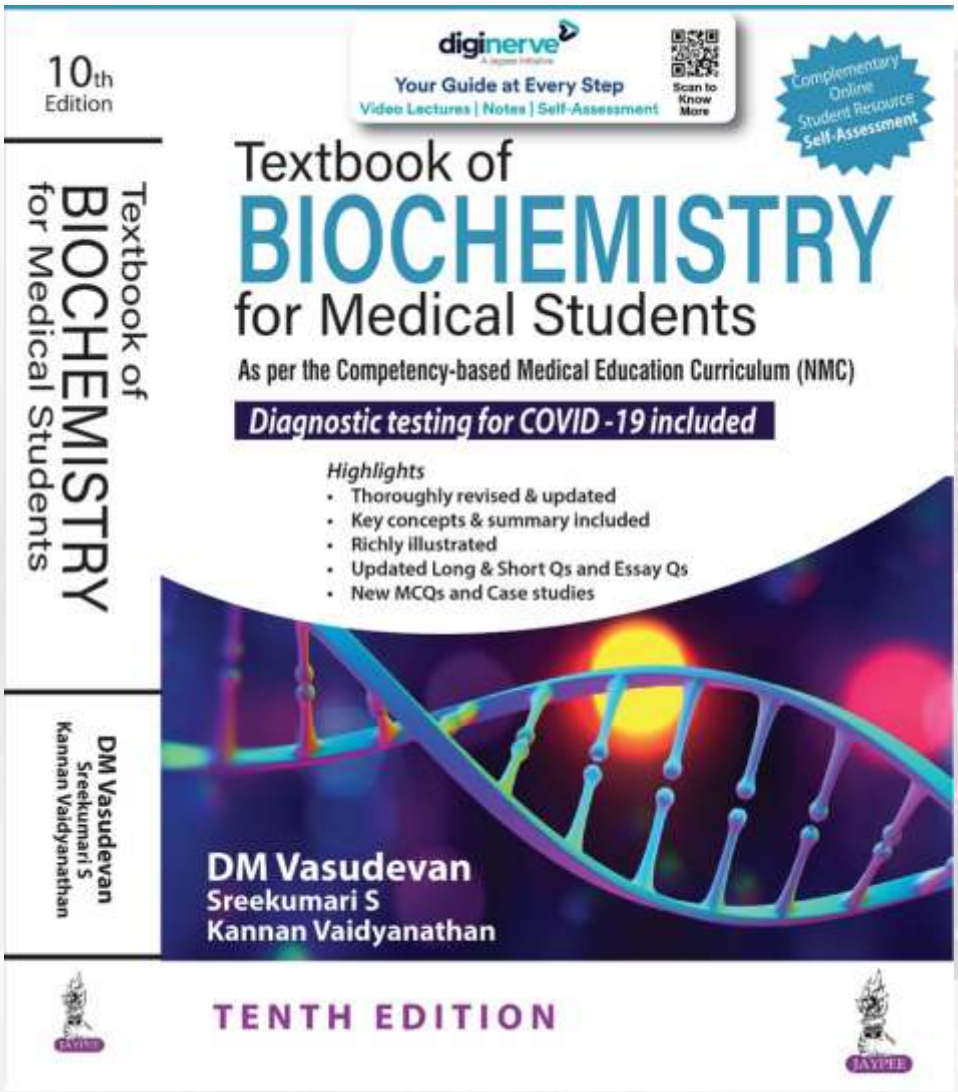


Chapter 11A:

Lipids, Digestion & absorption, Beta oxidation

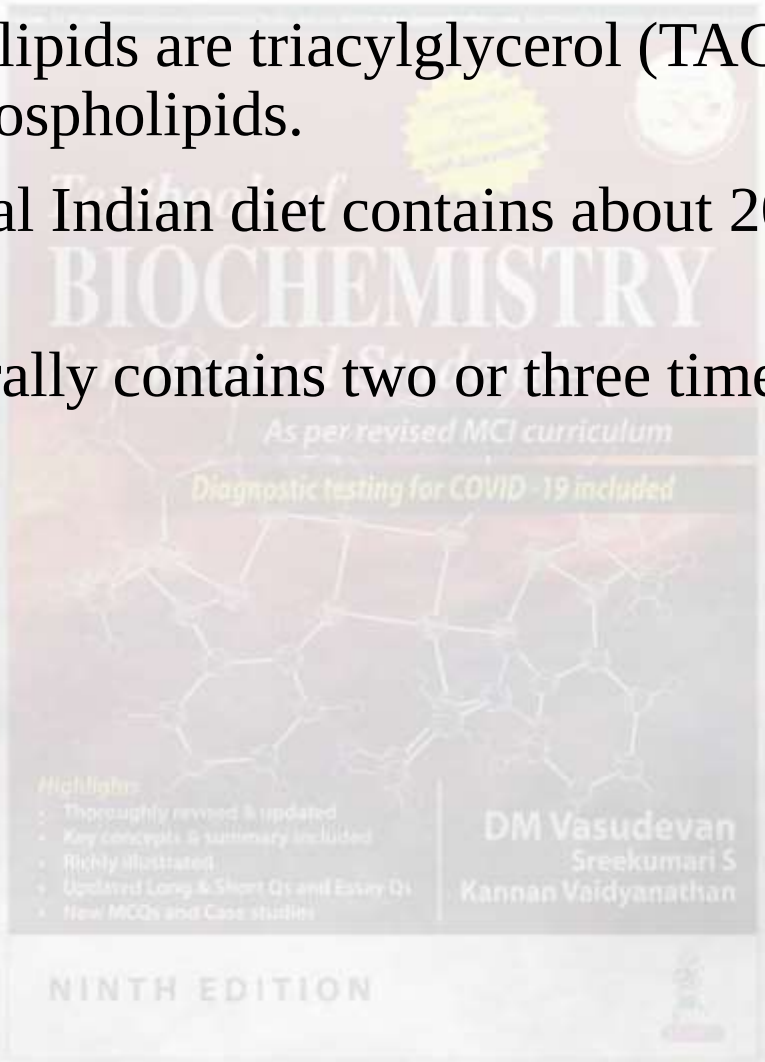
Textbook of
BIOCHEMISTRY
for Medical Students

By DM Vasudevan, *et al.*

TENTH EDITION

Digestion of Lipids

- The major dietary lipids are triacylglycerol (TAG) (triglycerides), cholesterol and phospholipids.
- The average normal Indian diet contains about 20–30 g of lipids per day.
- Western diet generally contains two or three times more than this quantity.



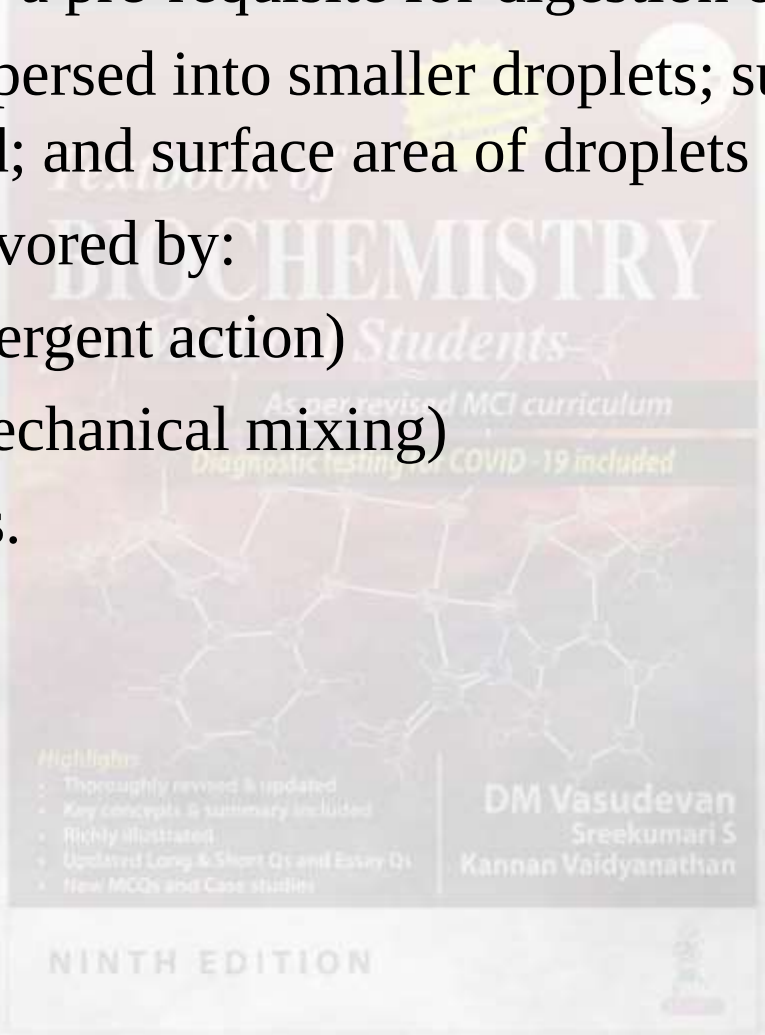
Digestion in Stomach

- The **lingual lipase** from the mouth enters stomach along with the food.
- It has an optimum pH of 2.5 – 5.
- The enzyme therefore continues to be active in the stomach.
- It acts on short chain triglycerides (SCT).
- SCTs are present in milk, butter and ghee.
- The action of lingual lipase is observed to be more significant in the newborn infants.
- **Gastric lipase** is acid stable, with an optimum pH about 5.4.
- It is secreted by Chief cells, the secretion is stimulated by Gastrin.
- Up to 30% digestion of triglycerides occurs in stomach.

Physiologically important lipases			
Lipase	Site of action	Preferred substrate	Product(s)
Lingual/acid- stable lipase	mouth, stomach	TAGs with medium/short chain FAs	FFA+DAG
Pancreatic lipase + co-lipase	Small intestine	TAGs with long-chain FAs	FFA+2MAG
Intestinal lipase with bile acids	Small intestine	TAGs with medium chain FAs	3 FFA+ glycerol
Phospholipase A2 + bile acids	Small intestine	PLs with unsaturated FA on position 2	Unsaturated FFA lysolecithin
Lipoprotein lipase + insulin	Capillary walls	TAGs in chylomicron or VLDL	FFA+ glycerol
Hormone sensitive lipase	Adipocyte	TAG stored in adipose tissue cells	FFA + DAG/MAG

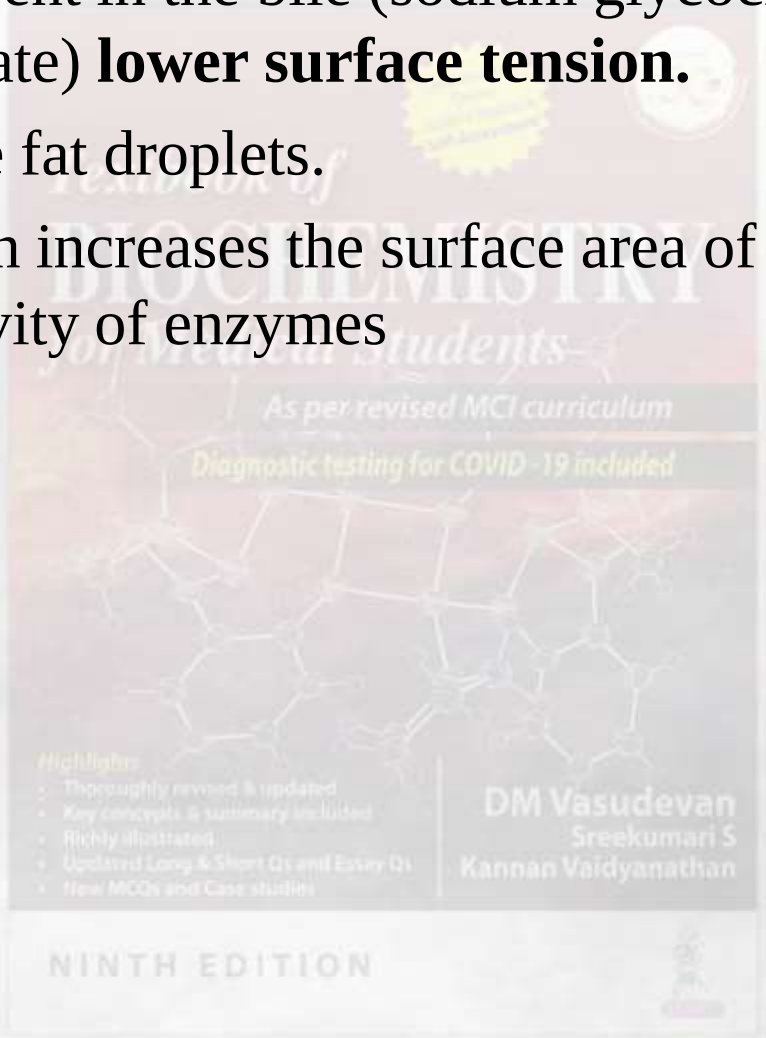
Digestion in Intestines

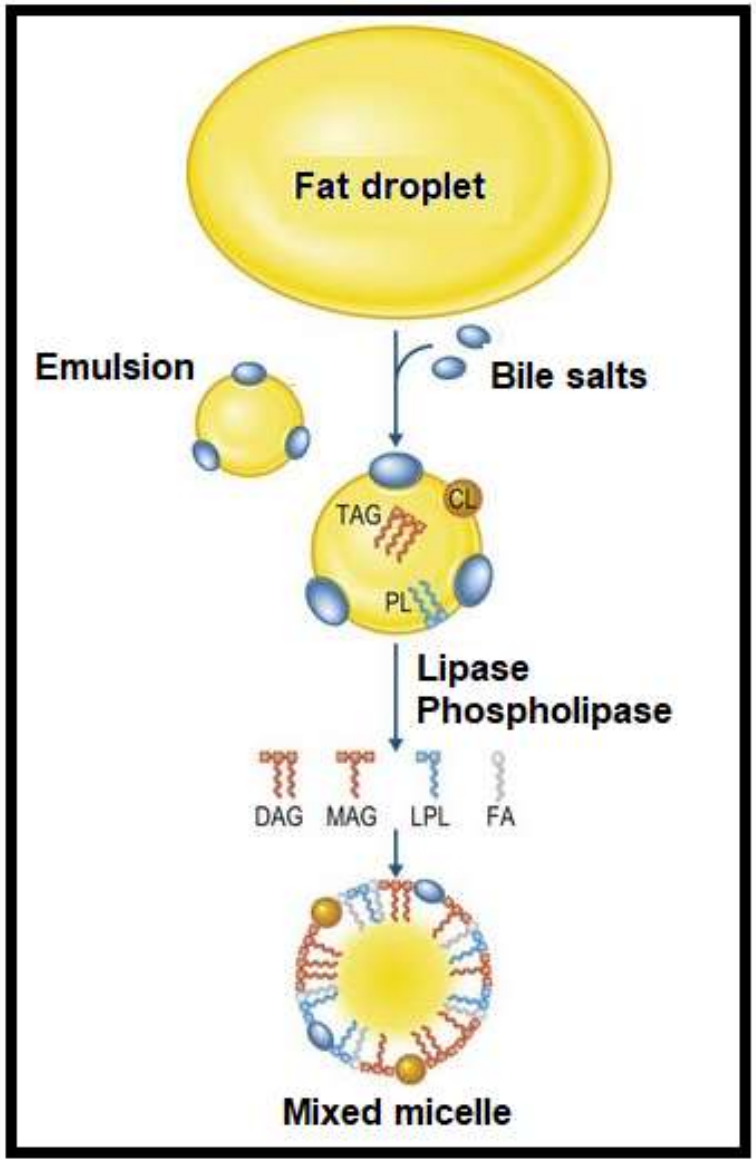
- **Emulsification** is a pre-requisite for digestion of lipids.
- The lipids are dispersed into smaller droplets; surface tension is reduced; and surface area of droplets is increased.
- This process is favored by:
  1. Bile salts (detergent action)
  2. Peristalsis (mechanical mixing)
  3. Phospholipids.



