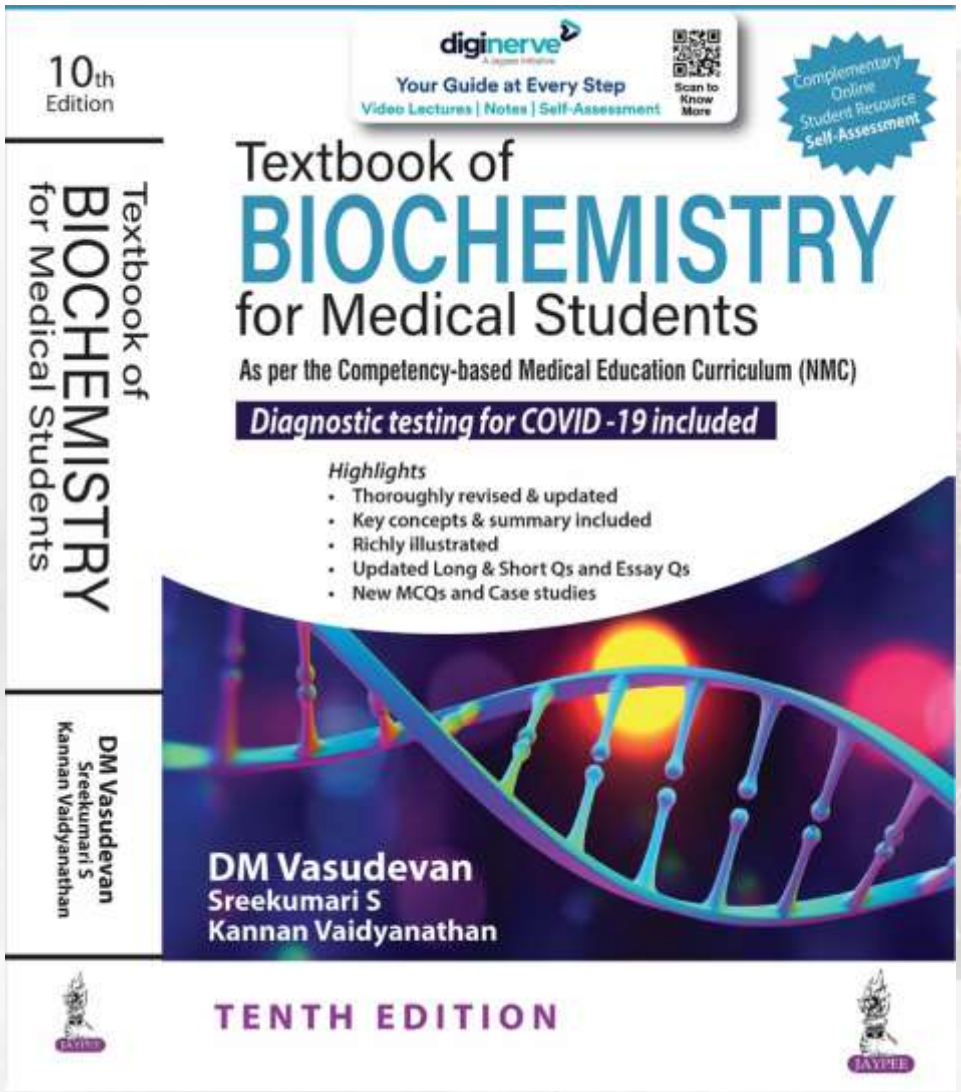


Chapter 11B:

