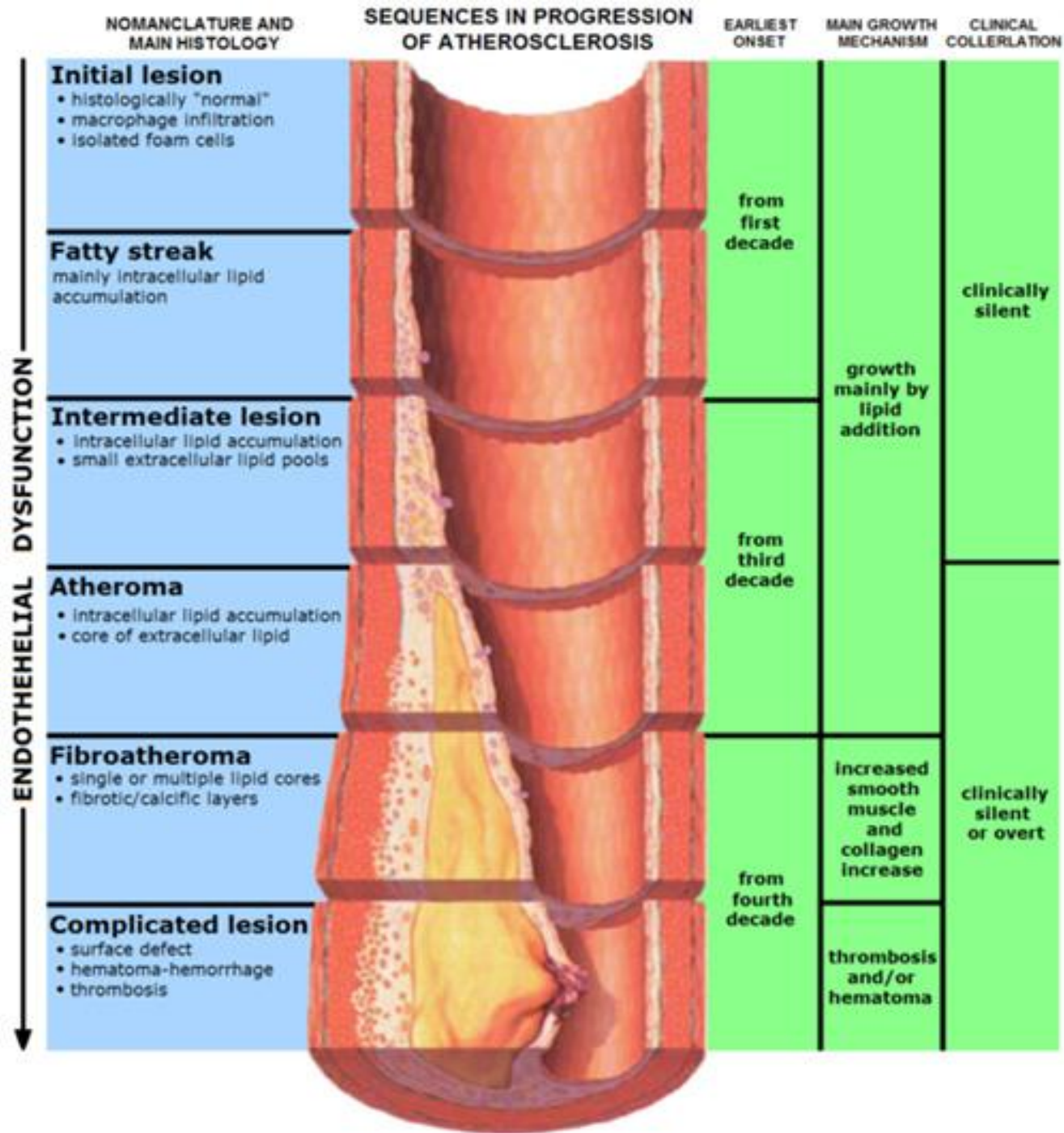
From third decade

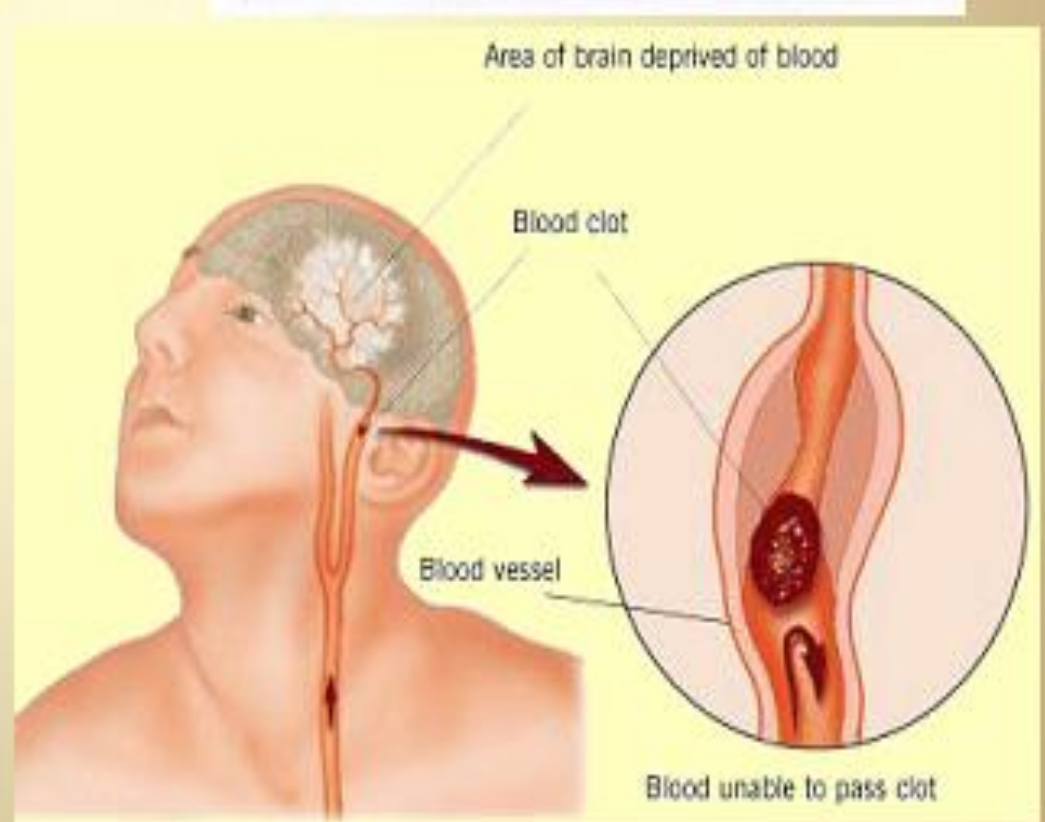
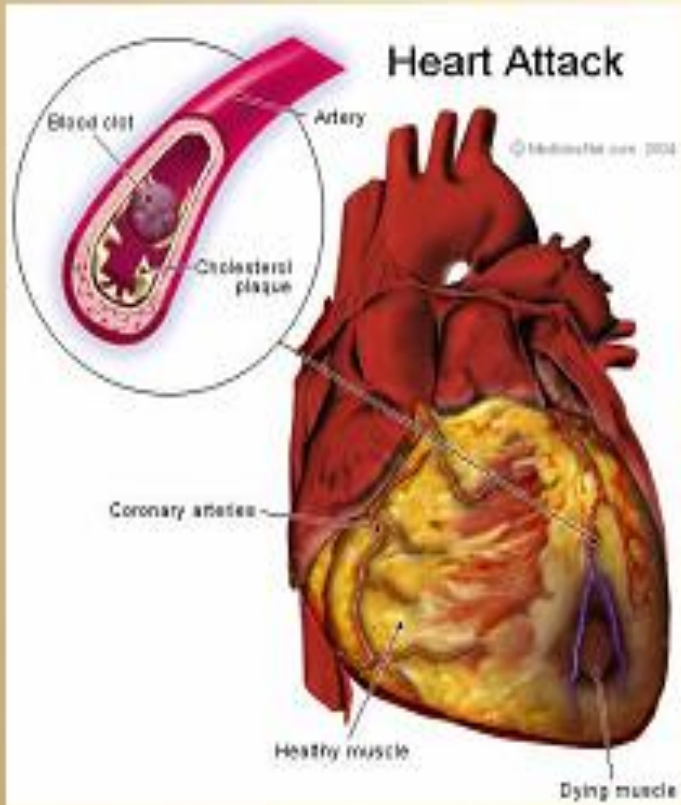
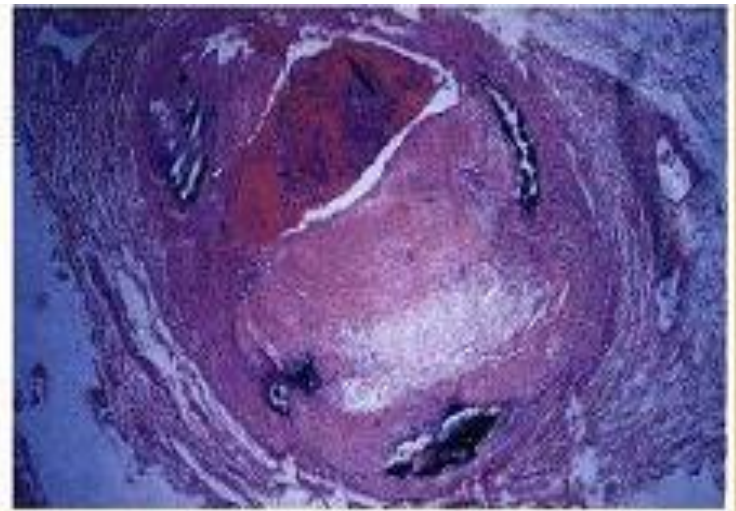
From fourth decade