Bile Salts are Important for Digestion of Lipids

- The bile salts present in the bile (sodium glycocholate and sodium taurocholate) **lower surface tension.**
- They emulsify the fat droplets.
- The emulsification increases the surface area of the particles for enhanced activity of enzymes

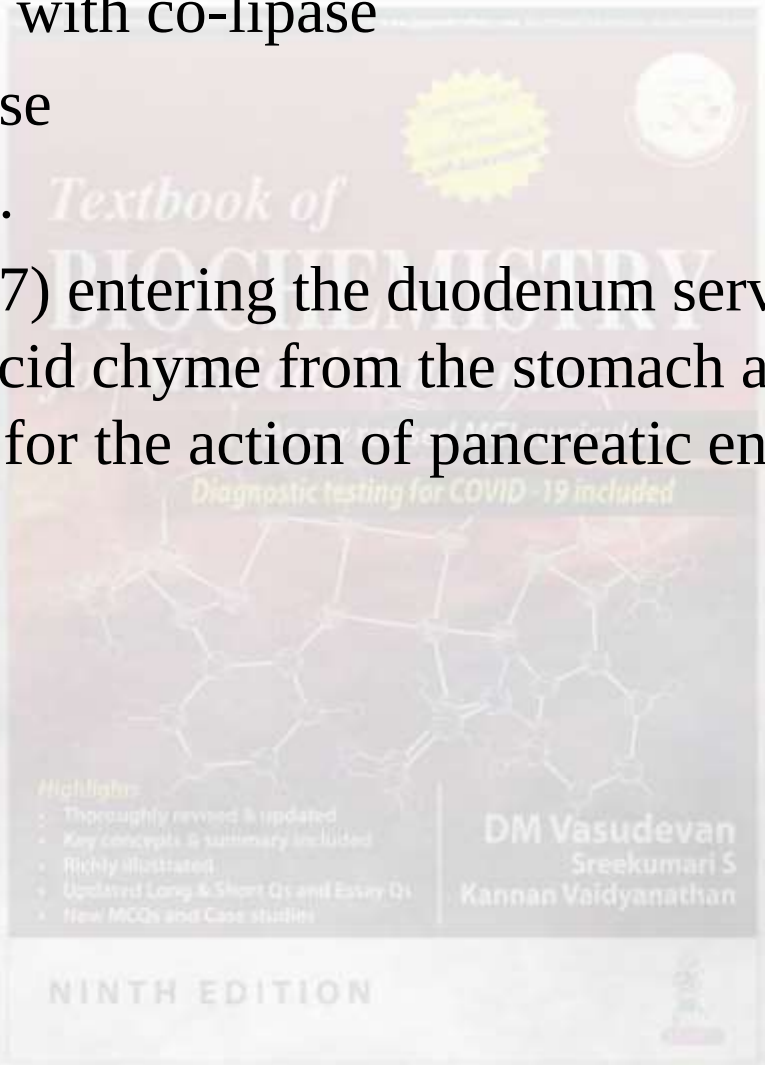




Action of bile salts. The hydrophobic portions of bile salts intercalate into the large aggregated lipid, with the hydrophilic domains remaining at the surface. This leads to the breakdown of large aggregates into smaller droplets and finally forms an emulsion. Thus, the surface area for the action of lipase is increased. With the help of lipase, colipase and phospholipase, TAG is successively broken to DAG, MAG and free fatty acids (partial hydrolysis). These along with cholesterol, lysophospholipids are incorporated into molecular aggregates to form mixed micelle. TAG= triacylglycerol, PL= phospholipid, DAG= diacylglycerol, MAG= monoacylglycerol, LPL= lysophospholipid, FA= fatty acid.

Lipolytic Enzymes in Intestines

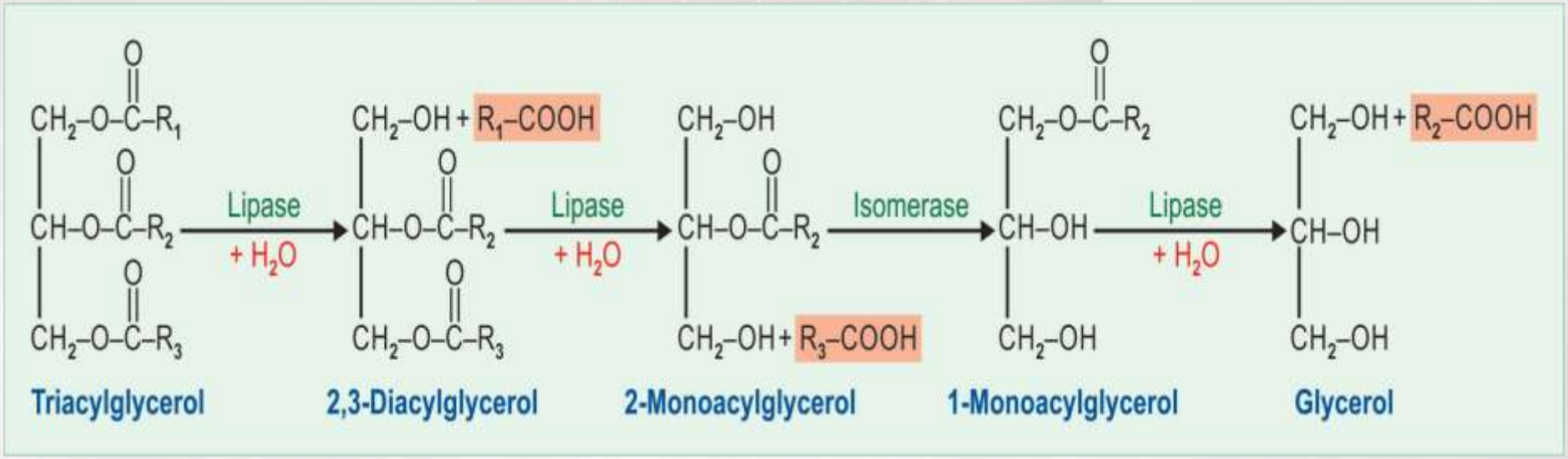
1. **Pancreatic lipase** with co-lipase
2. Cholesterol esterase
3. Phospholipase A2.
   - The bile (pH 7.7) entering the duodenum serves to neutralize the acid chyme from the stomach and provides a pH favorable for the action of pancreatic enzymes.



Physiologically important lipases			
Lipase	*Site of action*	*Preferred substrate*	*Product(s)*
Lingual/acid-stable lipase	Mouth, stomach	TAGs with short and medium chain FAs	FFA + DAG
Pancreatic lipase + co-lipase	Small intestine	TAGs with long-chain FAs	FFA + 2MAG
Intestinal lipase with bile acids	Small intestine	TAGs with medium chain FAs	3 FFA + glycerol
Phospholipase A_2 + bile acids	Small intestine	PLs with unsat. FA on position 2	Unsat FFA Lysolecithin
Lipoprotein lipase	Capillary walls	TAGs in chylomicron or VLDL	FFA + glycerol
Hormone-sensitive lipase	Adipocytes	TAG stored in adipose tissue	FFA + DAG

Digestion of Triacylglycerols (TAG)

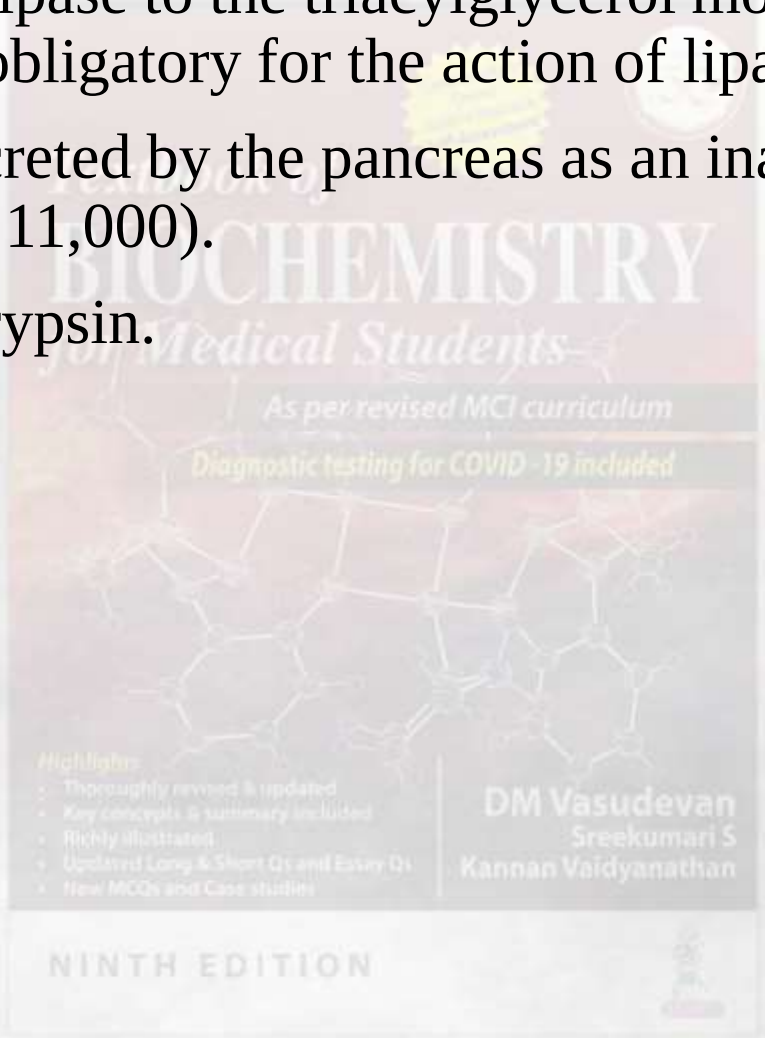
- **Pancreatic lipase** can easily hydrolyze the fatty acids esterified to the 1st and 3rd carbon atoms of glycerol forming 2-monoacylglycerol and two molecules of fatty acid.
- Then an **isomerase** shifts the ester bond from position 2 to 1.
- The bond in the 1st position is then hydrolyzed by the **lipase** to form free glycerol and fatty acid.



- The major end products of the digestion of TAG are 2-MAG (78%), 1-MAG (6%), glycerol and fatty acids (14%).
- Thus digestion of TAG is partial (incomplete).
- **Cholesterol** ester may be hydrolysed to free cholesterol and fatty acid.
- The action of **phospholipase** A2 produces lysophospholipid and a fatty acid.

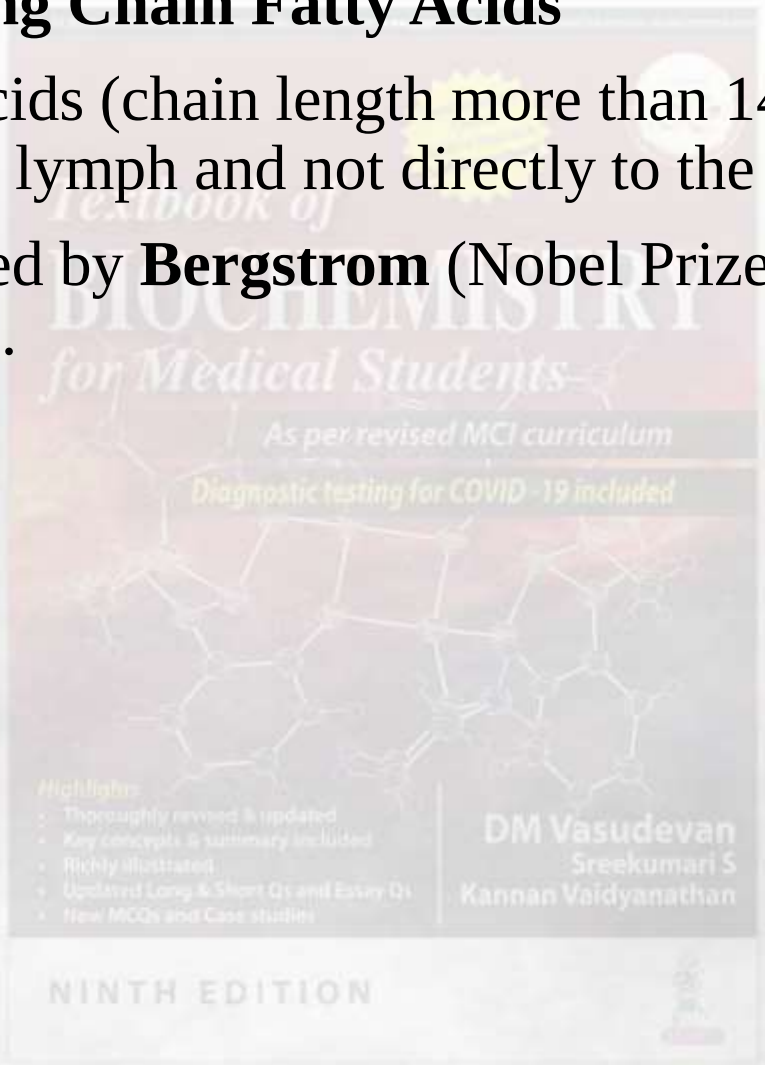
Colipase

- The binding of colipase to the triacylglycerol molecules at the oil water interface is obligatory for the action of lipase.
- The colipase is secreted by the pancreas as an inactive zymogen (molecular weight 11,000).
- It is activated by trypsin.



Absorption of Lipids

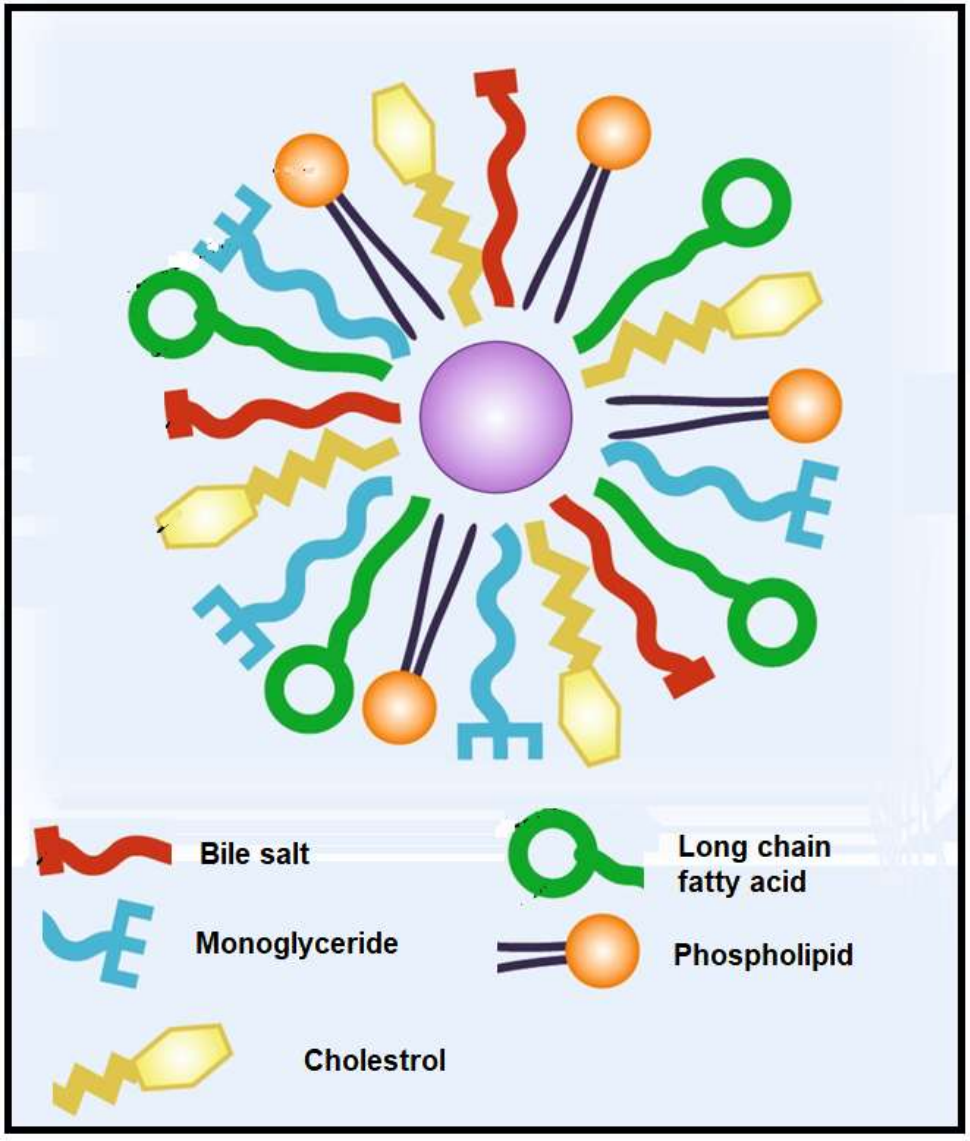
- **Absorption of Long Chain Fatty Acids**
- Long chain fatty acids (chain length more than 14 carbons) are absorbed to the lymph and not directly to the blood.
- The theory proposed by **Bergstrom** (Nobel Prize, 1982) has the following steps.