Fatty acid synthesis, Fatty liver, Ketosis

Textbook of
BIOCHEMISTRY
for Medical Students

By DM Vasudevan, *et al.*

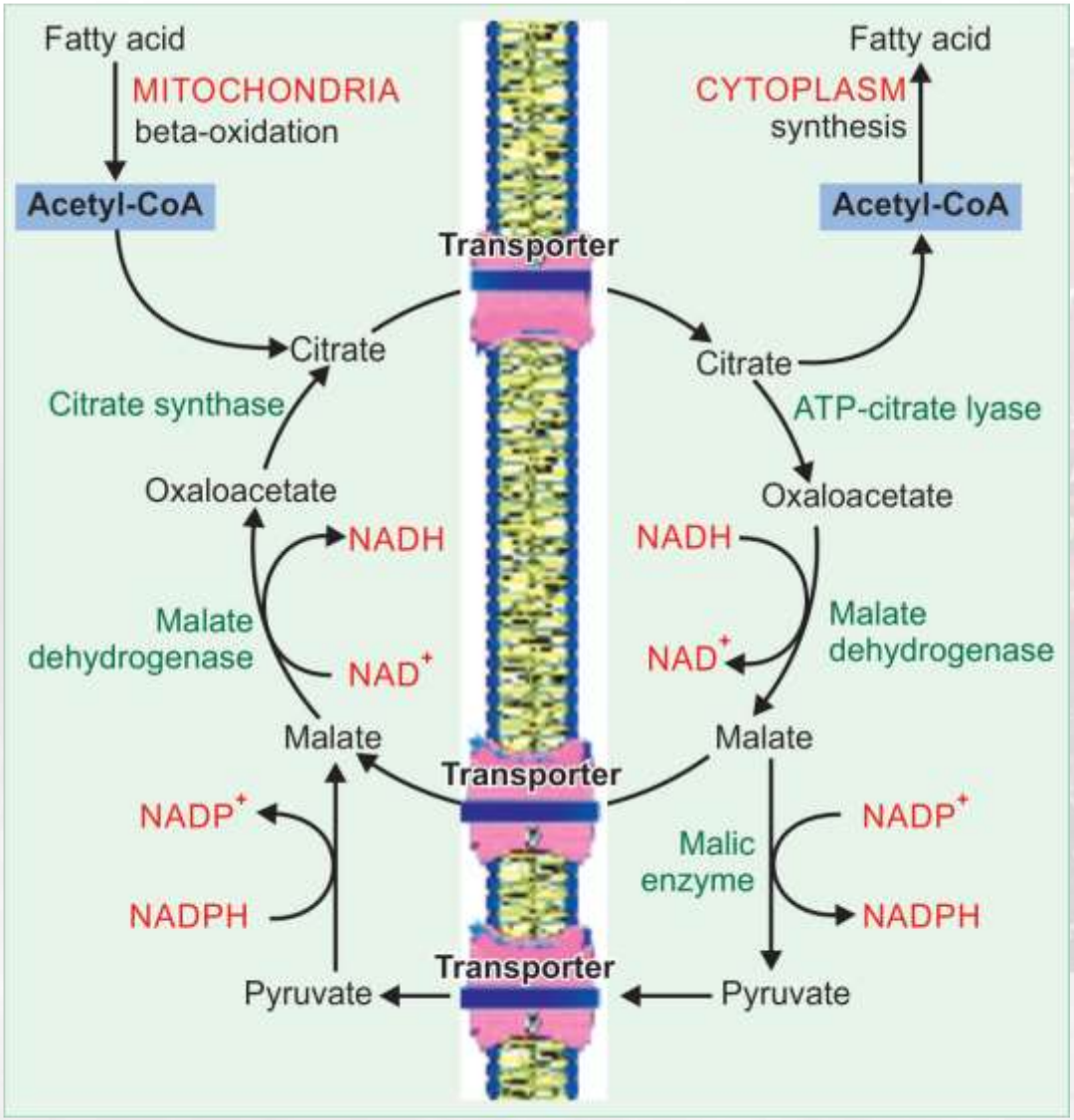
TENTH EDITION

De novo synthesis of fatty acids

- The process of fatty acid synthesis was studied by Feodor Lynen, who got Nobel prize in 1964. The pathway is referred to as **Lynen's spiral.**
- It is not a reversal of oxidation.
- This pathway operates in the **cytoplasm.**
- So it is referred to as **extramitochondrial** or cytoplasmic fatty acid synthase system.
- The major fatty acid synthesized de novo is **palmitic acid**, the 16C saturated fatty acid.
- The process occurs in liver, adipose tissue, kidney, brain, and mammary glands.

Transport of Acetyl-CoA to Cytoplasm

- Acetyl-CoA is formed inside the mitochondria from pyruvate.
- The inner membrane is not freely permeable to acetyl-CoA.
- Hence the **acetyl-CoA units are delivered to the cytoplasm as citrate.**
- In the cytoplasm, citrate is cleaved to oxaloacetate and acetyl-CoA in the cytoplasm.
- The enzyme is **ATP citrate lyase.**
- The oxaloacetate can return to the mitochondria as malate or pyruvate.