Growth mainly by lipid accumulation

Smooth muscle and collagen

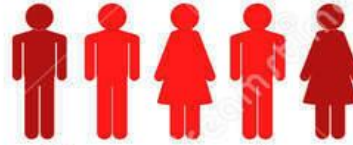
Thrombosis, hematoma







Atherosclerosis



Men more suffer a atherosclerosis than women

Complications



Stroke



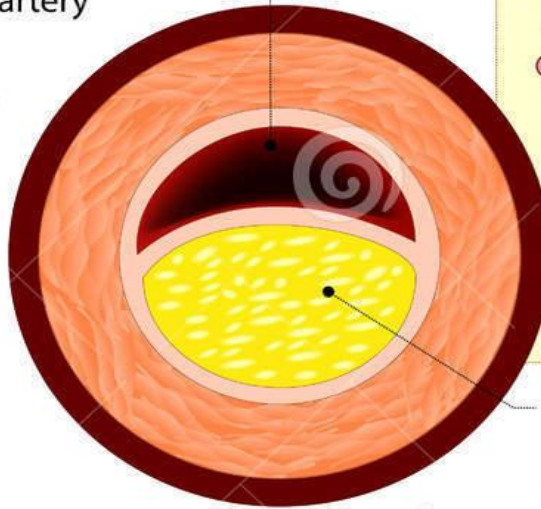
Heart attack



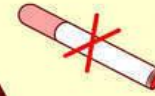
Gangrene

Risk

Narrowed artery



Prevention & Treatment



Weight loss



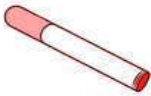
Diet



Exercise



Diabetes



Smoking



Vitamin B6 deficiency



Advanced age



Obesity



Male sex



Genetic abnormalities



Sedentary lifestyle



Unhealthy food



Hypertension



White blood cells



Postmenopausal estrogen deficiency



Fat



Chlamydia pneumoniae



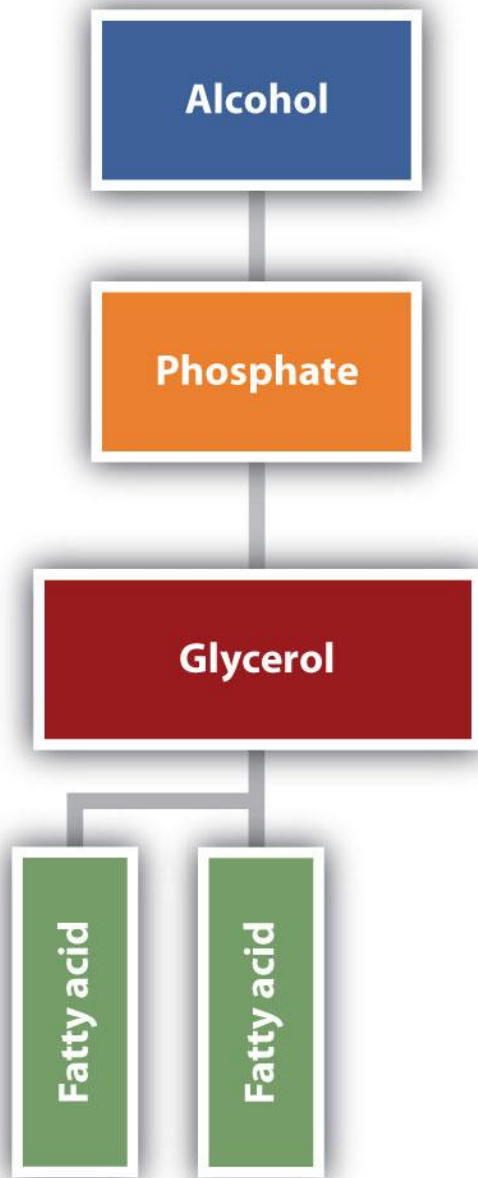
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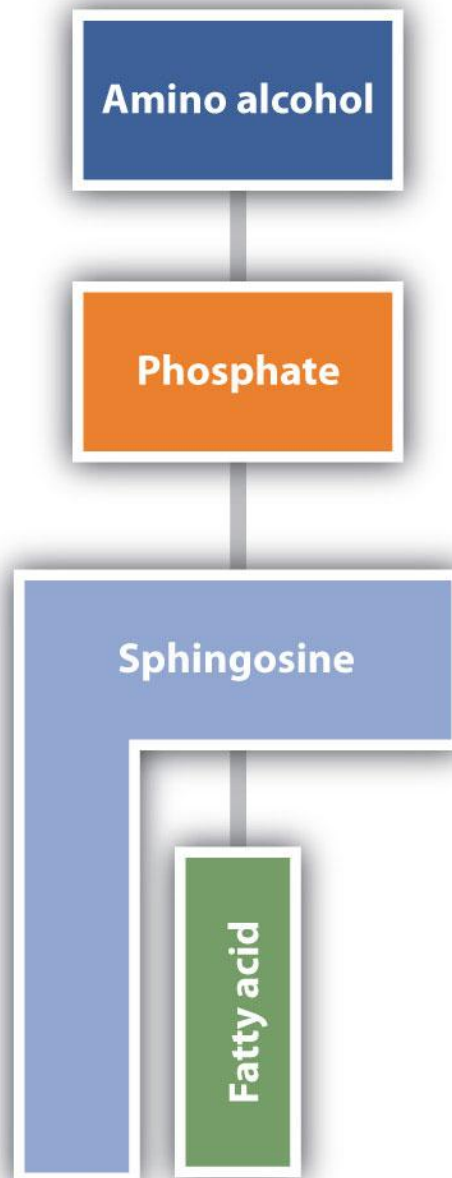
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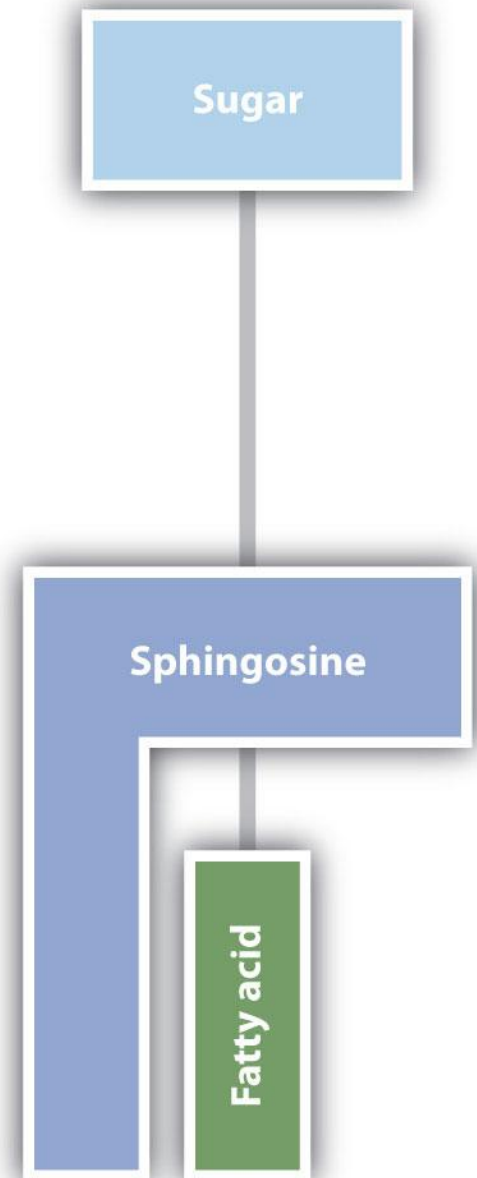
Metabolism of sphingolipids