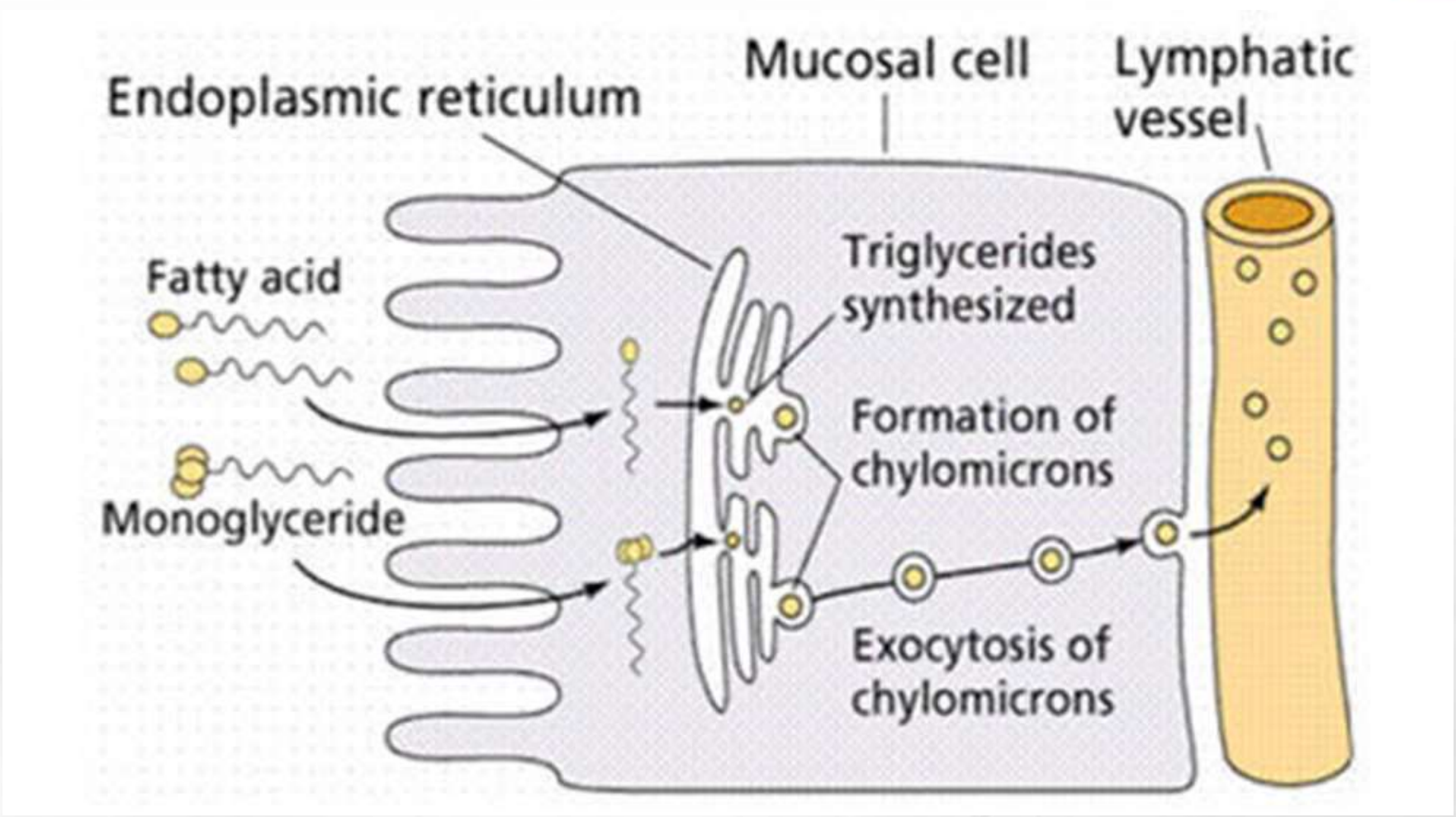
Mixed Micelle Formation

- The bile salt micelle incorporates products of digestion, namely 2 monoacyl-glycerols, long chain fatty acids, cholesterol, phospholipids and lysophospholipids into molecular aggregates to form mixed micelle.
- The micelles are spherical particles with a hydrophilic exterior and hydrophobic interior core.
- Due to their amphipathic nature, the **bile salts** help to form micellar aggregates.

Mixed Micelle

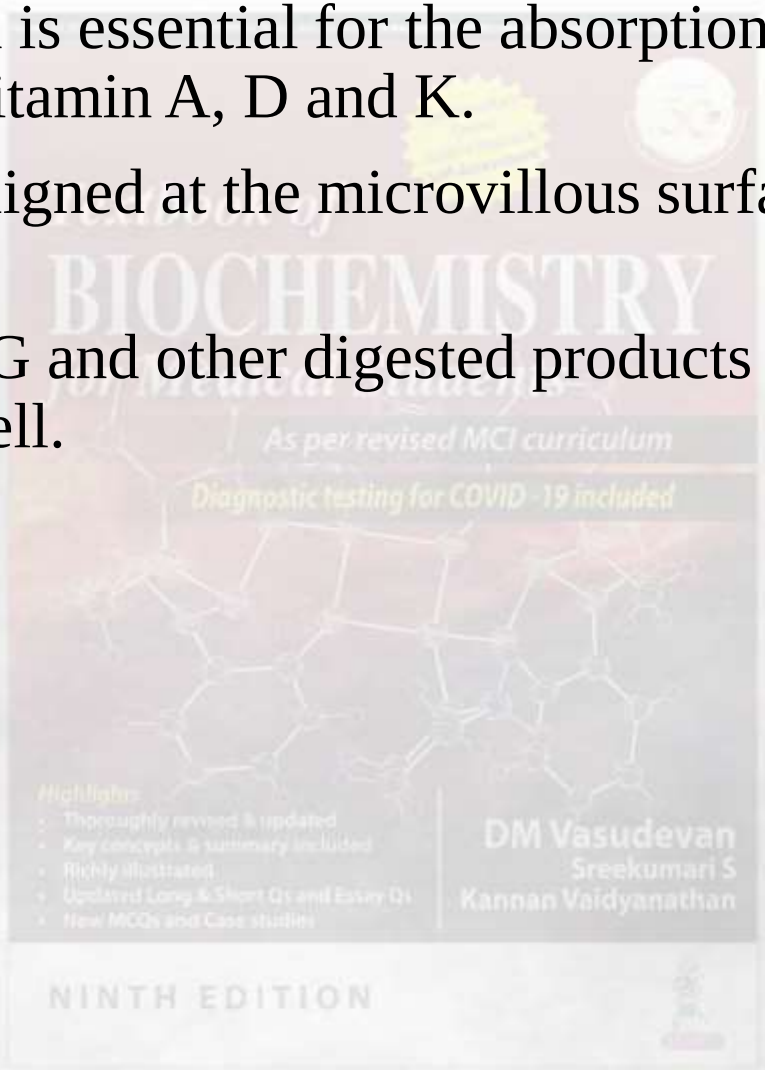


Absorption of fat as chylomicrons to lymphatics

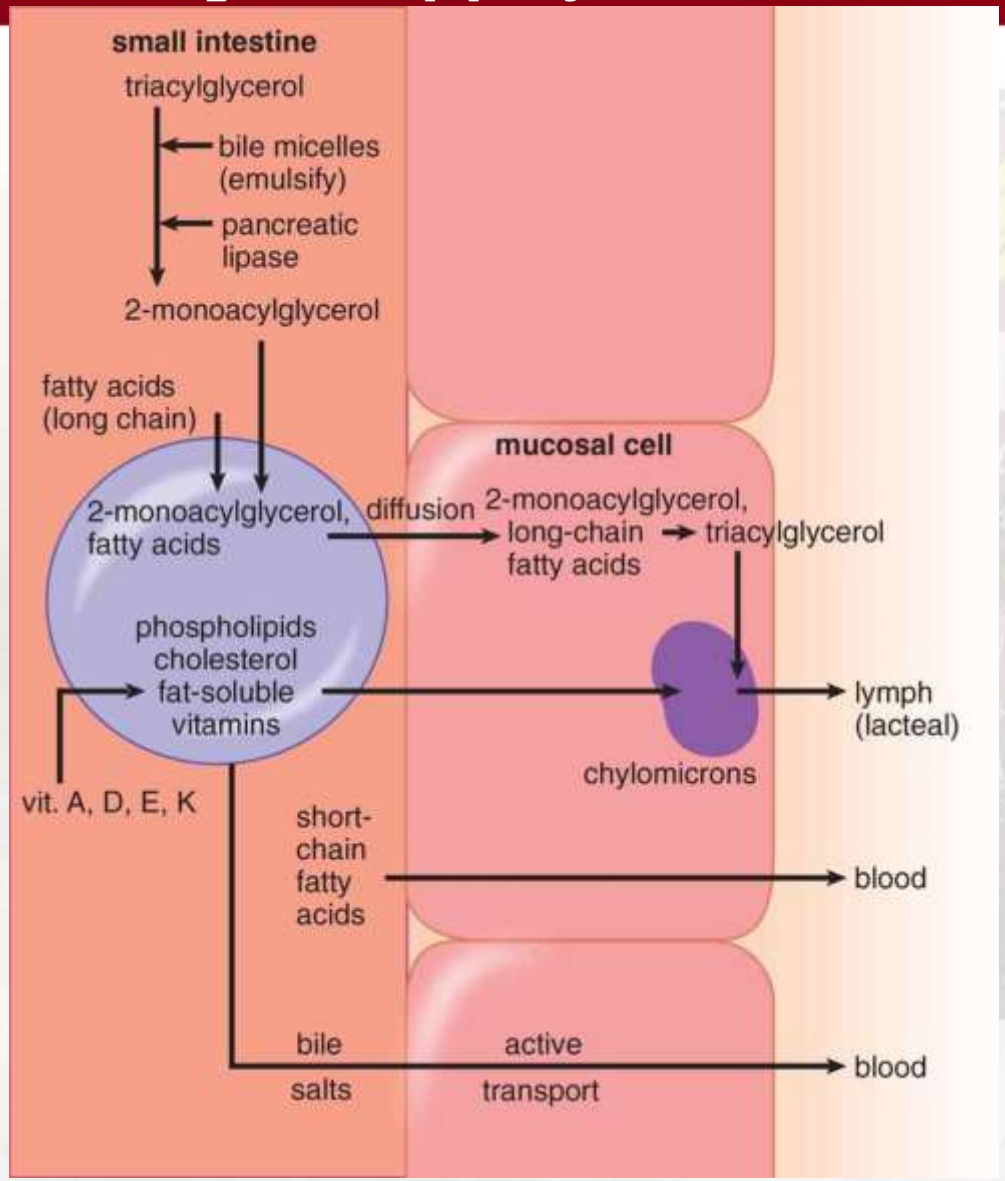


Absorption of fat as chylomicrons to lymphatics.

- Micellar formation is essential for the absorption of fat-soluble vitamins such as vitamin A, D and K.
- The micelles are aligned at the microvillous surface of the **jejunal mucosa.**
- Fatty acids, 2-MAG and other digested products passively diffuse into the mucosal cell.



Absorption of fatty acids



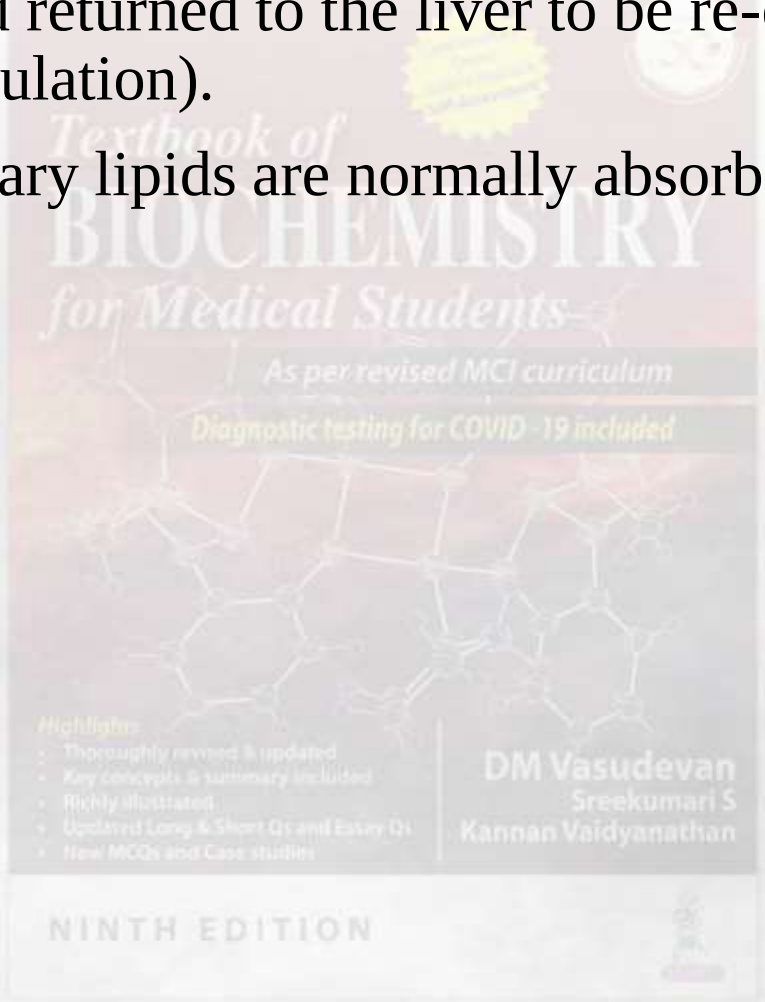
Absorption of fatty acids.

Long-chain fatty acids are absorbed into the intestinal cell wall, where they are re-esterified, incorporated into chylomicrons and enter into lymphatics.

Short chain and medium chain fatty acids are directly absorbed into blood capillaries. Bile acids are reabsorbed into portal vein.

Enterohepatic Circulation of Bile Salts

- The bile salts are left behind which are mostly reabsorbed from the ileum and returned to the liver to be re-excreted (enterohepatic circulation).
- About 98% of dietary lipids are normally absorbed.

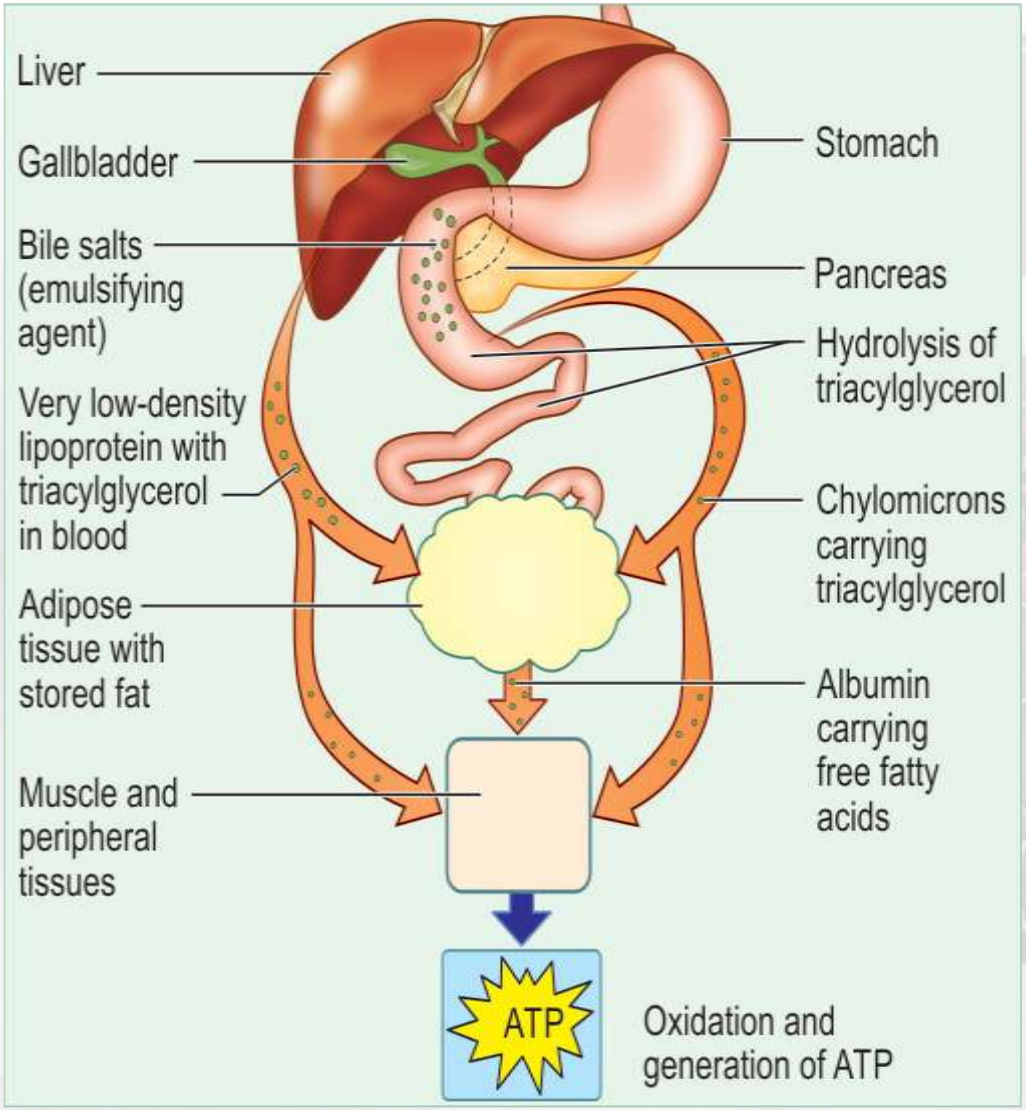


Re-esterification Inside the Mucosal Cell

- Once inside the intestinal mucosal cell, the long chain fatty acids are re-esterified to form triacylglycerols.
- The fatty acids are first activated to fatty acyl-CoA by the enzyme, **acyl-CoA synthetase** or thiokinase.
- This needs lysis of two high energy bonds.
- Two such activated fatty acids react with monoacyl-glycerol (MAG) to form the triacylglycerol.
- Majority of molecules follow this MAG pathway.
- Free **glycerol** absorbed from intestinal lumen directly enters into the bloodstream.
- So free glycerol is not available for re-esterification.
- But the cells can derive glycerol phosphate from glucose by glycolysis, and add 3 molecules of acyl groups to synthesize TAG.