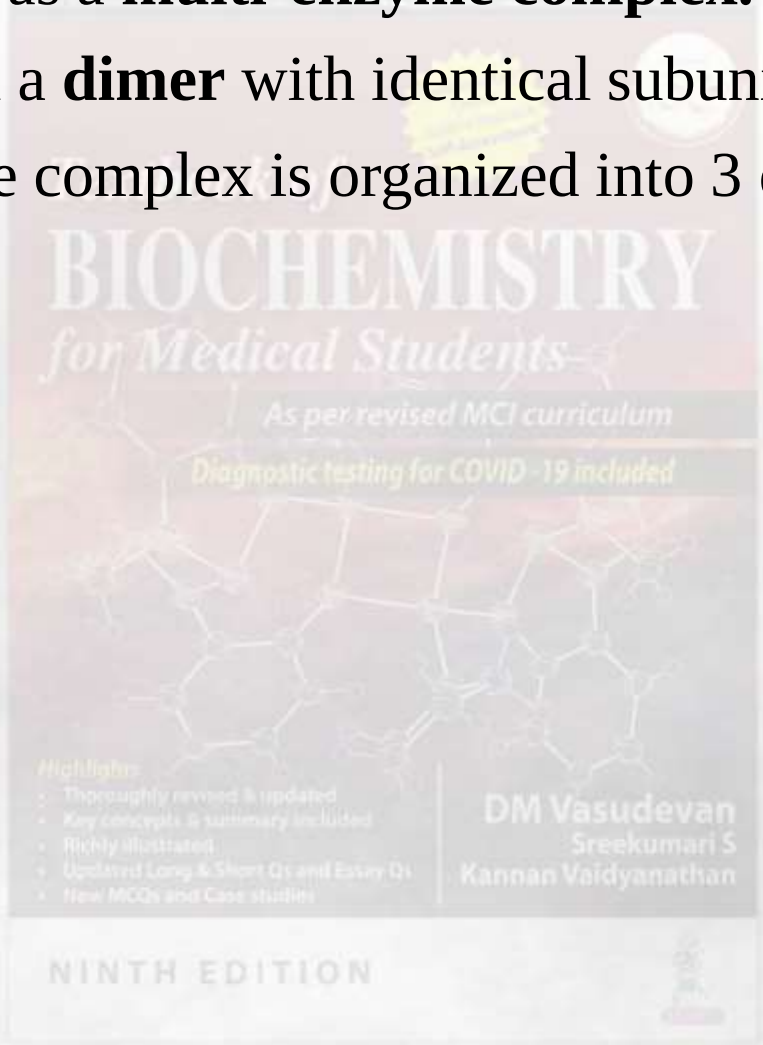


Transfer of acetyl-CoA from mitochondria to cytoplasm by malate–oxaloacetate shuttle.

	Beta oxidation	Fatty acid synthesis
Site	Mitochondria	Cytoplasm
Intermediates	Present as CoA derivatives	Covalently linked to SH group of ACP
Enzymes	Present as independent proteins	Multi-enzyme complex
Sequential units	2 carbon units split off as acetyl CoA	2 carbon units added, as 3 carbon malonyl CoA
Co-enzymes	NAD^+ and FAD are reduced	NADPH used as reducing power
Transporter	Carnitine	Citrate
Regulation	Insulin ↓ Glucagon ↑	Insulin ↑ Glucagon ↓

Fatty Acid Synthase (FAS) Complex

- This system exists as a **multi-enzyme complex.**
- The enzymes form a **dimer** with identical subunits.
- Each subunit of the complex is organized into 3 **domains** with 7 enzymes.