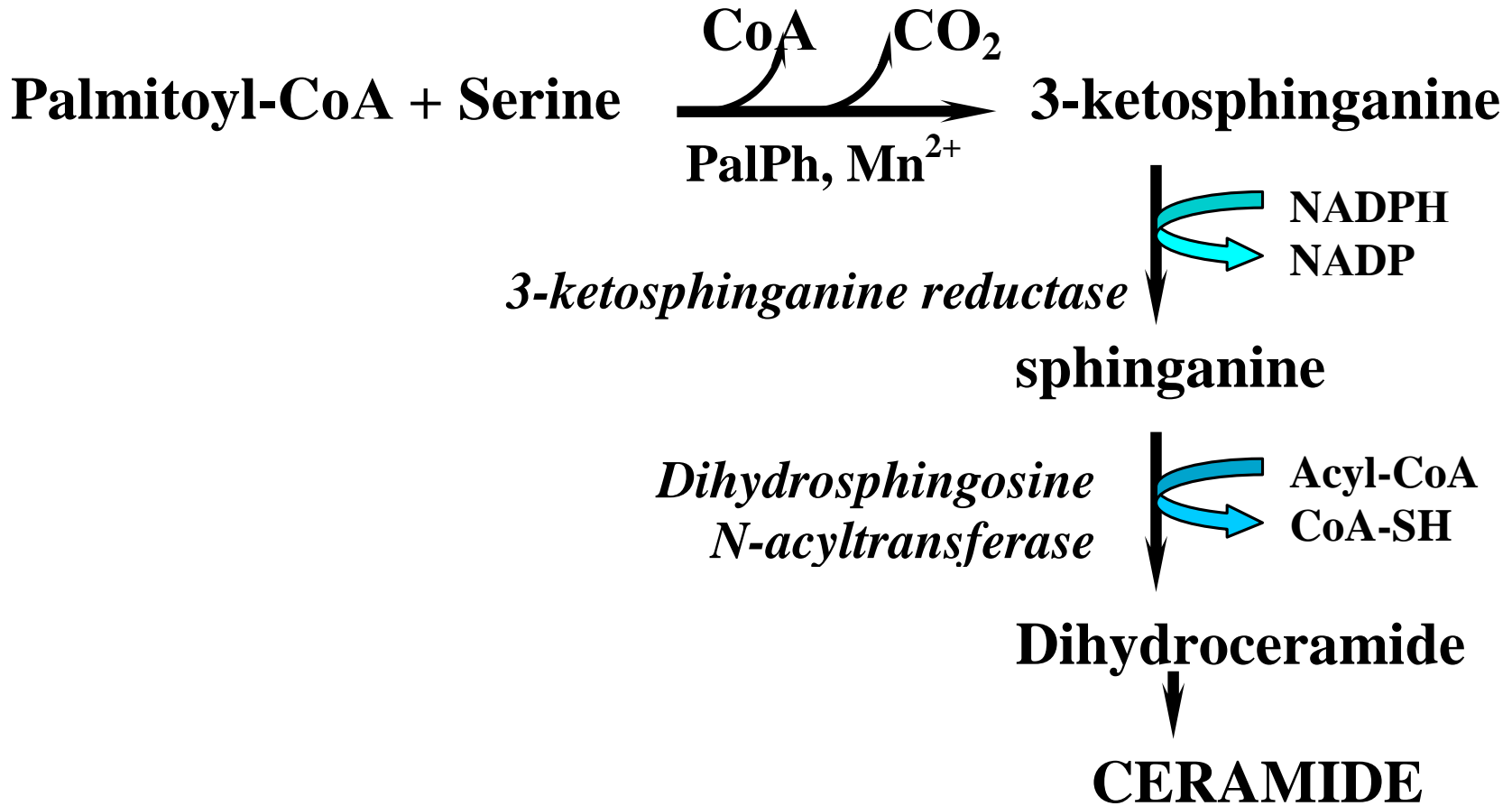
**Phosphoglyceride
(a phospholipid)**



**Sphingomyelin
(both a phospholipid
and a sphingolipid)**

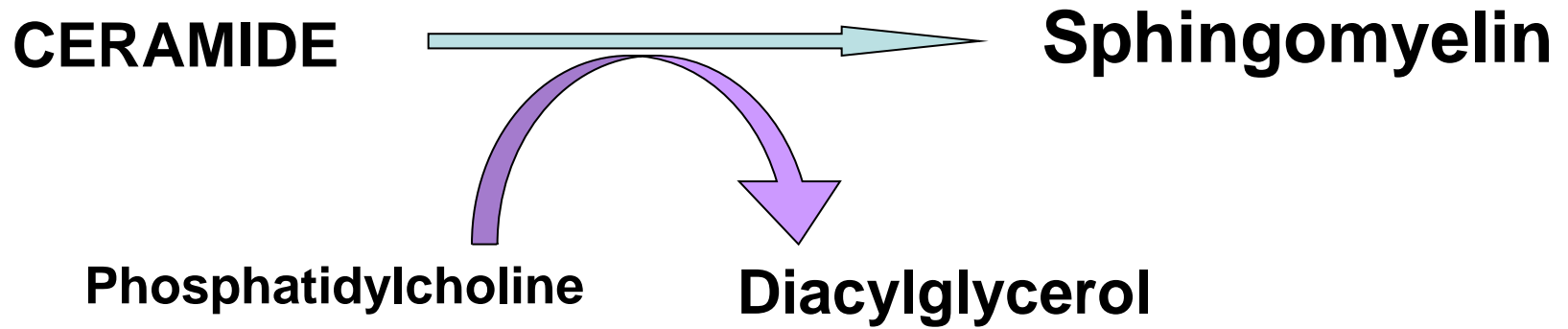


**Cerebroside
(both a sphingolipid
and a glycolipid)**

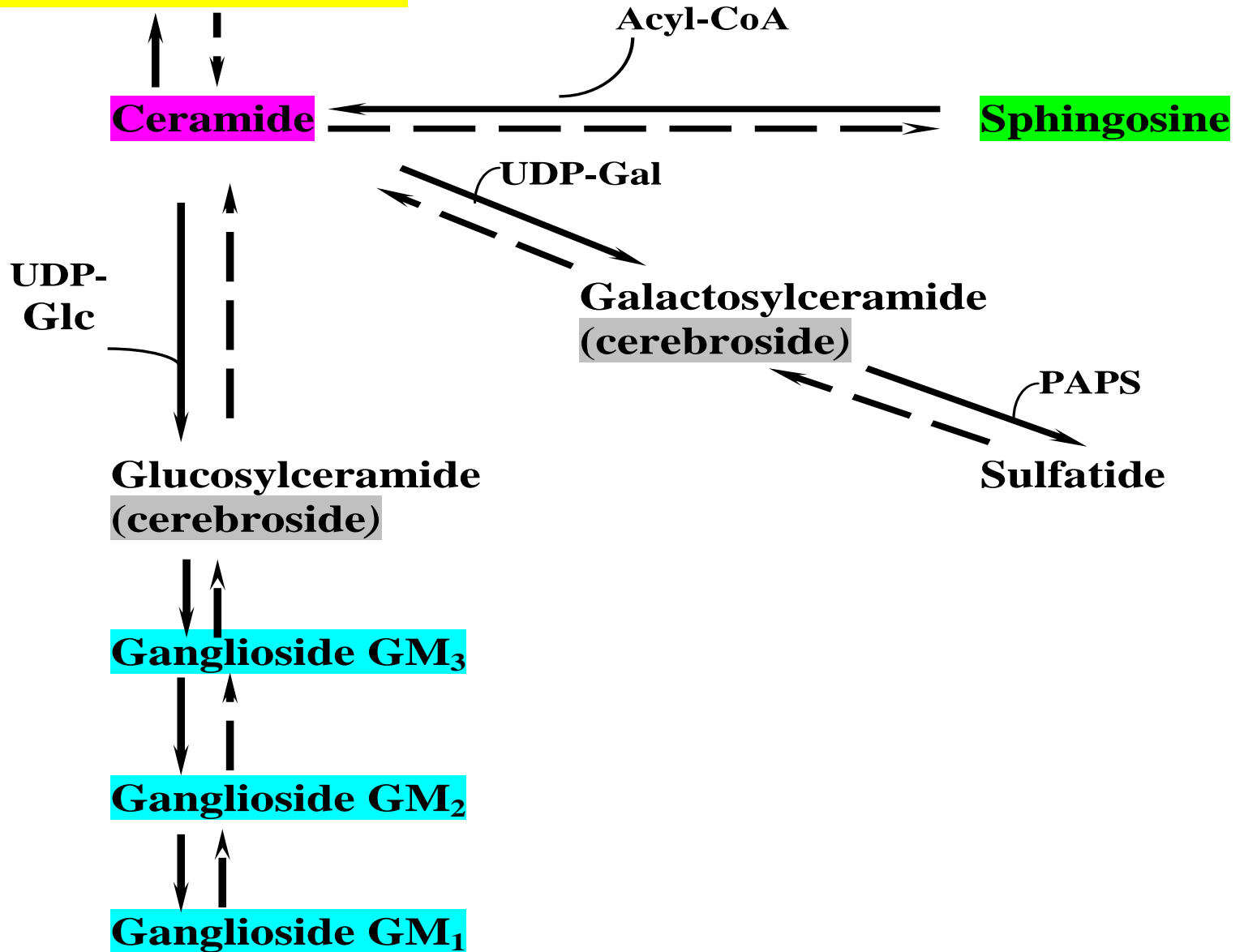


Biosynthesis of ceramide