Chylomicrons

- The TAG, cholesterol ester and phospholipid molecules along with apoproteins B48, and apo-A are incorporated into chylomicrons.
- The chyle (milky fluid) from the intestinal mucosal cells loaded with chylomicrons are transported through the lacteals into the thoracic duct and then emptied into systemic circulation.
- The serum may appear milky after a high fat meal (post-prandial lipemia) due to the presence of chylomicrons in circulation.
- Normally the lipemia clears within a few hours by the uptake of chylomicrons by tissues.



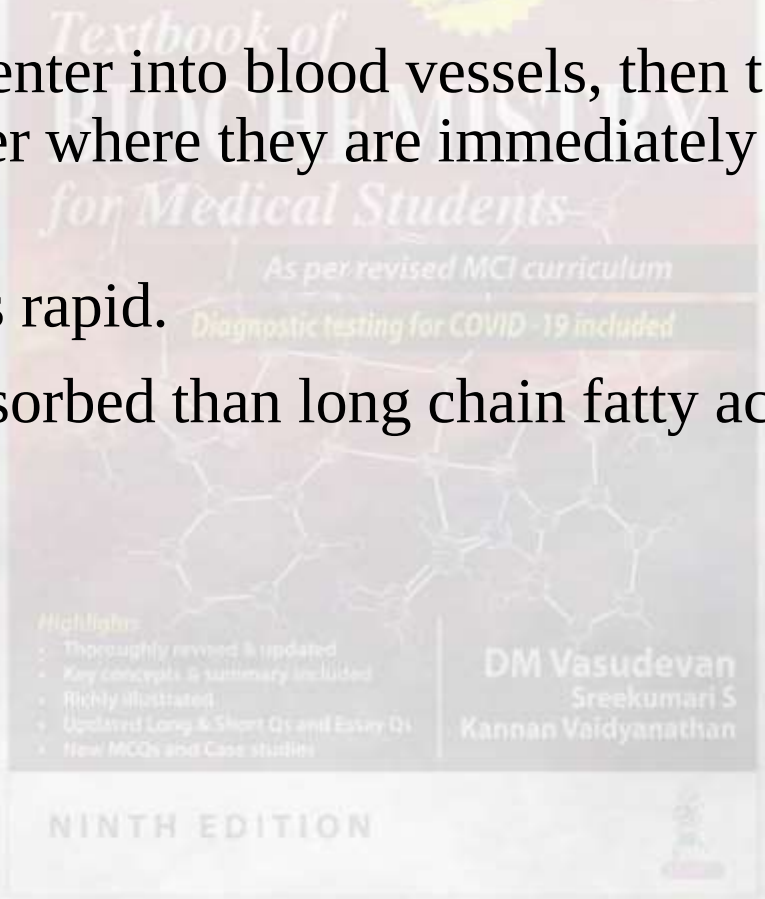
Summary of utilization of fat.

Steps of Lipid Absorption

1. Minor digestion of triacylglycerols in mouth and stomach by lingual (acid-stable) lipase.
2. Major digestion of all lipids in the lumen of the duodenum / jejunum by pancreatic lipolytic enzymes.
3. Bile acids facilitate the formation of mixed micelles.
4. Passive absorption of the products of lipolysis from the mixed micelle into the intestinal epithelial cell.
5. Re-esterification of 2-monoacylglycerol with free fatty acids inside the intestinal enterocyte.
6. Assembly of chylomicrons containing Apo B-48, triacylglycerol, cholesterol esters and phospholipids and export from intestinal cells to the lymphatics.
7. Absorption of short chain free fatty acid is different, they are not re-esterified, they are absorbed directly to blood stream (not to lymphatics).

SCFA Absorption is Different

- **Short chain** fatty acids (SCFA) (seen in milk, butter, ghee) and **medium chain** fatty acids (MCFA) (in coconut oil and mother's milk) do not need re-esterification.
- They can directly enter into blood vessels, then to portal vein, finally to liver where they are immediately utilized for energy.
- Their absorption is rapid.
- They are better absorbed than long chain fatty acids.



Abnormalities in Absorption of Lipids

- **Defective digestion:**
- In steatorrhea, daily excretion of fat in feces is more than 6 g per day. (Greek word, "steat", means fat).
- It is due to chronic diseases of pancreas.
- In such cases, unsplit fat is seen in feces.
- **Defective absorption:**
- On the other hand, if the absorption alone is defective, most of the fat in feces may be split fat, i.e. fatty acids and monoglycerides. Defective absorption may be due to diseases:

  A. **Celiac** disease, sprue, Crohn's disease.

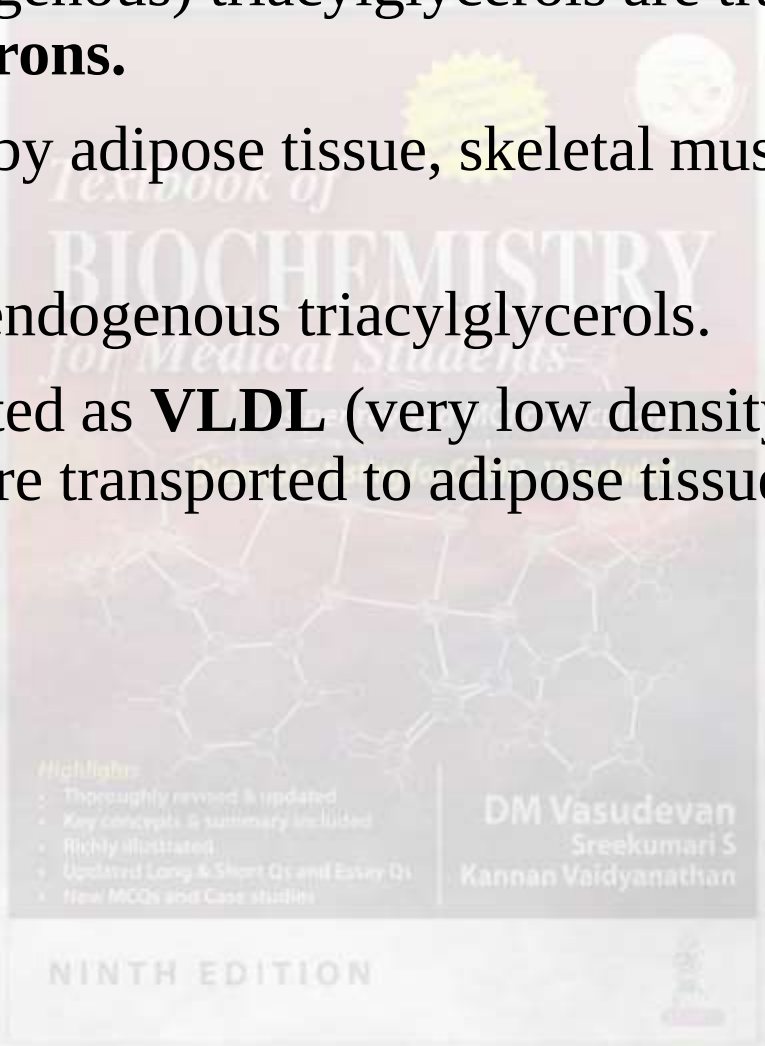
  B. **Surgical removal** of intestine.

C. **Obstruction of bile duct**: This may be due to gallstones, tumors of head of pancreas, enlarged lymph glands, etc.

- The result is deficiency of bile salts.
- In such cases, triacylglycerols with short chain and medium chain fatty acids (SCT and MCT) are digested and absorbed properly, because they do not require micellerization for absorption.
- Since milk fat and coconut oil are made up of MCT, they are therapeutically useful in malabsorption syndromes.
- **Chyluria**. There is an abnormal connection between the urinary tract and lymphatic drainage system of the intestine.
- Urine appears milky due to lipid droplets.
- **Chylothorax** can result from an abnormal connection between the pleural cavity and thoracic duct.

Fate of Chylomicrons

- The absorbed (exogenous) triacylglycerols are transported in blood as **chylomicrons.**
- They are taken up by adipose tissue, skeletal muscle and liver.
- Liver synthesizes endogenous triacylglycerols.
- These are transported as **VLDL** (very low density lipoproteins) and are transported to adipose tissue.

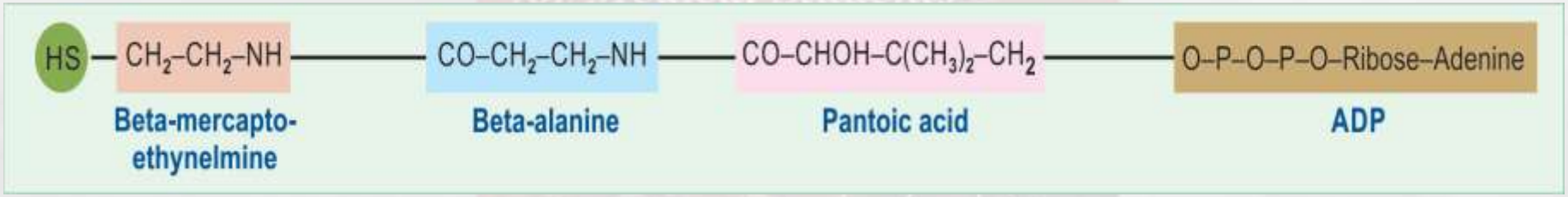


Digestion of Medium Chain Fatty Acids

- Digestion and metabolism of SCFAs and MCFAs are entirely different from those of LCFAs.
- Triglycerides containing small and medium chain fatty acids (SCT and MCT) do not require prolonged digestion.
- **Pancreatic lipase and bile salts are not required.**
- MCT-specific lipase catalyzes the complete hydrolysis of SCT/MCT into glycerol and small/medium chain fatty acids.
- These free MCFAs **diffuse directly into portal circulation.**
- SCFA and MCFA are preferentially oxidized by peripheral cells, and so they are not deposited in adipose tissues.

Beta Oxidation

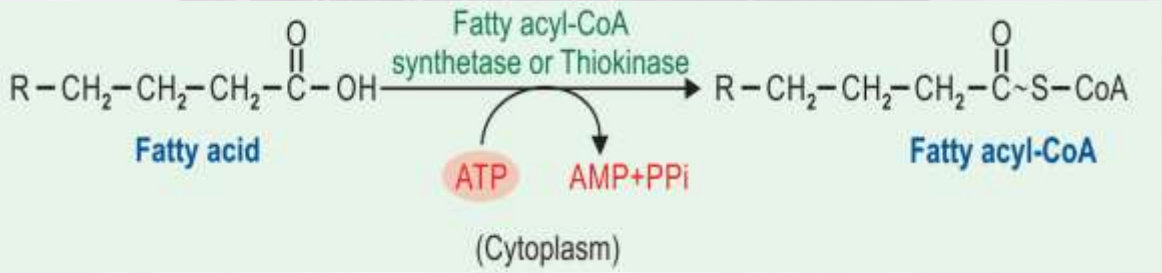
- This process is known as beta-oxidation, because the oxidation and splitting of **two-carbon** units occur at the beta-carbon atom.
- The oxidation of the hydrocarbon chain occurs by a sequential cleavage of two-carbon atoms
- **PREPARATIVE STEP**
- The co-enzyme A is a complex molecule containing B complex vitamin pantothenic acid and a molecule of beta mercapto ethanolamine; this SH group forms thioester bond in acyl-CoA.
- To emphasize the function of the SH group, the CoA is sometimes written as CoA-SH.



Structure of coenzyme A (Co-A) (CoA-SH).

Preparative Step 1: Activation of Fatty Acids

- Fatty acids are activated to their coenzyme A (CoA) derivative.
- This activation is taking place in **cytoplasm.**
- ATP is hydrolyzed to AMP and PPi and the energy from hydrolysis of PPi drives the reaction forward. Thus **two high energy bonds** are utilized in this reaction.
- The enzyme is a **thiokinase** or fatty acyl-CoA **synthetase** (Step 0).
- Three different enzymes, one each for short chain, medium chain and long chain fatty acids have been identified.
- Small chain fatty acids may also be activated by thiophorase enzyme, using succinyl-CoA.

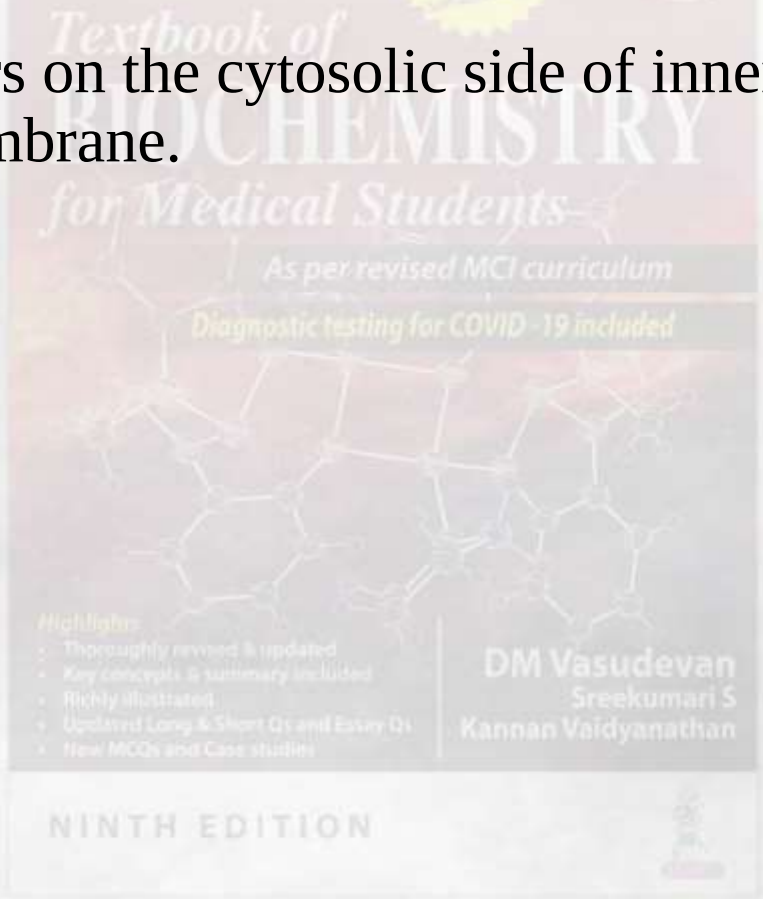


Preparative Step 2: Role of Carnitine

- Fatty acids are activated in the cytoplasm; but **beta oxidation is in mitochondria**.
- So transport of fatty acids through the mitochondrial membrane is essential.
- The long chain fatty acyl-CoA cannot pass through the inner mitochondrial membrane.
- Therefore a transporter, carnitine is involved in transfer of fatty acids.
- Carnitine is β-hydroxy-γ-trimethyl ammonium butyrate:
- $(CH3)_3–N+–CH2–CHOH–CH2–COOH$.