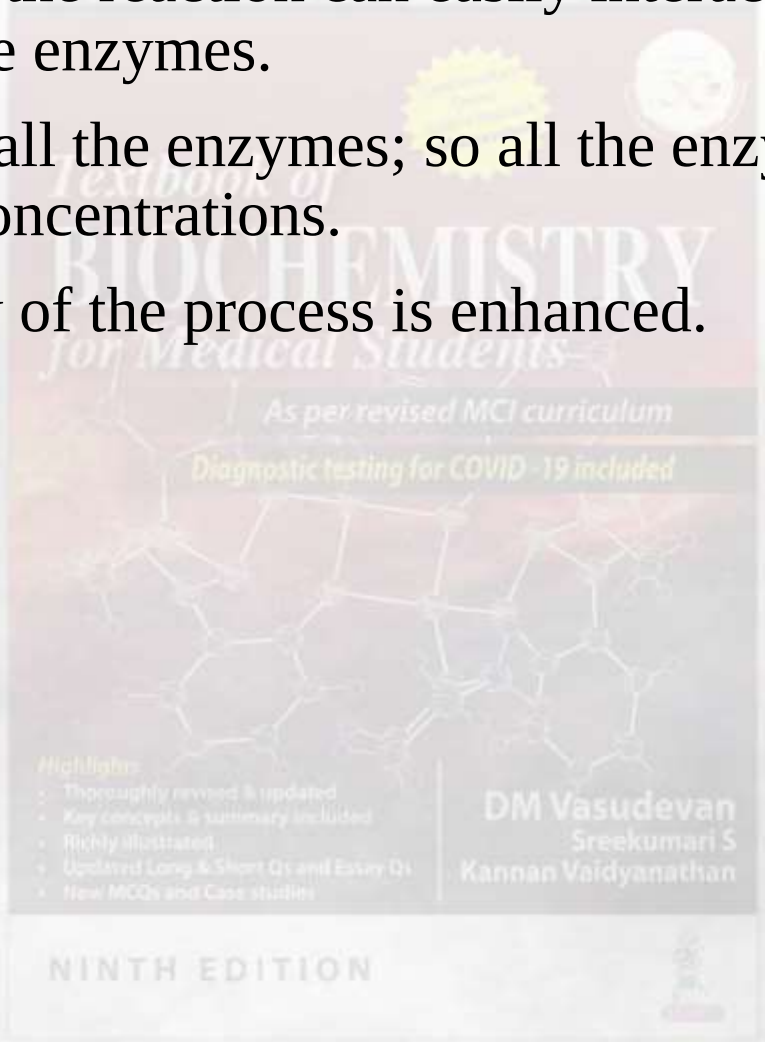


Advantages of Multi-enzyme Complex

a. Intermediates of the reaction can easily interact with the active sites of the enzymes.

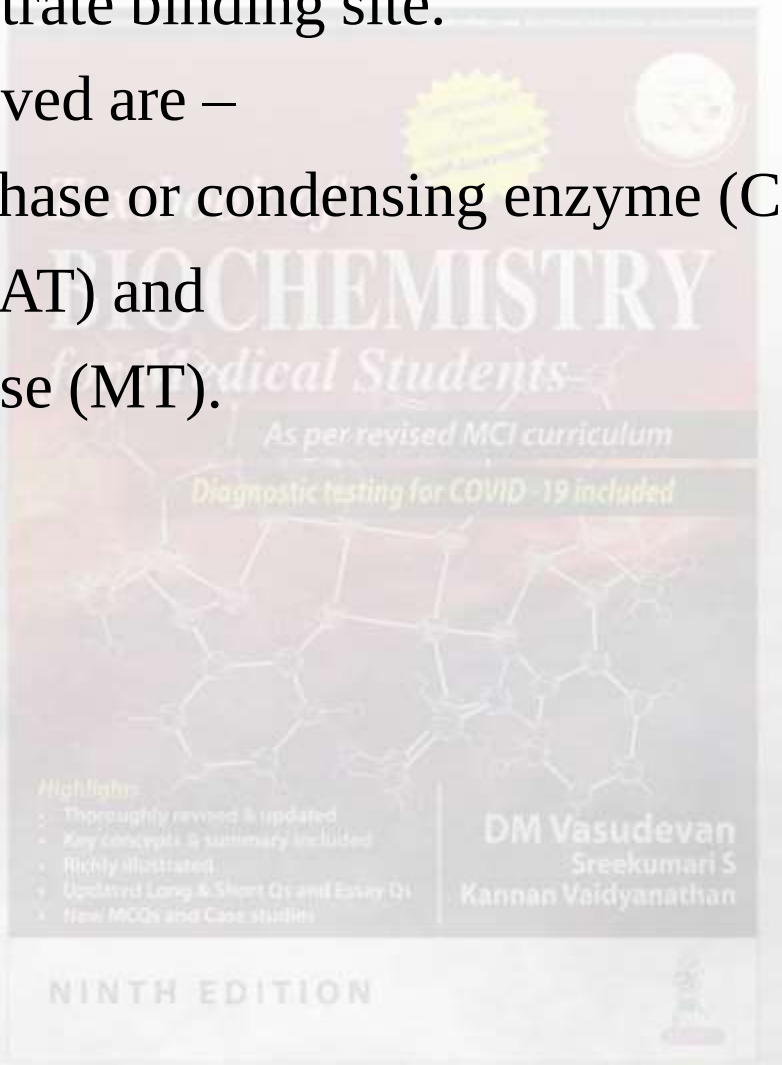
b. One gene codes all the enzymes; so all the enzymes are in equimolecular concentrations.

c. So the efficiency of the process is enhanced.