Biosynthesis of sphingomyelin

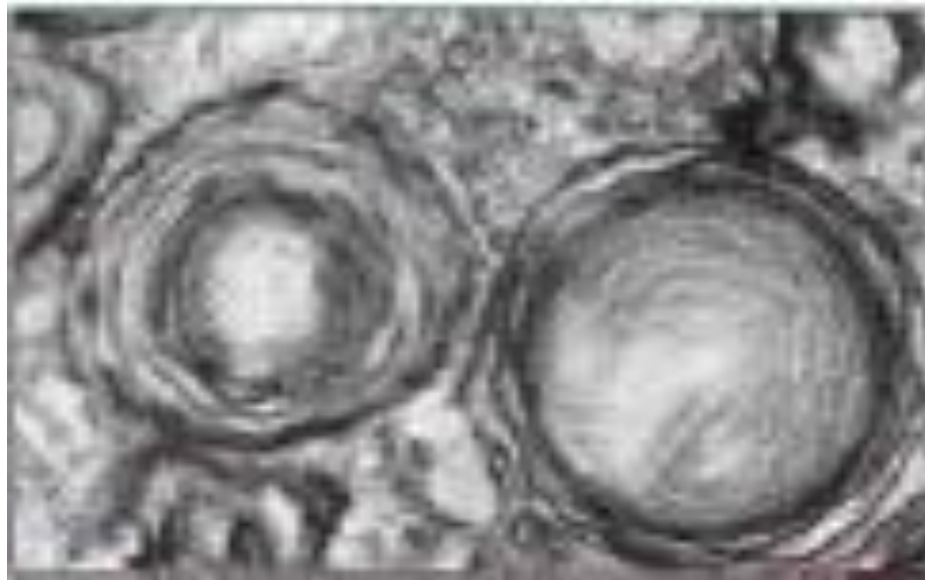


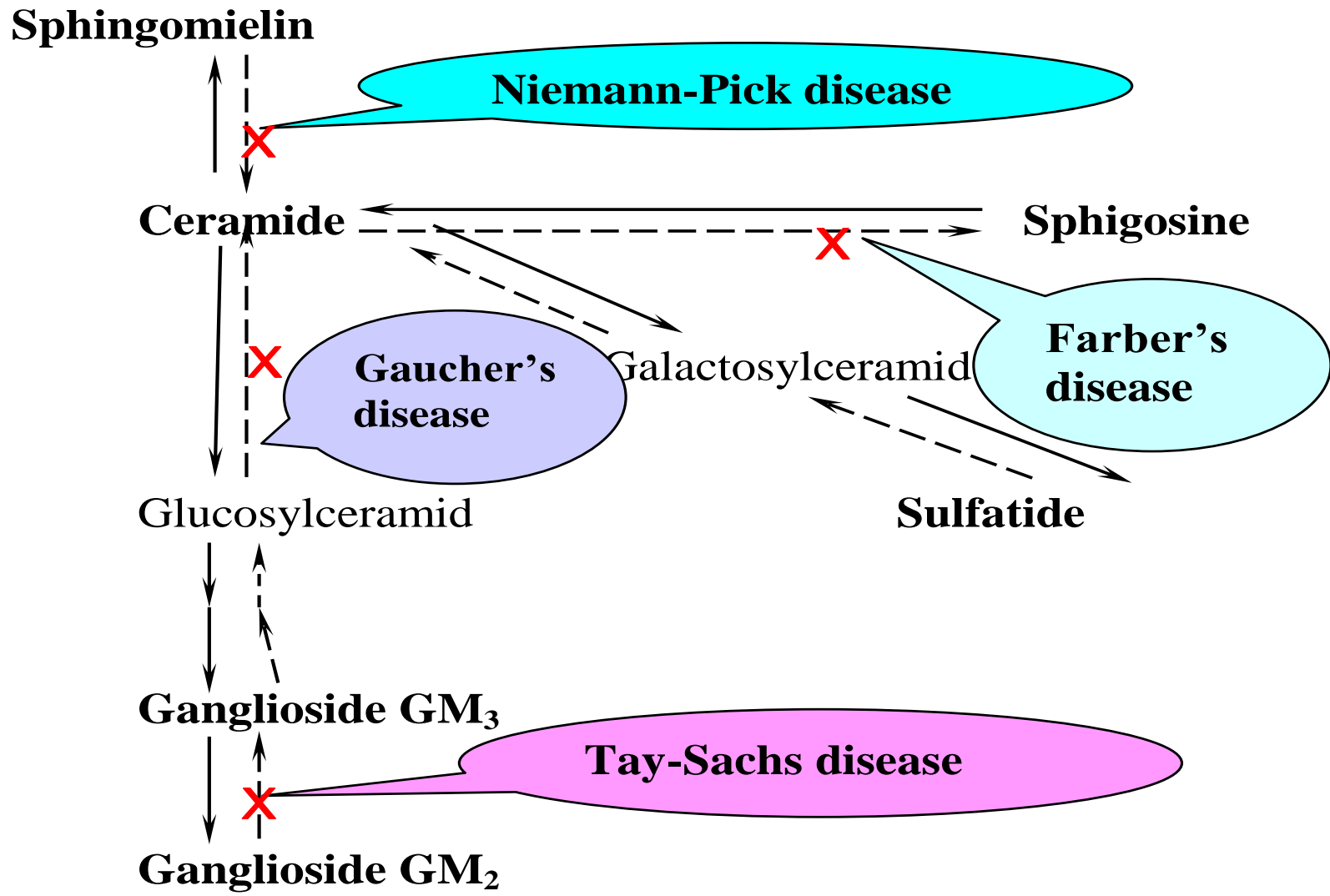
SPHINGOMYELIN



Sphingolipidoses (Lipid storage diseases)

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





Treatment

There is no effective treatment for many of these diseases.