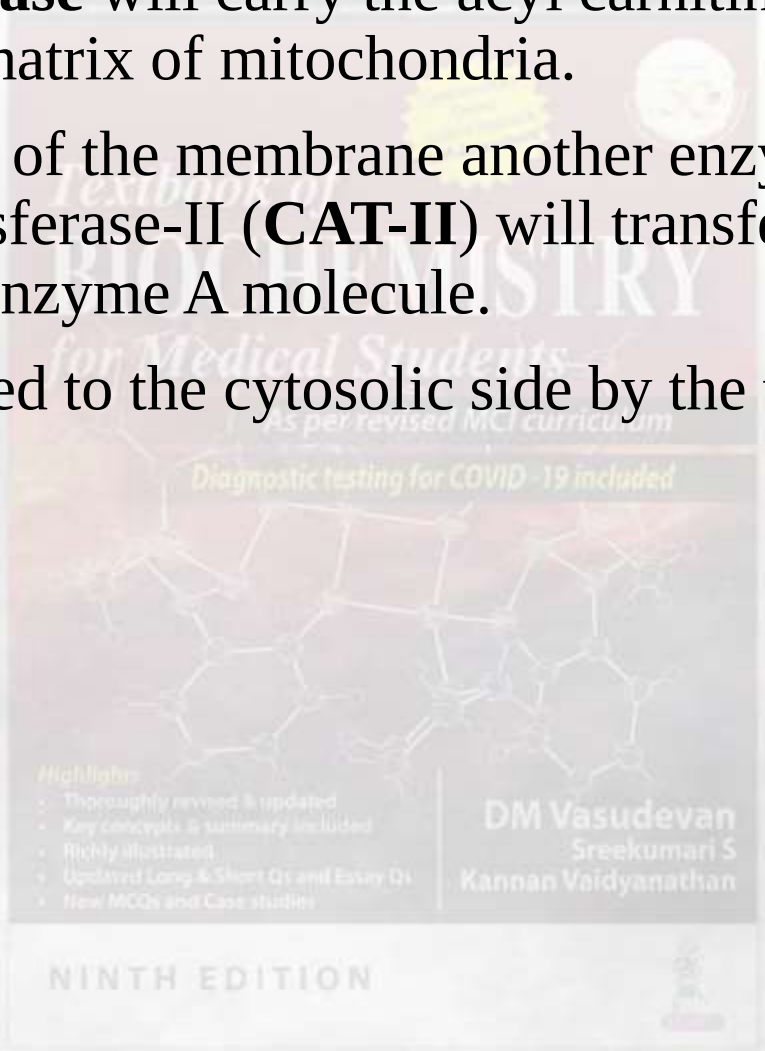
Preparative Step 3: Carnitine Acyl Transferase

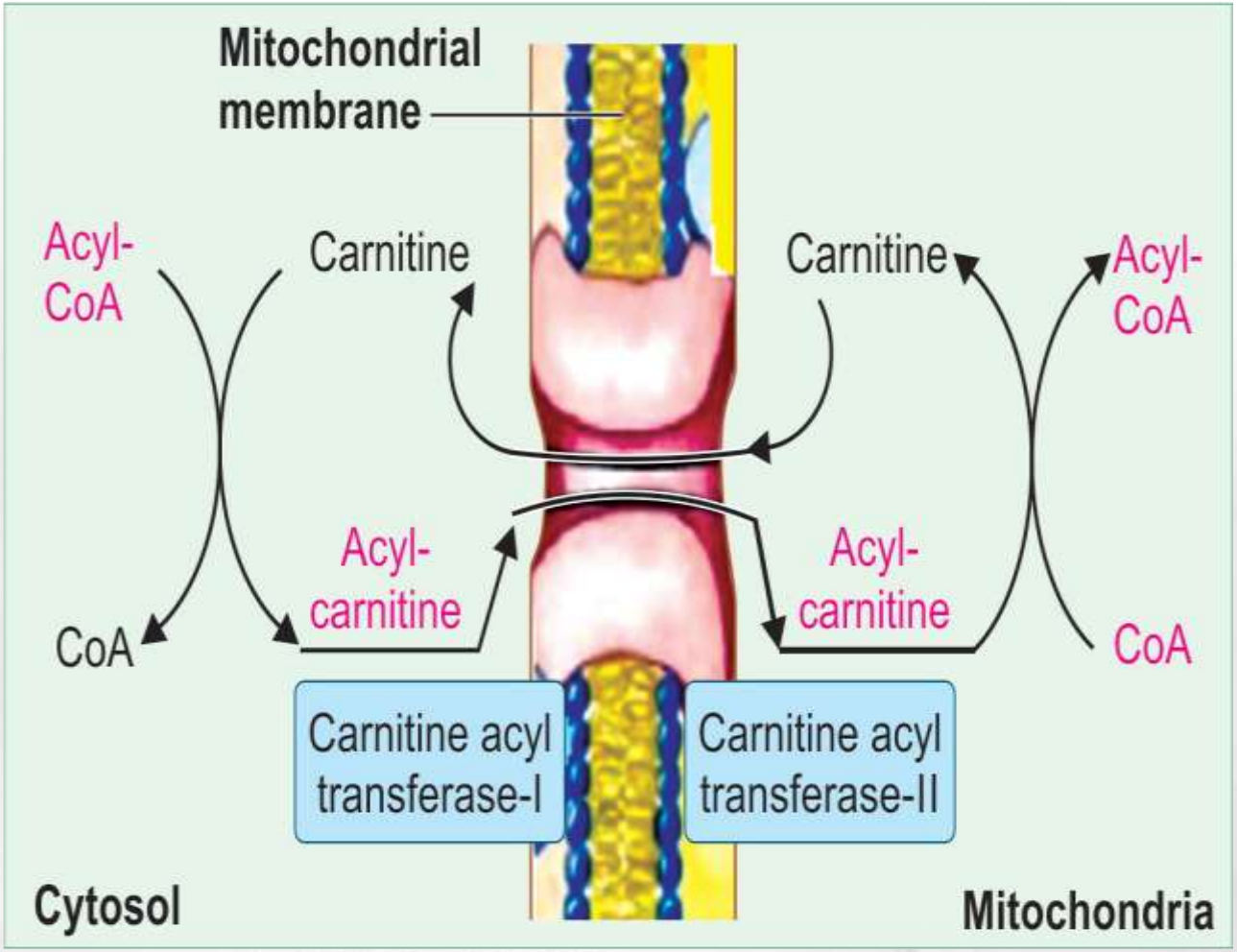
- The enzyme carnitine acyl transferase-I (**CAT-I**) will transfer the fatty acyl group to the hydroxyl group of carnitine to form **acyl carnitine.**
- The reaction occurs on the cytosolic side of inner mitochondrial membrane.



Preparative Step 4: Translocase

- A protein **translocase** will carry the acyl carnitine across the membrane to the matrix of mitochondria.
- On the matrix side of the membrane another enzyme, carnitine acyl transferase-II (**CAT-II**) will transfer the acyl group back to co-enzyme A molecule.
- Carnitine is returned to the cytosolic side by the translocase.

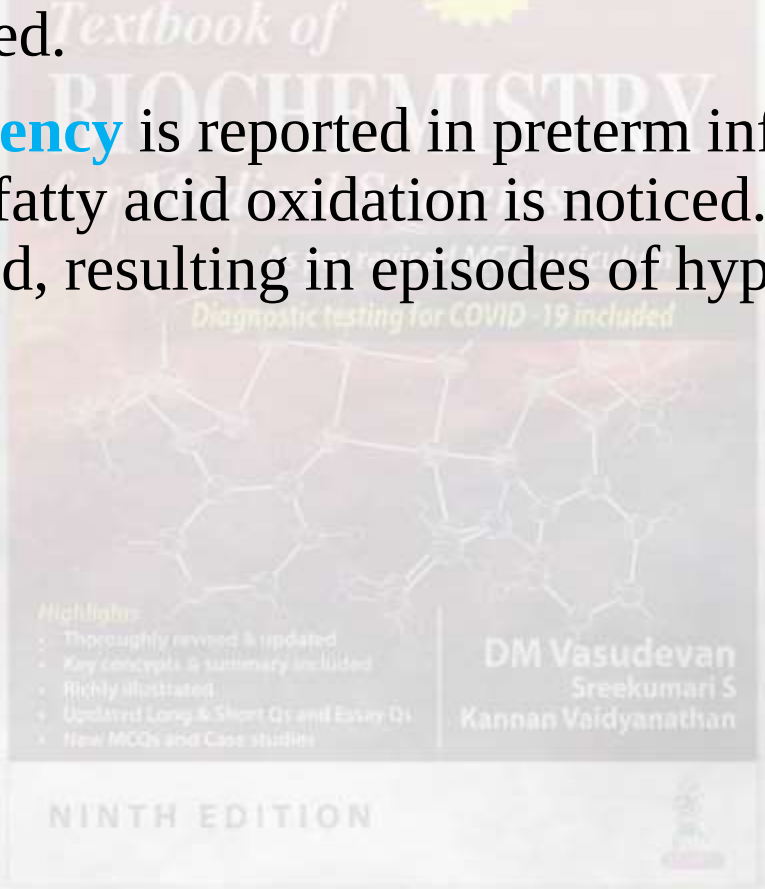




Role of carnitine in transport of acyl groups

Clinical Applications

1. **Medium chain** and short chain fatty acids do not require carnitine for transport across the inner mitochondrial membrane. So, medium chain and short chain fatty acids are easily oxidized.
2. **Carnitine deficiency** is reported in preterm infants, in whom impaired fatty acid oxidation is noticed. So more glucose is utilized, resulting in episodes of hypoglycemia.



Carnitine

- Carnitine is synthesized in the liver and kidneys from lysine and methionine.
- During growth or pregnancy, the requirement of carnitine might exceed its natural production.
- Human genetic disorders, affecting different steps of carnitine metabolism will cause deficiency of fatty acid oxidation.
- During the aging process, carnitine concentration in cells diminishes.
- Bones are particularly affected adversely, leading to osteoporosis in elderly subjects.
- Administration of carnitine is capable of improving the clinical condition.
- The classical presentation of primary carnitine deficiency is hepatomegaly, elevated transaminases, and hyperammonemia.
- The causes for secondary carnitine deficiency are organic acidurias, and drug-induced (valproic acid, zidovudine).

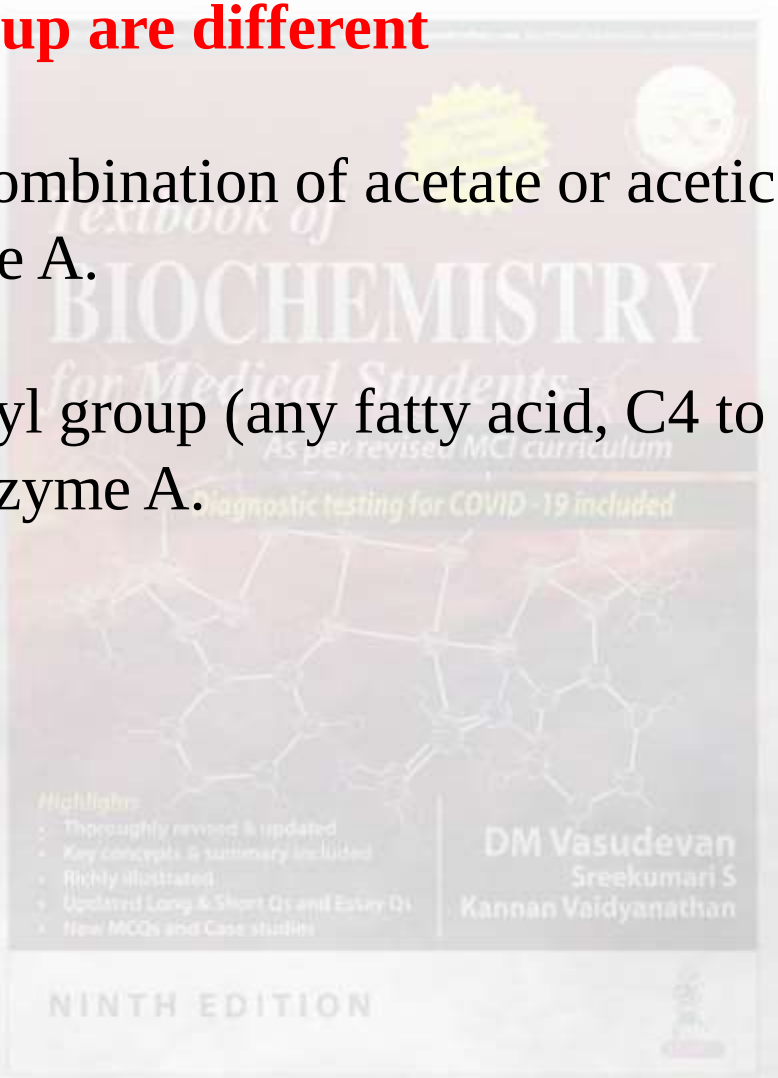
Clinical Applications, continued

1. **Deficiency of translocase:** It leads to defective metabolism of long-chain fatty acids. In this condition, muscle cramps are precipitated by fasting, exercise and high fat diet.
2. **Inherited CAT-I deficiency** affects only the liver resulting in reduced fatty acid oxidation and ketogenesis with hypoglycemia. CAT-II deficiency affects primarily skeletal muscle and, when severe, the liver. The sulfonylurea drugs (glibenclamide and tolbutamide), used in the treatment of type 2 diabetes mellitus, reduce fatty acid oxidation and, therefore, hyperglycemia by inhibiting CPT-I.

Acetyl and acyl group are different

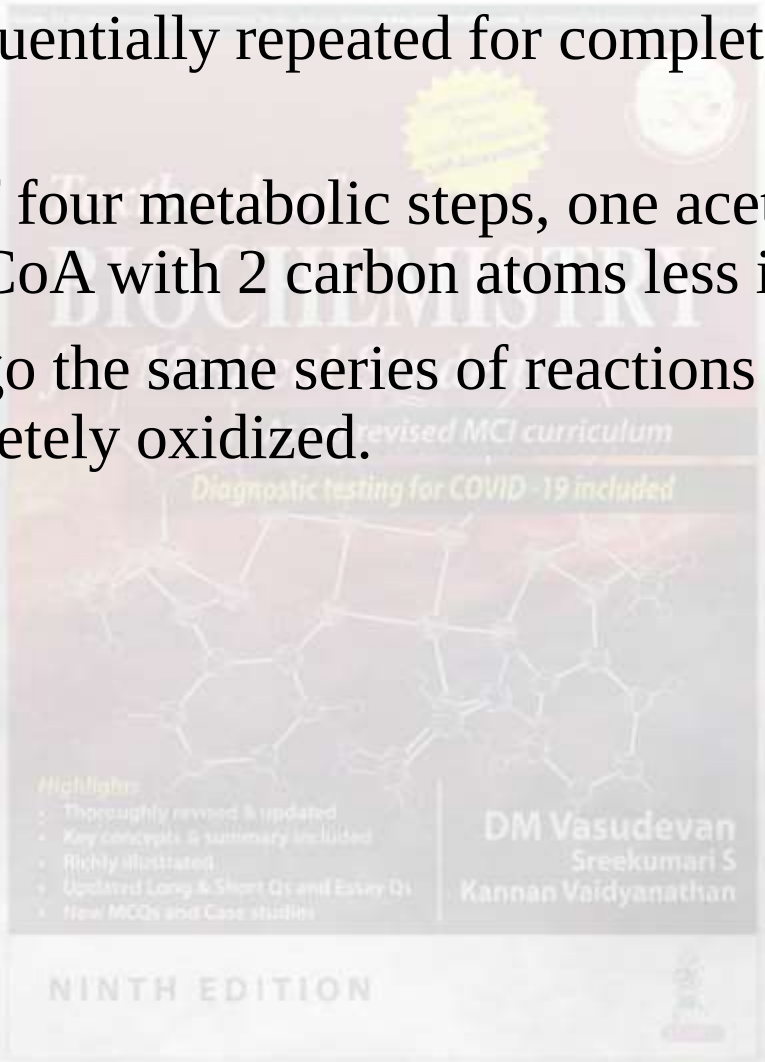
Acetyl-CoA is the combination of acetate or acetic acid (2 carbon units) with coenzyme A.

Acyl-CoA means acyl group (any fatty acid, C4 to C26 in length) combined with coenzyme A.