First Domain or Condensing Unit

- It is the initial substrate binding site.
- The enzymes involved are –
- beta-keto acyl synthase or condensing enzyme (CE);
- acetyl transferase (AT) and
- malonyl transacylase (MT).

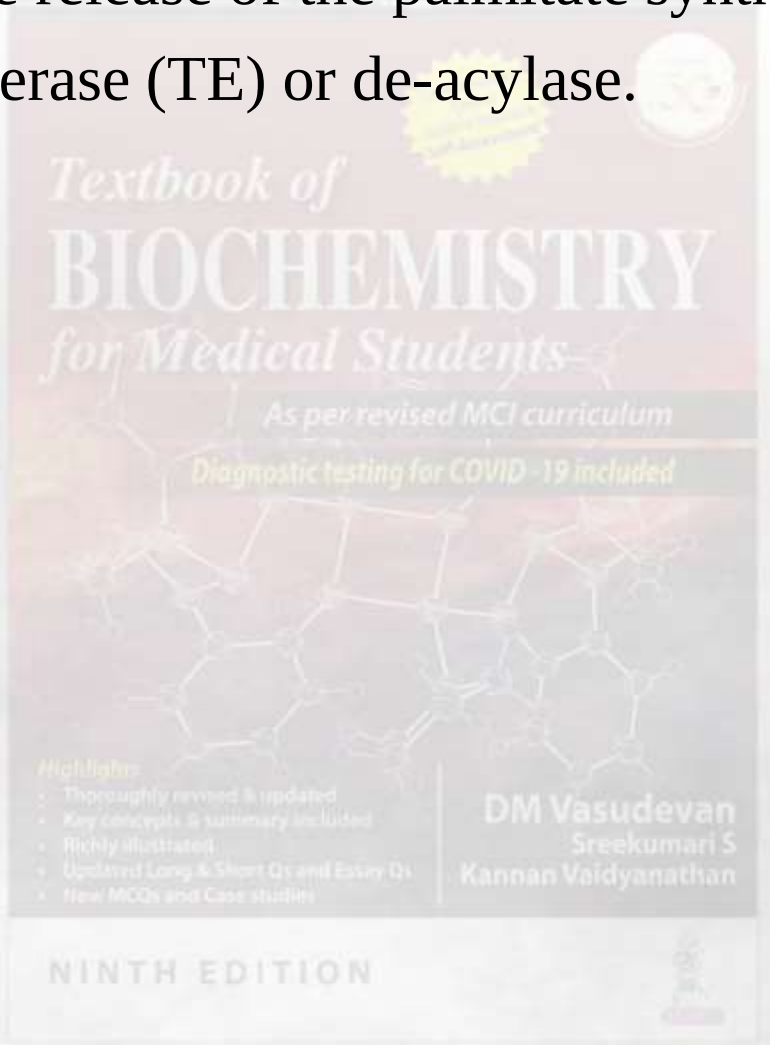


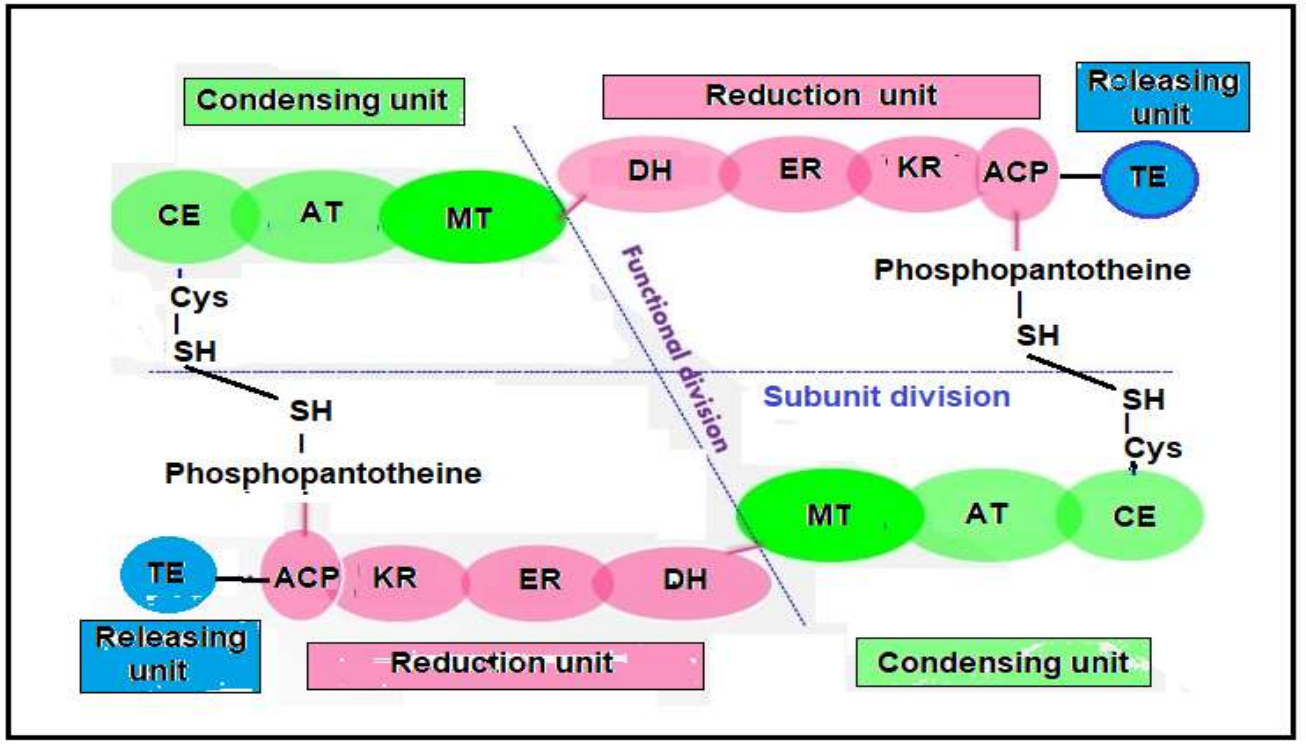
Second Domain or Reduction Unit

- It contains –
- Dehydratase (DH);
- Enoyl reductase (ER);
- Beta-keto acyl reductase (KR) and
- Acyl carrier protein (ACP).
- The acyl carrier protein has phosphopantotheine group, to which the acyl groups are attached in thioester linkage.
- So ACP acts like the CoA carrying fatty acyl groups.

Third Domain or Releasing Unit

- It is involved in the release of the palmitate synthesized.