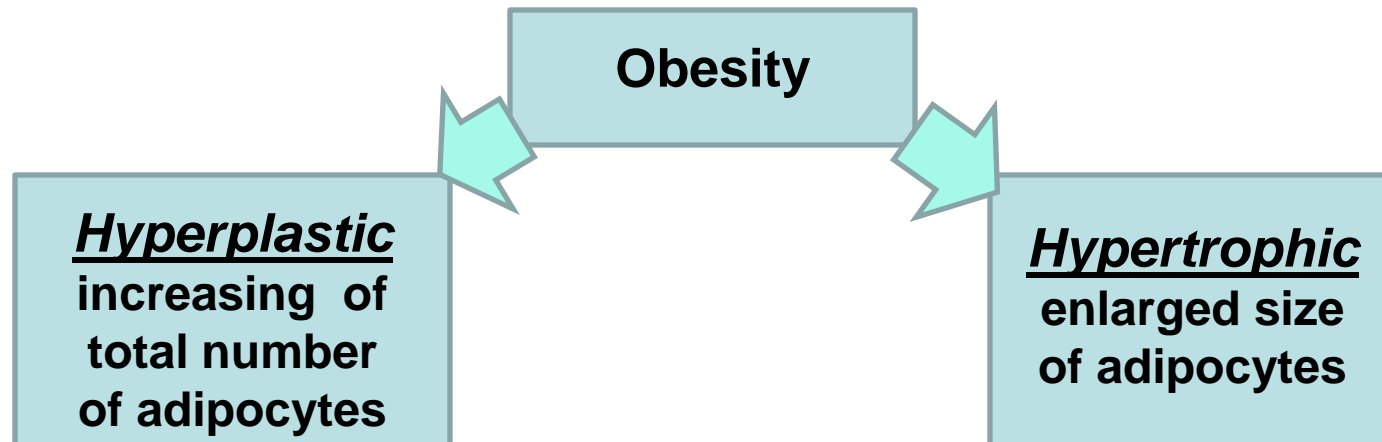
Recently some success has been achieved with enzymes that have been chemically modified to ensure binding to receptors of target cells, e.g. to macrophages in the liver in order to deliver β -glucosidase (glucocerebrosidase) in the treatment of Gaucher's disease.