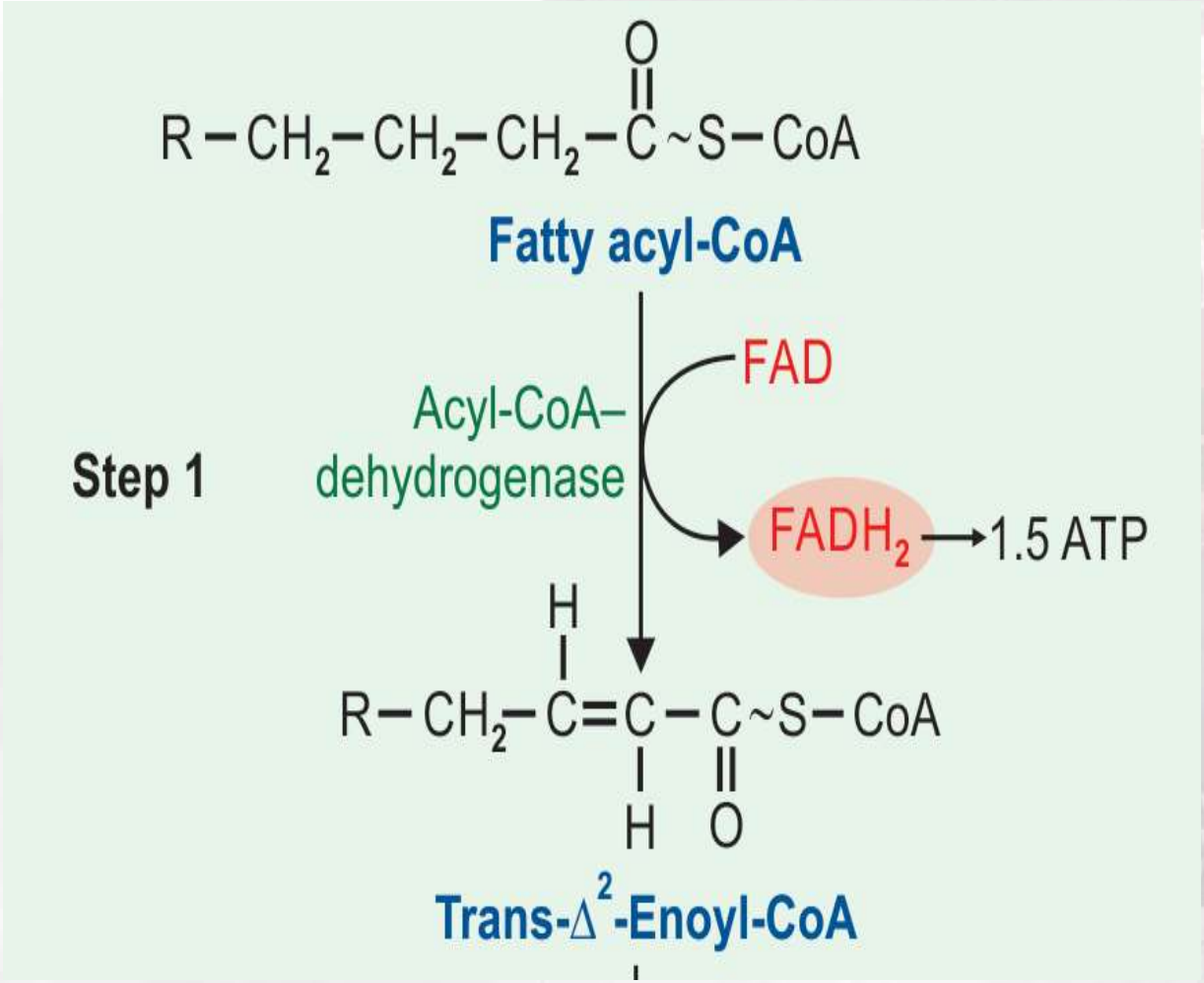


Beta-Oxidation Steps

- 4 reactions are sequentially repeated for complete oxidation of fatty acids.
- After one round of four metabolic steps, one acetyl-CoA unit is split off and acyl-CoA with 2 carbon atoms less is generated.
- This would undergo the same series of reactions again until the fatty acid is completely oxidized.

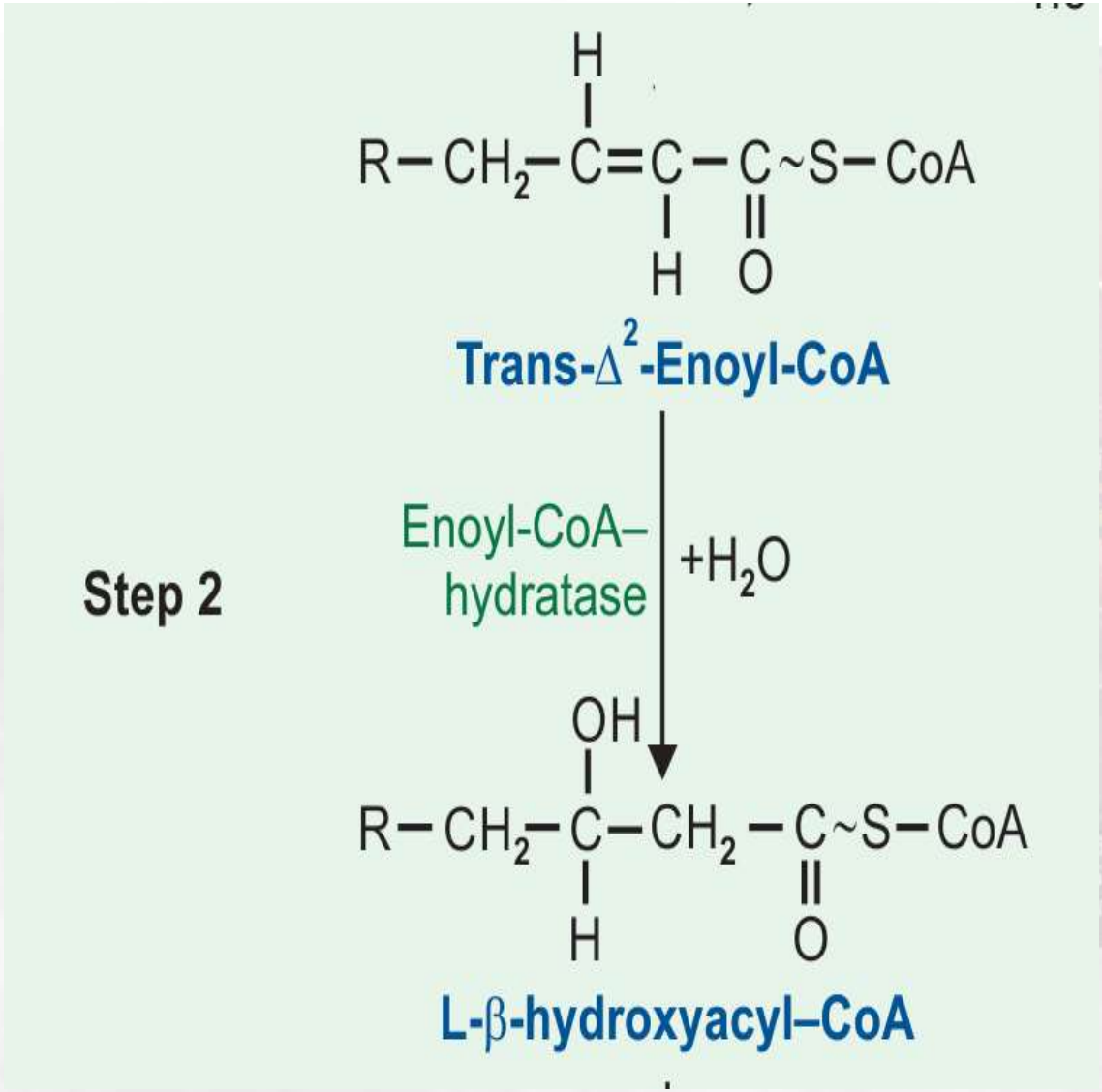


Step 1: FAD Linked Dehydrogenase



- The fatty acyl-CoA is dehydrogenated to a transenoyl CoA with FAD accepting the hydrogen atoms (Step 1).
- **FADH2** when oxidised in electron transport chain will produce **1.5 ATP** molecules.

Step 2: Hydration

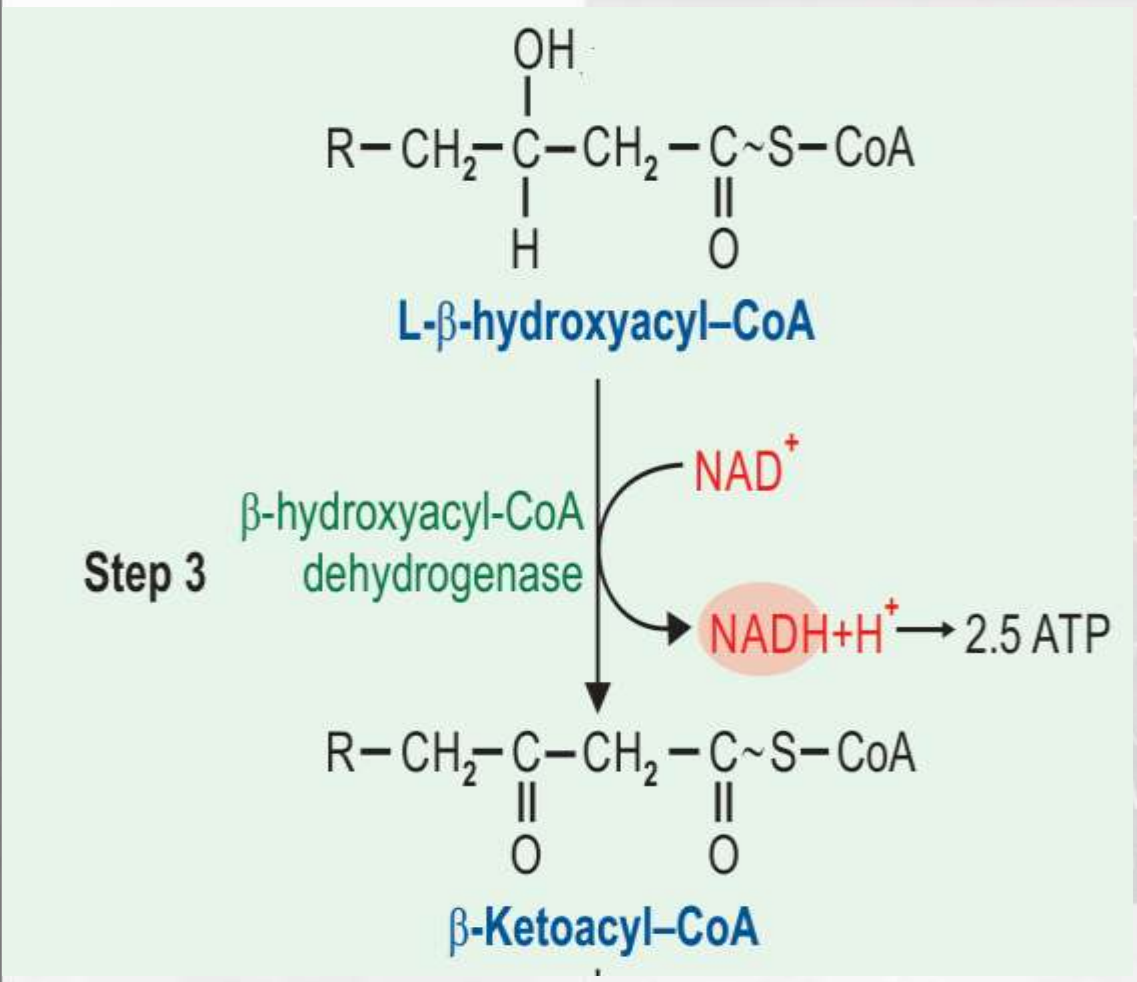


This is catalyzed by an enoyl-CoA hydratase (step 2).

This step forms a beta-hydroxy fatty acyl-CoA.

The L isomer alone is formed during the hydration of the trans double bond

Step 3: NAD+ Dependent Dehydrogenase

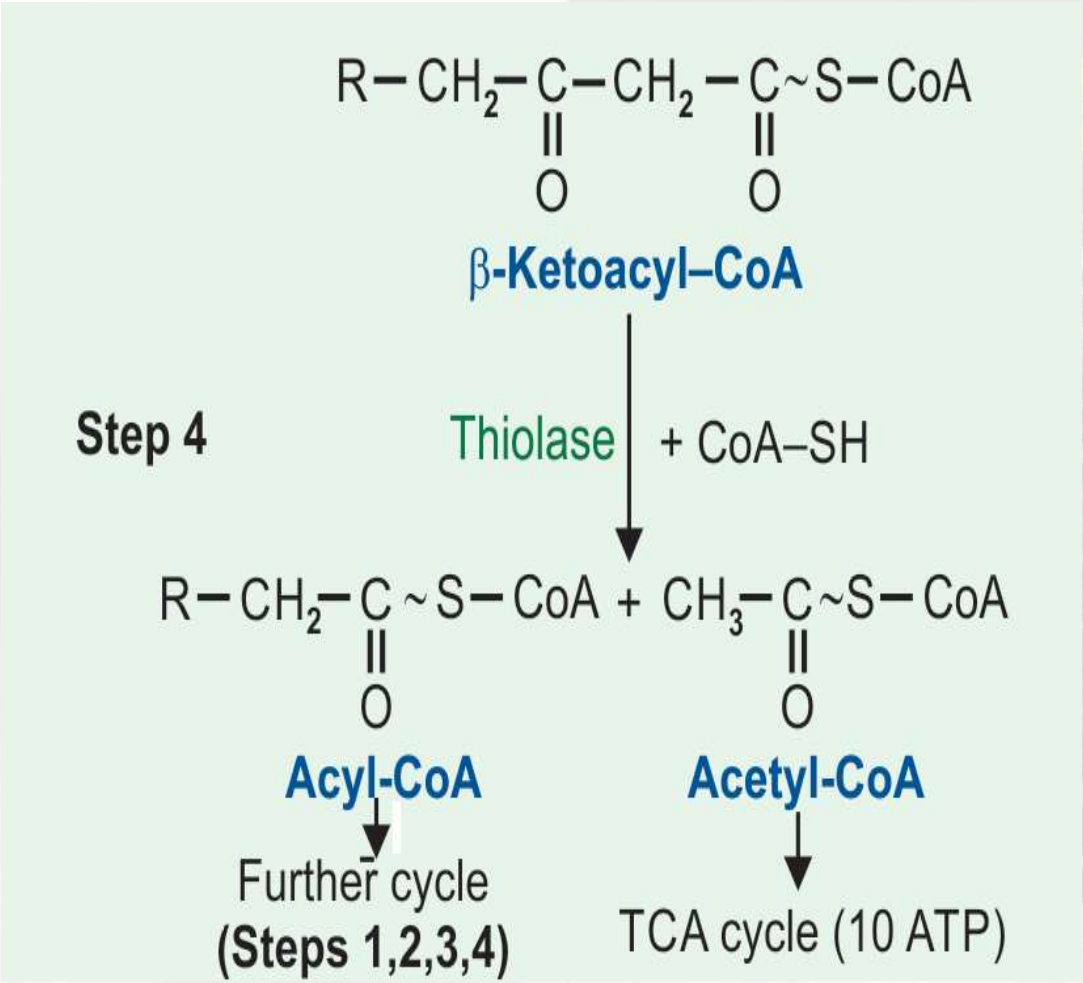


The beta-hydroxy fatty acyl-CoA is again oxidized to form beta-keto fatty acyl-CoA. (Step 3).

This dehydrogenase acts only on L isomer.

The **NADH** when oxidized in electron transport chain will generate **2.5 ATPs.**