- It contains thio-esterase (TE) or de-acylase.

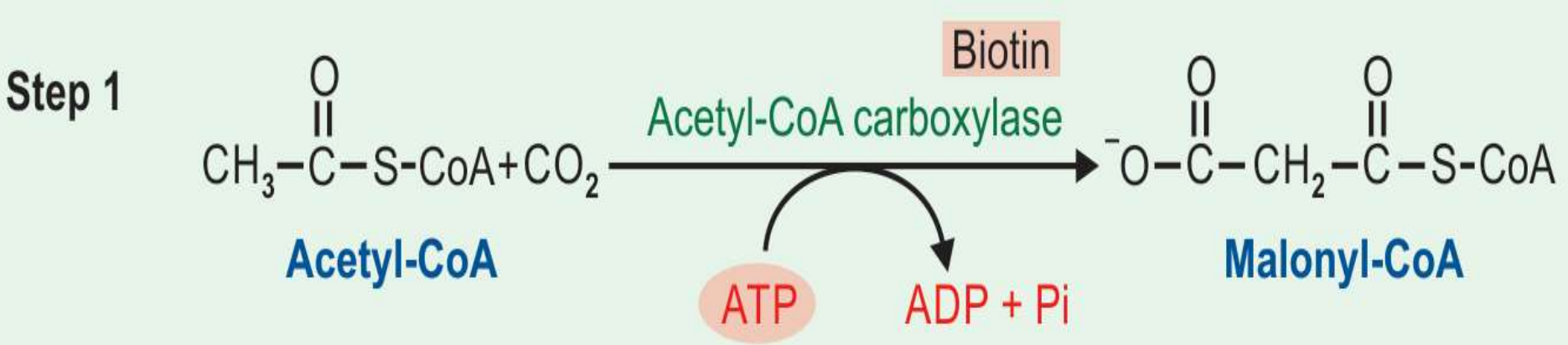




Fatty acid synthase complex. Upper and lower units are two monomers of the complex. Dotted line represents functional division. (CE: condensing enzyme; ER: enzoyl; AT: acetyltransacylase; KR: ketoacyl reductase; MT: malonyl transacylase; ACP: acyl carrier protein; DH: dehydratase; TE: thoesterase)

Step 1: Carboxylation of Acetyl-CoA

- The first step in the fatty acid synthesis is the carboxylation of acetyl-CoA to form malonyl-CoA.
- Acetyl-CoA carboxylase is not a part of the multi-enzyme complex.
- But it is the **rate-limiting enzyme.**
- **Biotin**, a member of B complex vitamins, is necessary for this reaction (Step 1).