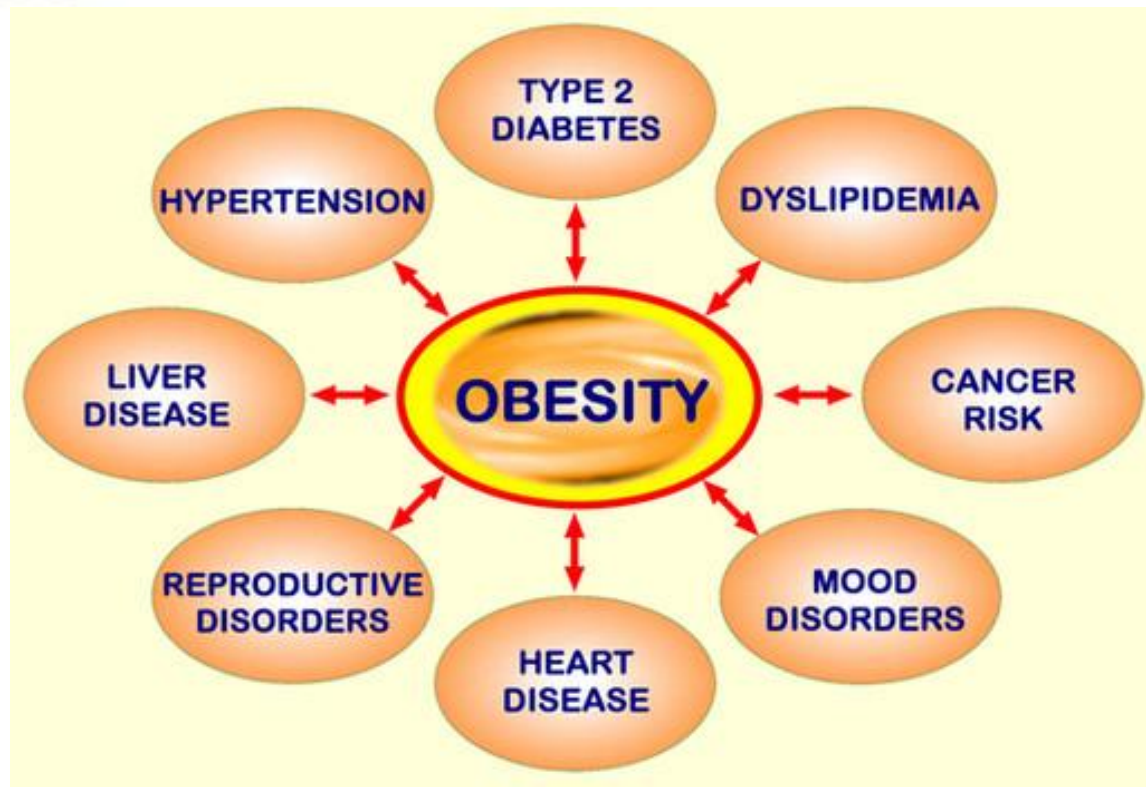
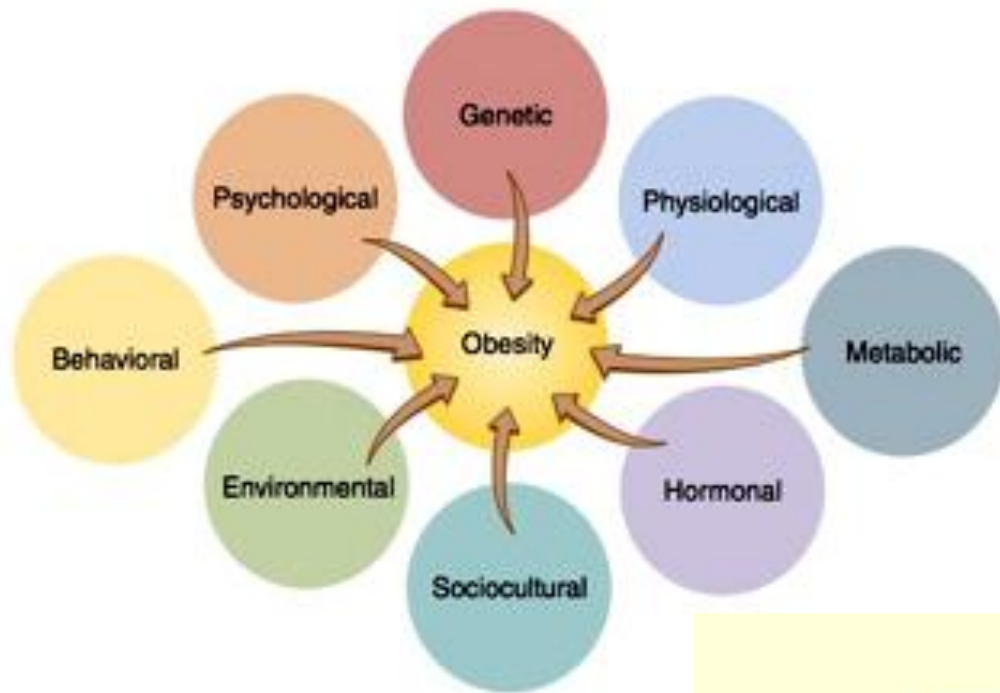
A recent promising approach is substrate reduction therapy to inhibit the synthesis of sphingolipids.