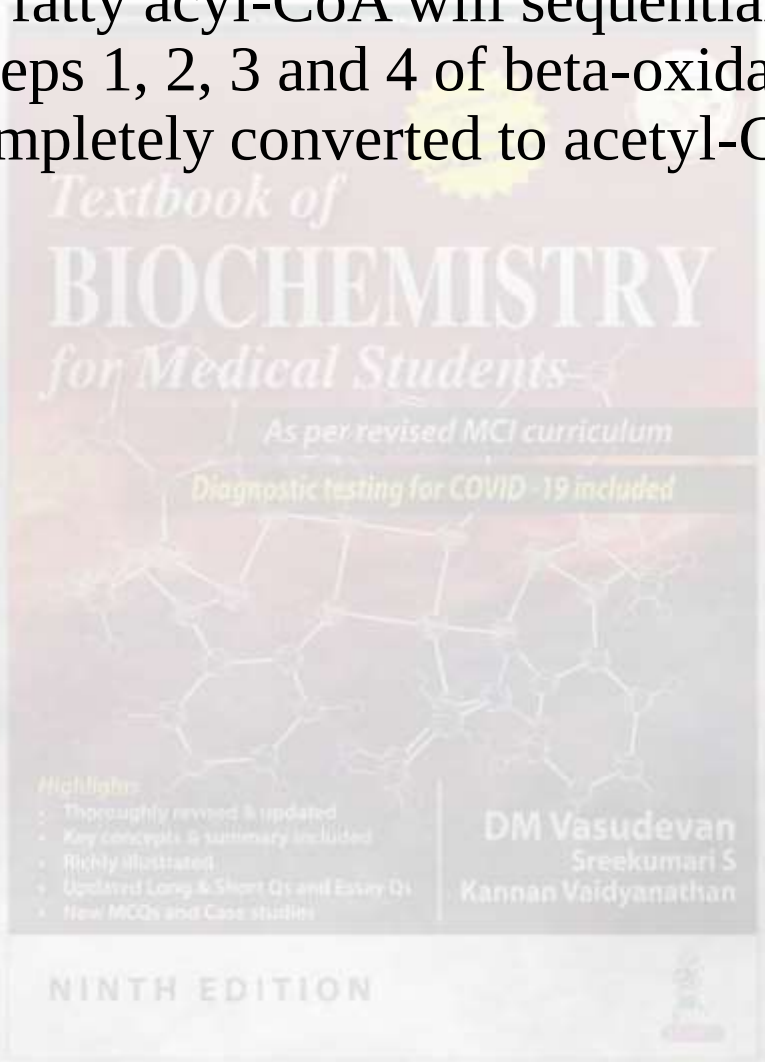
Step 4: Cleavage

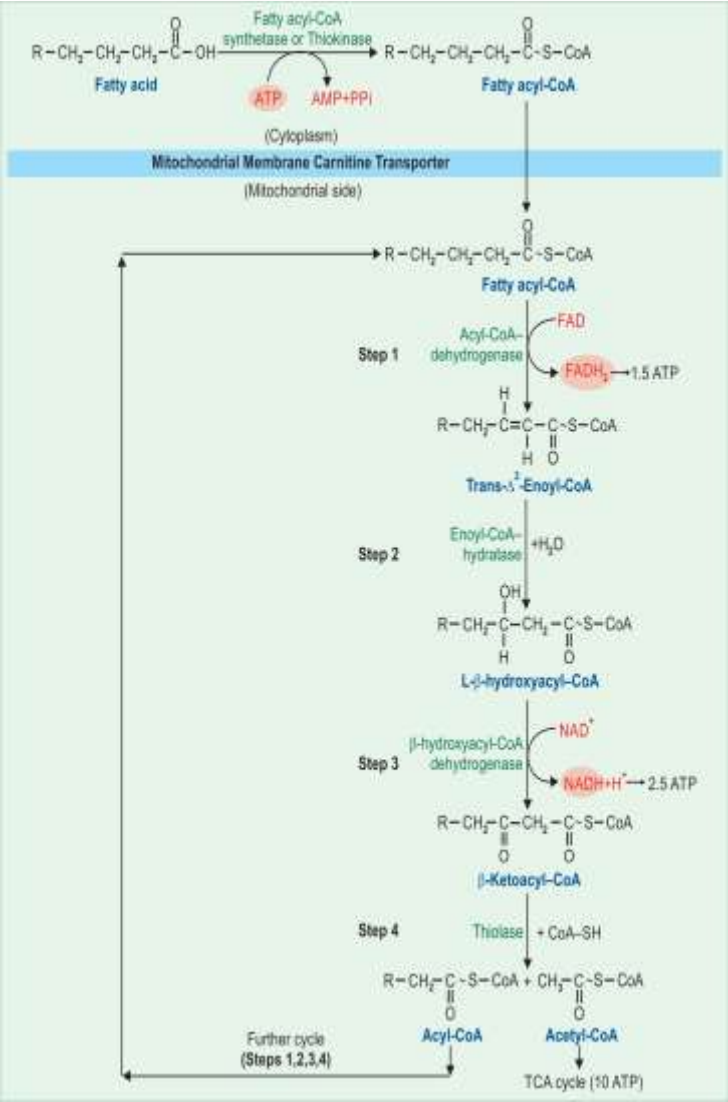


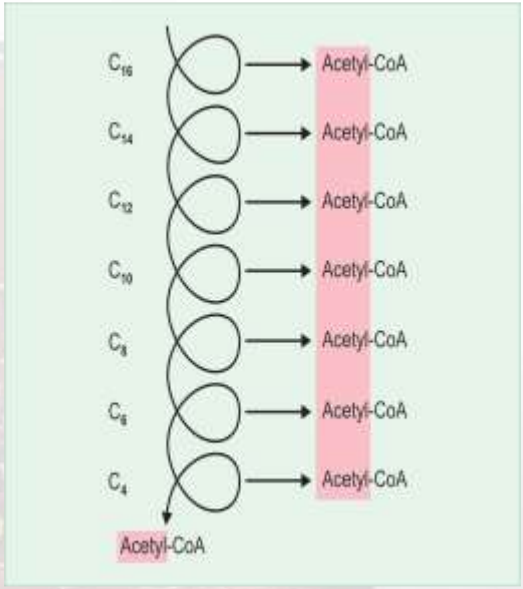
The beta-keto fatty acyl-CoA now undergoes thiolytic cleavage, splitting off a molecule of acetyl-CoA and leaving behind a fatty acid with 2 carbon atoms less (Step 4).

Further Cycles

- The newly formed fatty acyl-CoA will sequentially undergo further cycles of steps 1, 2, 3 and 4 of beta-oxidation until the fatty acid is completely converted to acetyl-CoA.

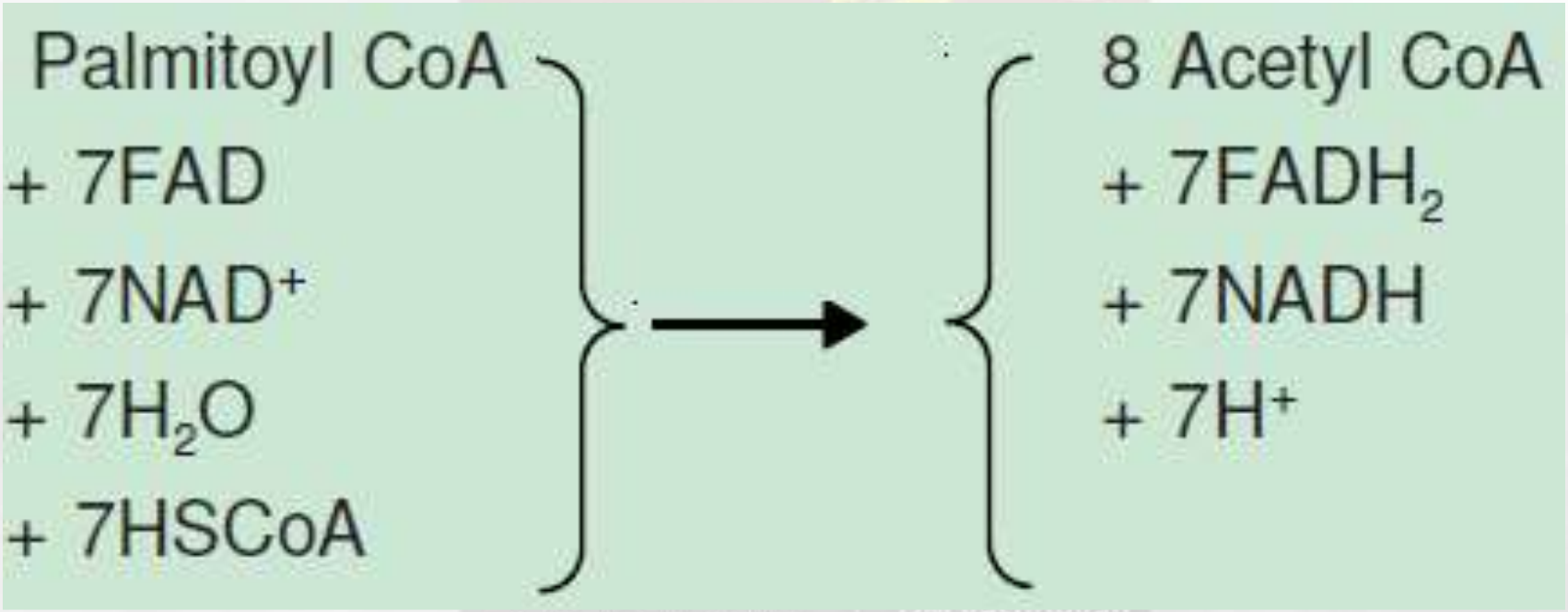






Summary of β-oxidation of palmitic acid (16 C). It undergoes 7 cycles, which give rise to 8 molecules of acetyl-CoA.

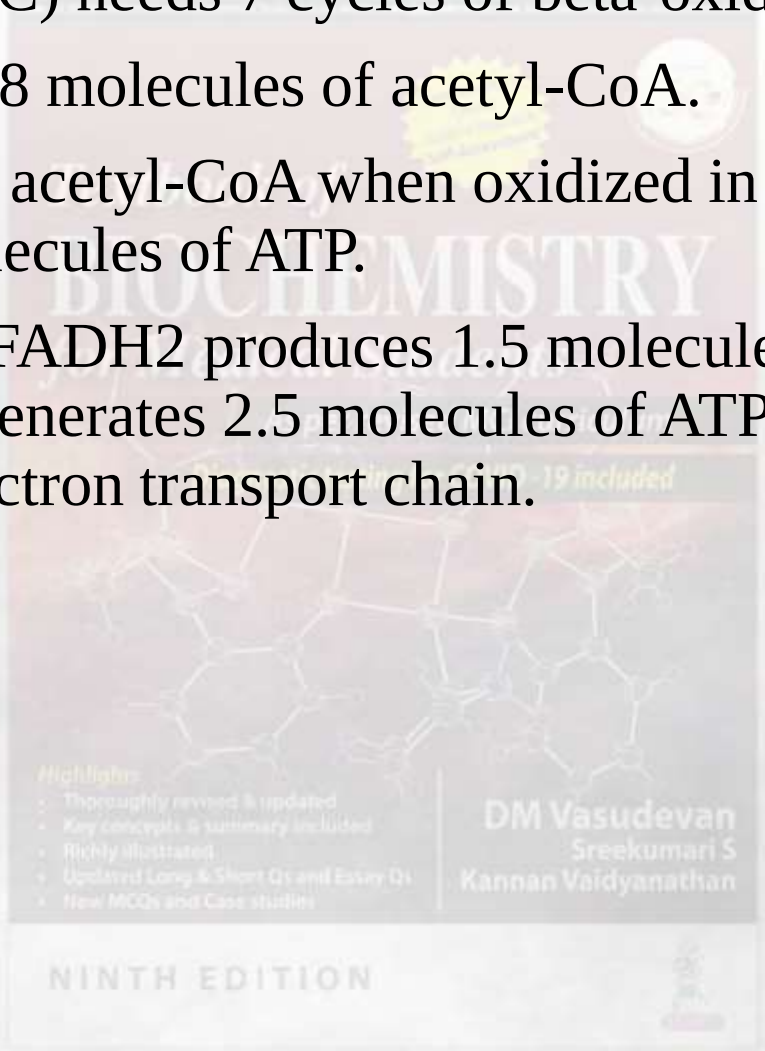
β-oxidation of fatty acids. See that the first step is FAD dependent and the third step is NAD+ dependent



When one molecule of palmitate undergoes beta-oxidation

Energetics of Beta-Oxidation (ATP Yield)

- **Palmitic acid** (16 C) needs 7 cycles of beta-oxidation.
- So, it gives rise to 8 molecules of acetyl-CoA.
- Every molecule of acetyl-CoA when oxidized in the TCA cycle gives 10 molecules of ATP.
- Each molecule of FADH2 produces 1.5 molecules of ATP and each NADH generates 2.5 molecules of ATP, when oxidized in the electron transport chain.



Energetics of Beta-Oxidation, continued

- Hence, the energy yield from one molecule of palmitate may be calculated as:
- 8 acetyl CoA × 10 = 80 ATP
- 7 FADH2 × 1.5 = 10.5 ATP
- 7 NADH × 2.5 = 17.5 ATP
- Gross total = 108 ATP
- **Net yield = 108 minus 2 =106 ATP**
- (In the initial activation reaction, the equivalents of 2 high energy bonds are utilized).
- The efficiency of beta oxidation is about 33%.

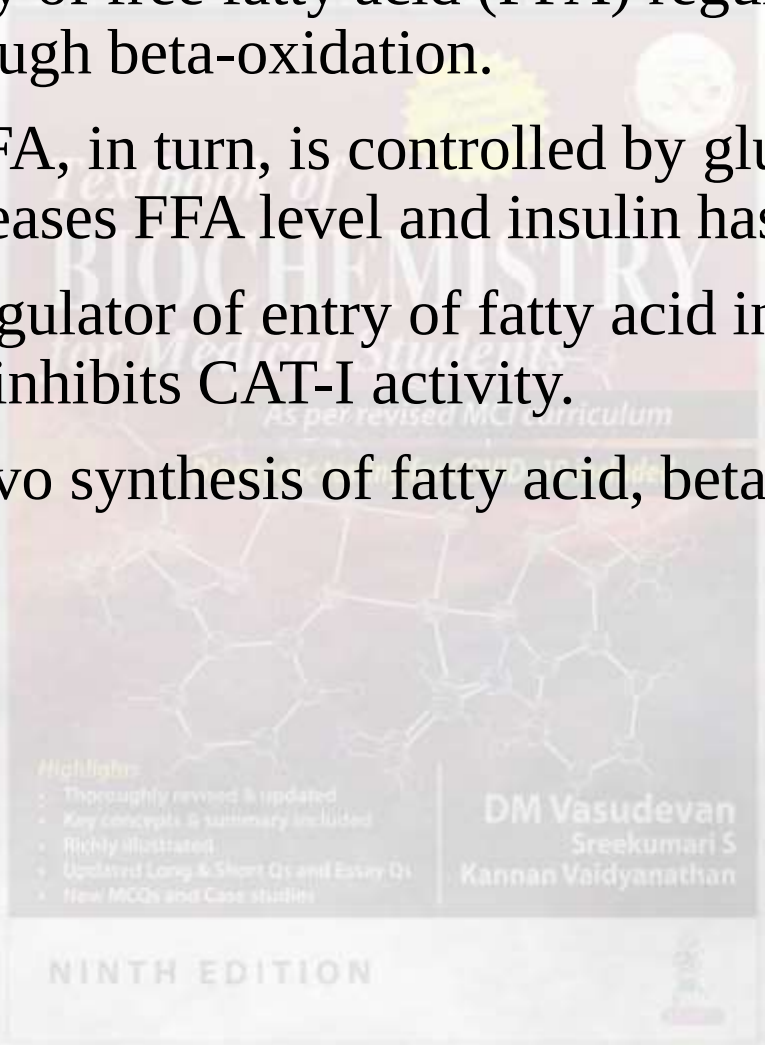
Regulation of Beta-Oxidation

i. The availability of free fatty acid (FFA) regulates the net utilization through beta-oxidation.

ii. The level of FFA, in turn, is controlled by glucagon:insulin ratio. Glucagon increases FFA level and insulin has the opposite effect.

iii. CAT-I is the regulator of entry of fatty acid into mitochondria. Malonyl-CoA inhibits CAT-I activity.

- Thus during de novo synthesis of fatty acid, beta-oxidation is inhibited.



Defects in Beta-Oxidation

- Abnormalities in transport of fatty acids into mitochondria and defects in oxidation can lead to deficient energy production by oxidation of long chain fatty acids.
- Common features are hypoketotic hypoglycemia, hyperammonemia, skeletal muscle weakness and liver diseases.
- **Acyl carnitine** accumulates when the transferases or translocase is deficient.
- Dietary supplementation of carnitine has been found to improve the symptoms in some cases.

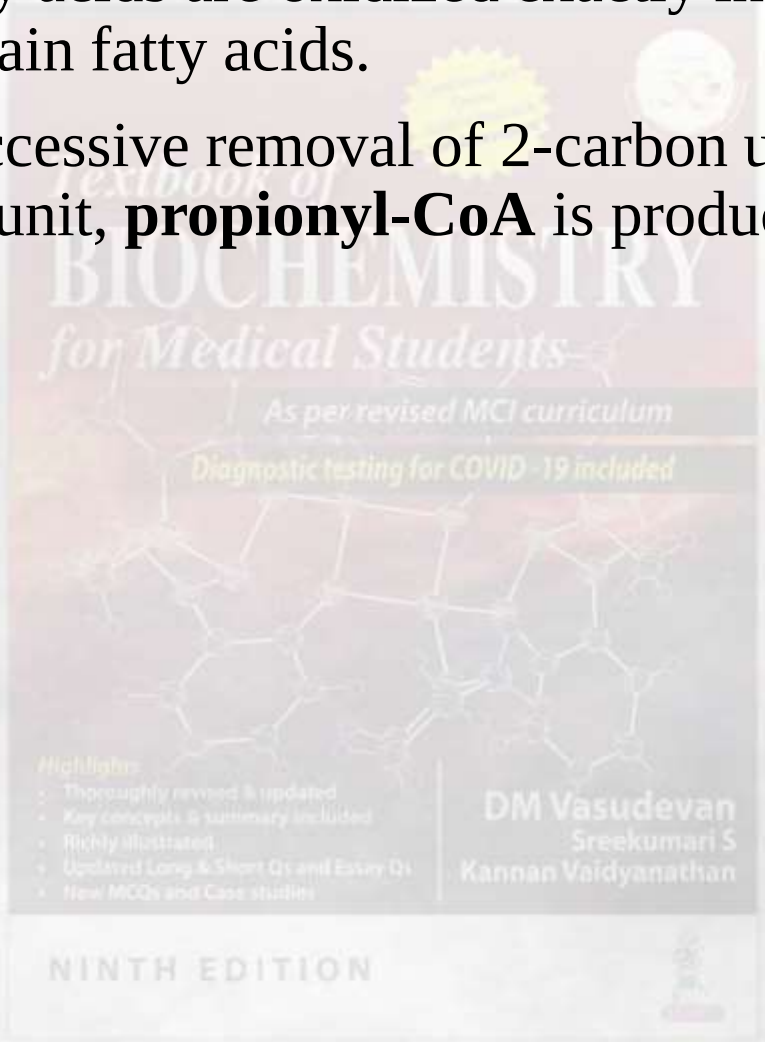
Organic Acidurias

- They are disorders of metabolism of fatty acids, branched chain and aromatic amino acids and citric acid cycle.
- They are all characterized by the accumulation of organic acids in body tissues and their excretion in urine.
- The patients present with acidosis, vomiting, **convulsions** and coma.
- The children often die in infancy; in case they survive, there is severe **mental** and physical retardation.
- Diagnosis is confirmed by showing the presence of organic acids in urine by chromatography.
- Dietary restriction, cofactor therapy and substrate removal are the general lines of management.