- The enzyme is allosterically regulated, the major effectors being citrate (positive) and palmitoyl-CoA (negative).
- The reaction is similar to carboxylation of pyruvate to form oxaloacetate.
- The elongation of the fatty acid occurs by addition of 2 carbon atoms at a time.
- But the 2-carbon units are added as 3-carbon, **malonyl units**.
- The whole reaction sequence occurs while the intermediates are bound to ACP (acyl carrier protein).

Units are Added

A. **Acetyl transacylase** (AT) catalyzes the transfer of the acetyl group (2 carbons) to the cysteinyl SH group of the **condensing enzyme** (CE) of the other monomer of the fatty acid synthase complex (Step 2A).

B. One molecule of acetyl-CoA (2 carbon) and one molecule of malonyl-CoA (3 carbon) bind to the multi-enzyme complex.

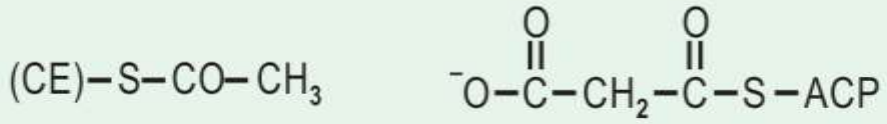
C. **C. Malonyl transacylase** (MT) transfers the malonyl group to the SH group of the ACP (Step 2B).

Step 2A

$$\text{Acetyl-CoA} + \text{(CE)}-\text{SH} \xrightarrow{\text{Acetyl transacylase (AT)}} \text{Acetyl S}-\text{(CE)} + \text{CoA}$$

Step 2B

$$\text{Malonyl-CoA} + \text{ACP}-\text{SH} \xrightarrow{\text{Malonyl transacylase (MT)}} \text{Malonyl}-\text{S}-\text{ACP} + \text{CoA}$$

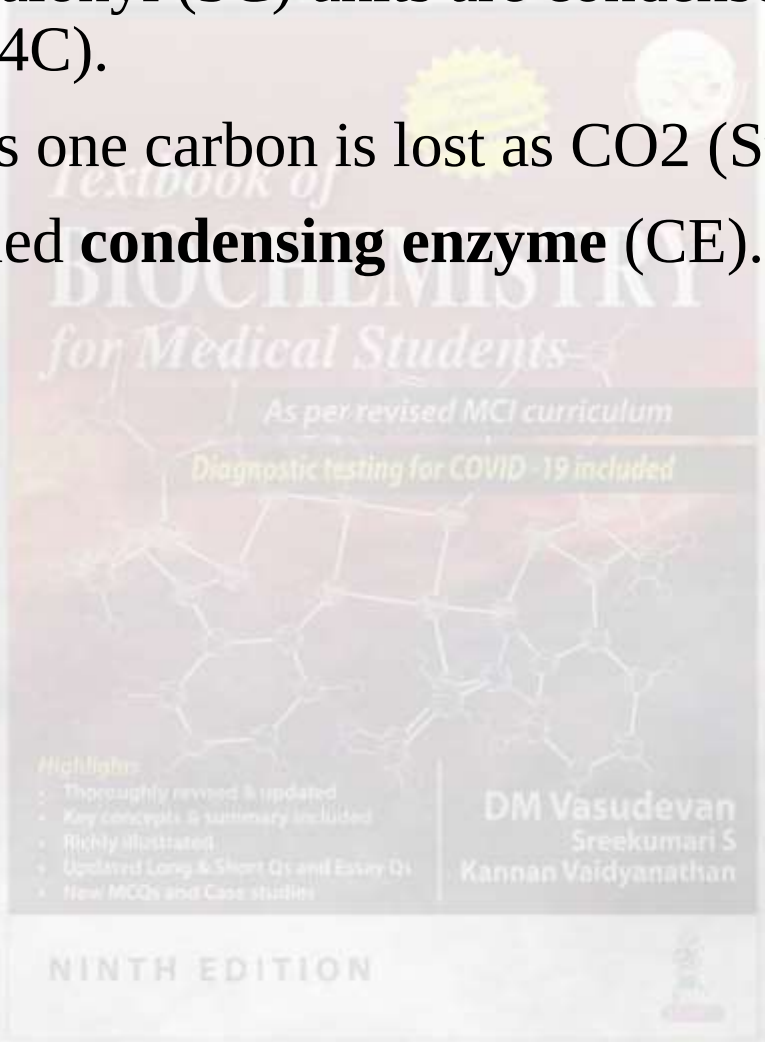


Acetyl-S-(CE)