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





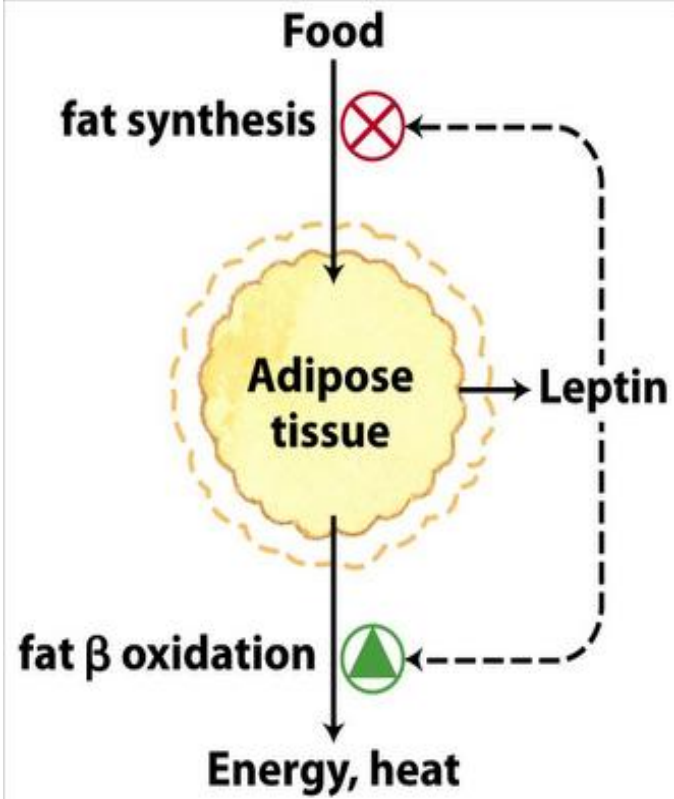
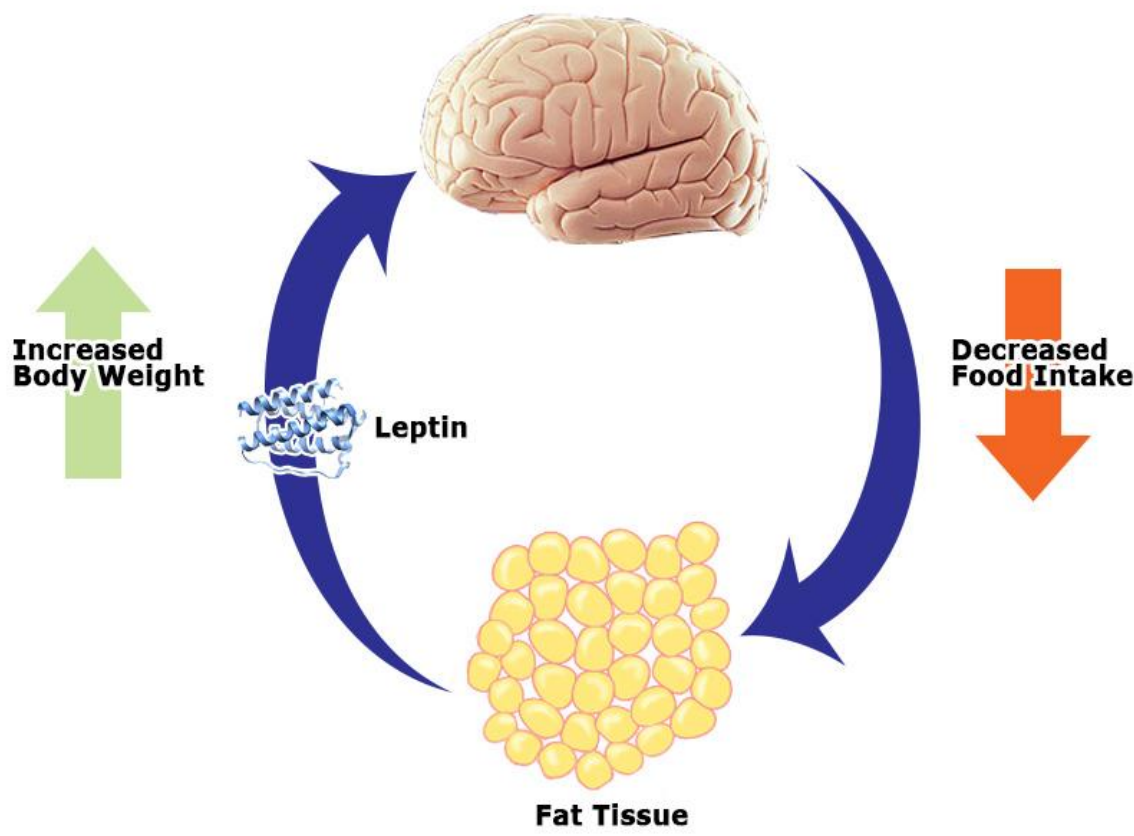
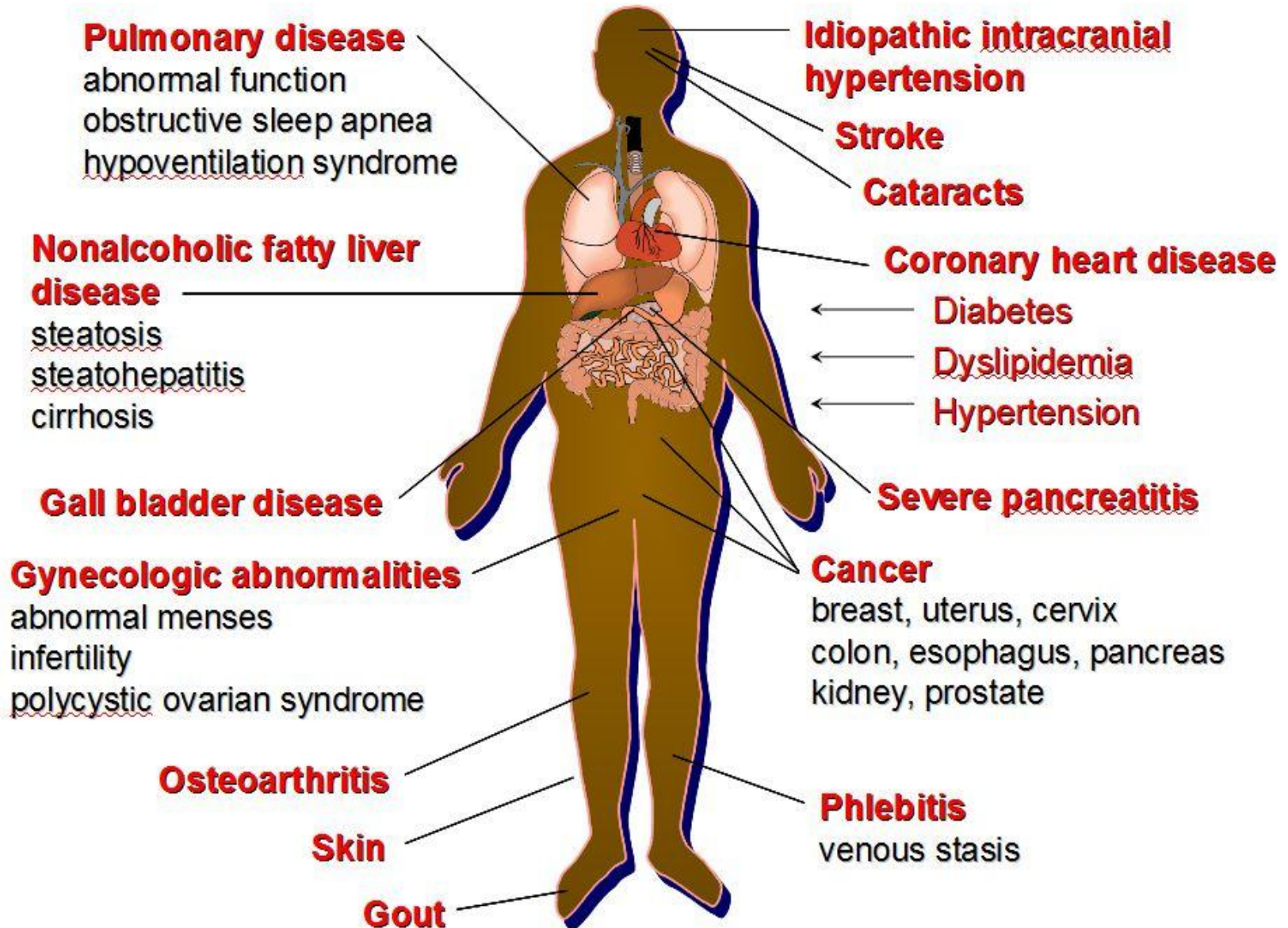


Figure 23-33
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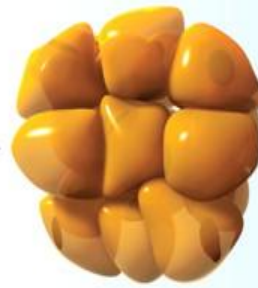