Some important organic acidurias		
Disorders	Deficient enzyme	Clinical features
Methyl malonic aciduria	Methyl malonyl CoA mutase or B12 co-enzyme	Ketoacidosis, hypotonia, hypoglycemia, hyperammonemia, hyperuricemia
Propionic acidemia	Propionyl CoA carboxylase	Ketoacidosis, hypotonia, vomiting, lethargy
MCADH deficiency	Medium chain acyl CoA dehydrogenase	Acidosis, hyperammonemia; hypoglycemia, fatty liver.
LCADH deficiency	Long chain acyl CoA dehydrogenase	Nonketotic hypoglycemia, low carnitine, increased acyl carnitine
Glutaric aciduria	Glutaryl CoA dehydrogenase	Ketoacidosis, convulsions, progressive neurological defects, cerebral palsy.

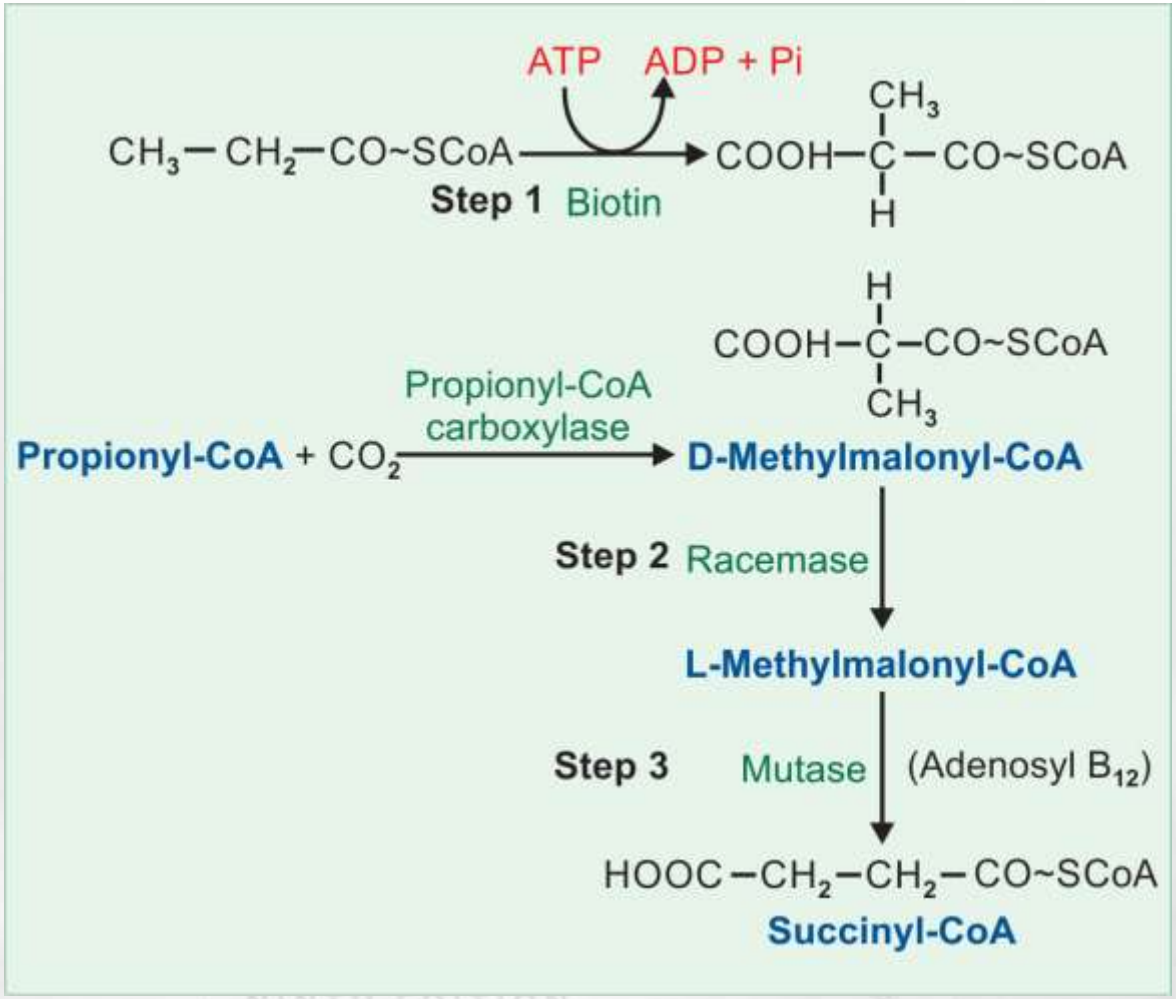
Oxidation of Odd Chain Fatty Acids

- The odd chain fatty acids are oxidized exactly in the same manner as even chain fatty acids.
- However, after successive removal of 2-carbon units, at the end, one 3 carbon unit, **propionyl-CoA** is produced.



Fate of Propionyl-CoA

- **Carboxylase:**
- Propionyl-CoA is first carboxylated to D-methyl-malonyl-CoA by a **biotin** dependent carboxylase.
- Biotin is a member of vitamin B complex group.
- One molecule of ATP is utilized to supply energy (step 1).
- **Racemase:** Then racemase acts upon D-methylmalonyl-CoA to give L-methylmalonyl-CoA. (step 2).
- **Mutase:** Then L-methylmalonyl-CoA is rearranged to form succinyl CoA by L-methylmalonyl-CoA mutase.
- The reaction needs **vitamin B12** coenzyme (Step 3).
- Succinyl-CoA then enters TCA cycle, finally converted to oxaloacetate, and is used for gluconeogenesis.
- Propionyl-CoA is also derived from the metabolism of valine and isoleucine.



Metabolism of propionyl-CoA

Propionate is Gluconeogenic

- Ordinary fatty acids are cleaved to acetyl-CoA units which on entering the Krebs cycle are completely oxidized to CO2, and hence as a general rule, **fatty acids cannot be used for gluconeogenesis.**
- However, propionate is entering into the citric acid cycle at a point after the CO2 elimination steps, so propionate can be channelled to gluconeogenesis.
- Thus **3 carbon units from odd carbon fatty acids are gluconeogenic.**
- Cow's milk contains significant quantity of odd chain fatty acids.

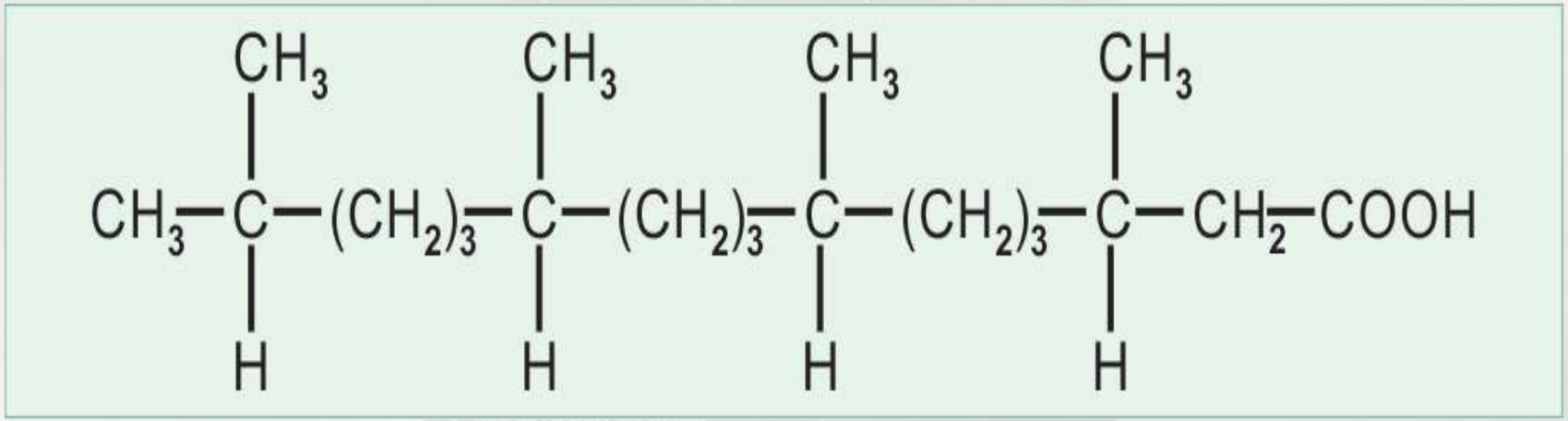
Inborn Errors of Propionate Metabolism

1. Propionyl-CoA carboxylase deficiency. It is characterized by propionic acidemia, ketoacidosis, and developmental abnormalities.
2. Methyl malonic aciduria. Some patients respond to treatment with pharmacological doses of B12.
   - This group had deficiency in the formation of adenosyl B12 with deficient mutase activity.
   - The second type did not respond to cyanocobalamin and had deficiency of the enzyme racemase or mutase.
   - Methylmalonate affects the metabolism of brain leading to mental retardation in these cases.

Alpha-Oxidation

- It is a process by which fatty acids are oxidized by removing carbon atoms, one at a time, from the carboxyl end.
- The process is **important in brain.**
- Hydroxylation occurs at the alpha-carbon atom.
- It is then oxidized to alpha-keto acid.
- The keto acid then undergoes decarboxylation yielding a molecule of CO_2 and a fatty acid with one carbon atom less.
- This process occurs in the **microsomes**, but **does not generate energy.**
- Some fatty acids undergo alpha oxidation in peroxisomes also.

- Alpha-oxidation is mainly used for fatty acids that have a methyl group at the beta-carbon, which blocks beta-oxidation.
- A major dietary methylated fatty acid is **phytanic acid.**
- It is derived from phytol present in chlorophyll, milk and animal fats.



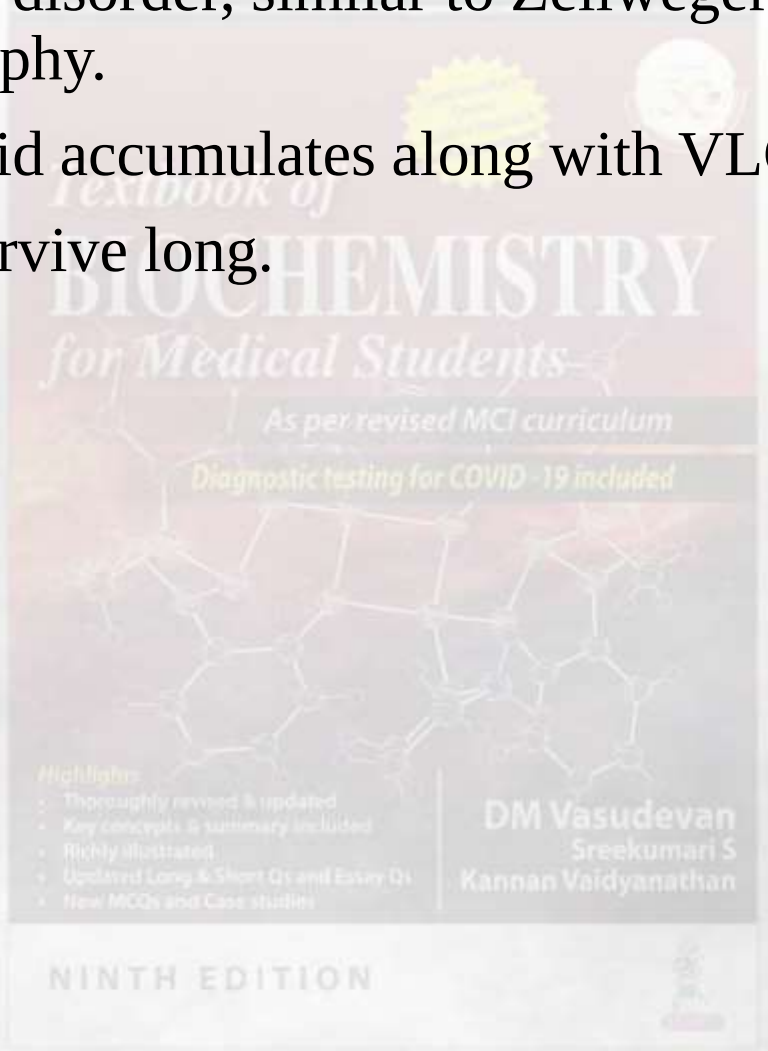
Phytanic Acid

Refsum's Disease

- It is a metabolic error due to lack of alpha-hydroxylase (phytanic acid oxidase) so that alpha oxidation does not occur and phytanic acid accumulates in the tissues.
- The patient presents with severe neurological symptoms, polyneuropathy, retinitis pigmentosa, nerve deafness and cerebellar ataxia.
- Regression of symptoms is observed with restricted dietary intake of phytanic acid.
- Milk is a good source of phytanic acid, which may be avoided.

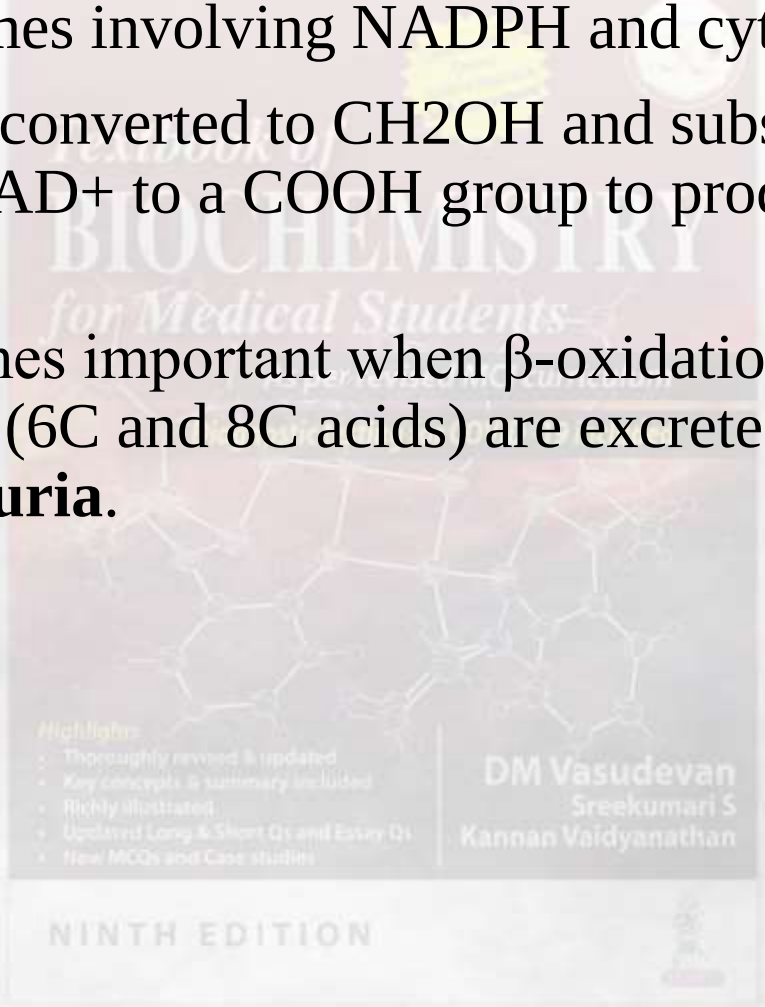
Infantile Refsum's Disease

- It is a peroxisomal disorder, similar to Zellweger syndrome and adrenoleukodystrophy.
- Hence phytanic acid accumulates along with VLCFA.
- Children do not survive long.



Omega Oxidation

- It is a minor pathway taking place in **microsomes**, with the help of hydroxylase enzymes involving NADPH and cytochrome P-450.
- The CH3 group is converted to CH2OH and subsequently oxidized with the help of NAD+ to a COOH group to produce dicarboxylic acids.
- ω-oxidation becomes important when β-oxidation is defective and dicarboxylic acids (6C and 8C acids) are excreted in urine causing **dicarboxylic aciduria**.



Inherited Disorders

- Inherited defects in the enzymes of beta-oxidation and ketogenesis also lead to nonketotic hypoglycemia, coma, and fatty liver.
- Defects are known in 3-hydroxyacyl-CoA dehydrogenase, 3-ketoacyl-CoA thiolase and HMG-CoA lyase deficiency.
- **Dicarboxylic aciduria** is characterized by the excretion of dicarboxylic acids and by nonketotic hypoglycemia.
- It is caused by a lack of mitochondrial medium-chain acyl-CoA dehydrogenase.
- More than 25 enzymes have been identified for fatty acid metabolism in humans, out of which about 15 are known to be associated with metabolic disorders.