Medical Complications of Obesity

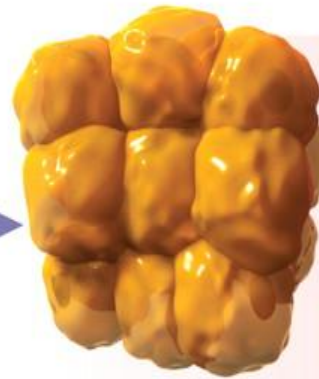


Positive energy balance

Subcutaneous adipose tissue expansion



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



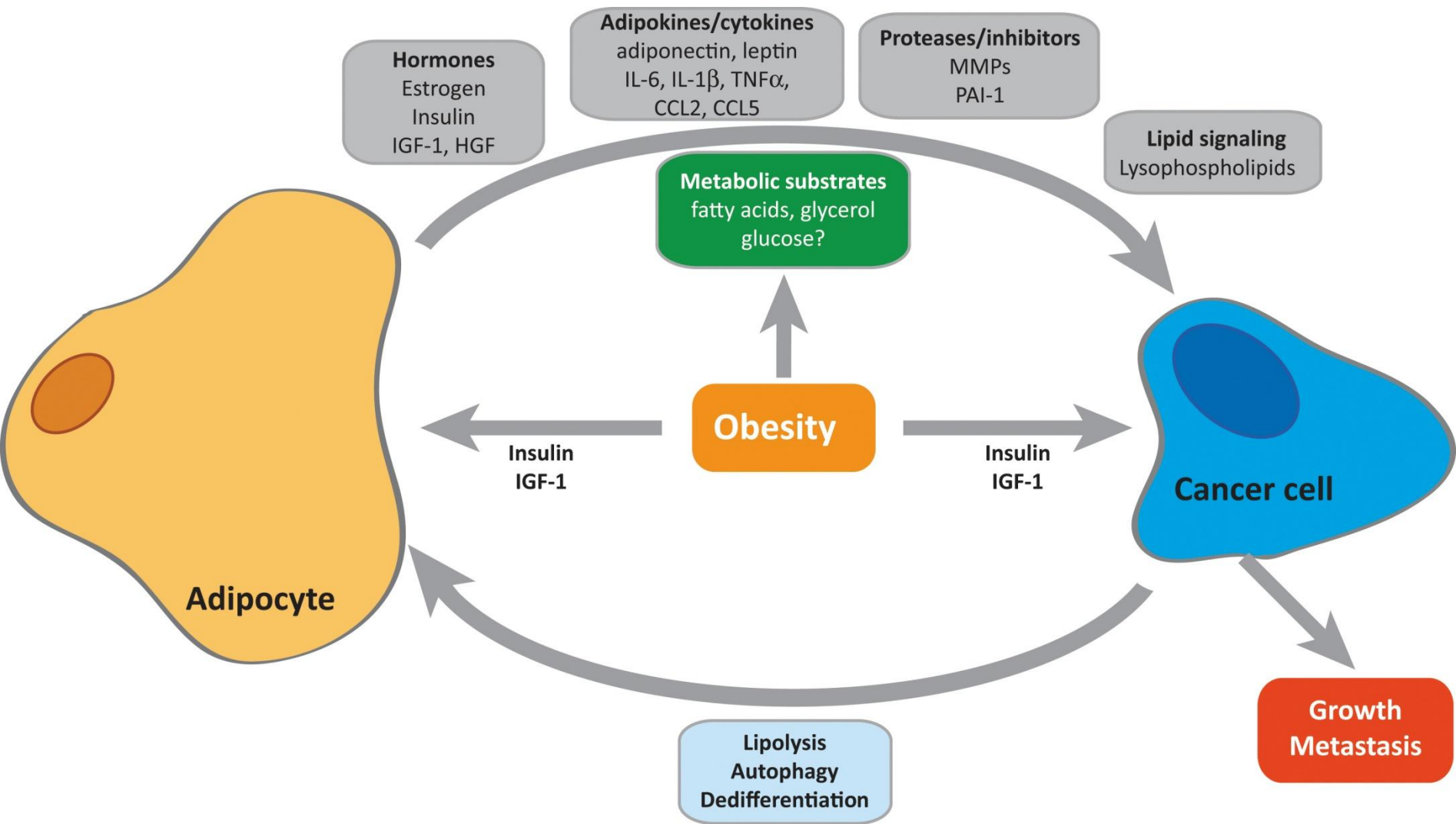
- Decreased adipogenesis; leads to adipocyte hypertrophy in the abdomen, thorax and possibly breasts
- Dysfunctional adipose tissue:
 - Storage capacity compromised
 - Increased lipolysis
 - Low-grade inflammation
 - Insulin resistance

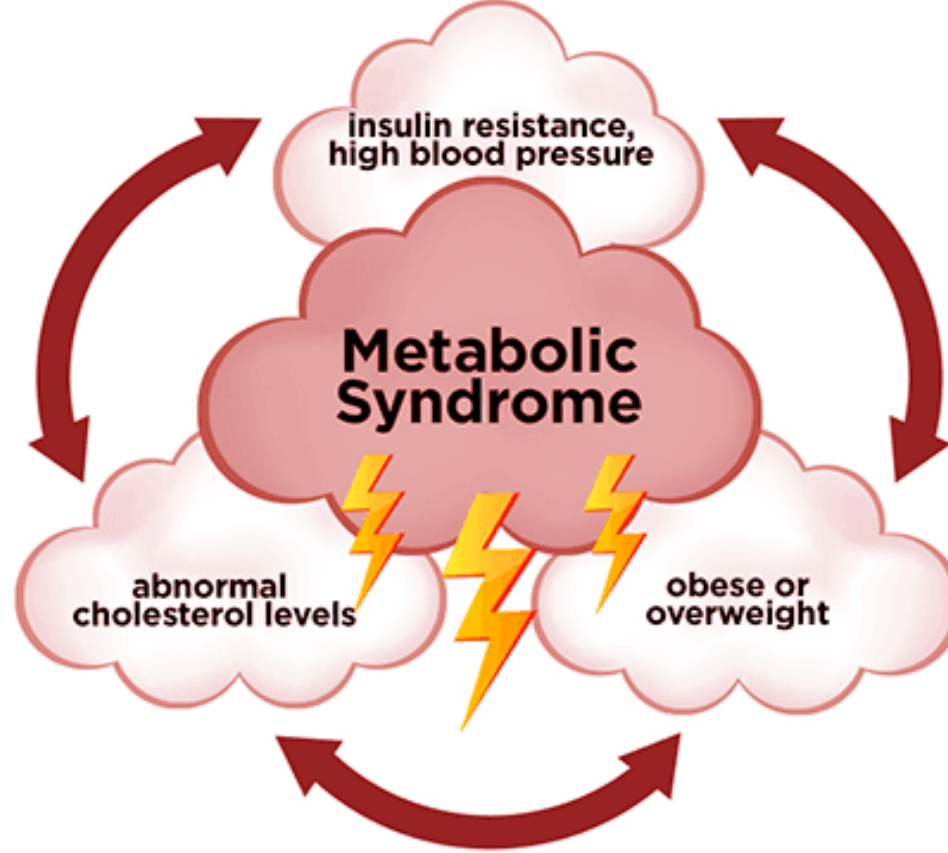
Pro-inflammatory adipokine profile

Increased visceral adipose tissue

Free fatty acids

Inflammation and malfunction of liver, skeletal muscle and islet insulin-secreting beta cells





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