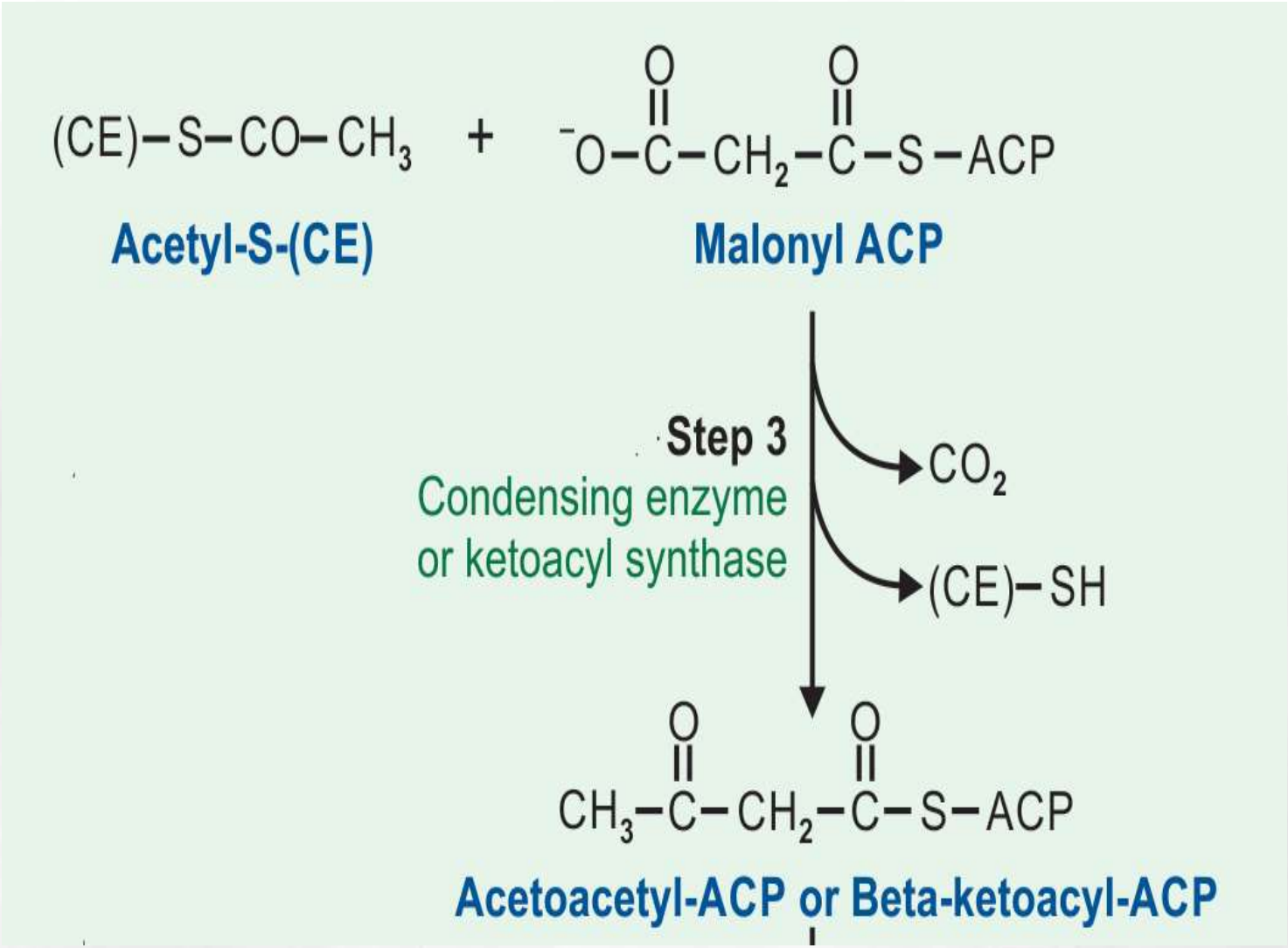
Malonyl ACP

Step 3: Condensation

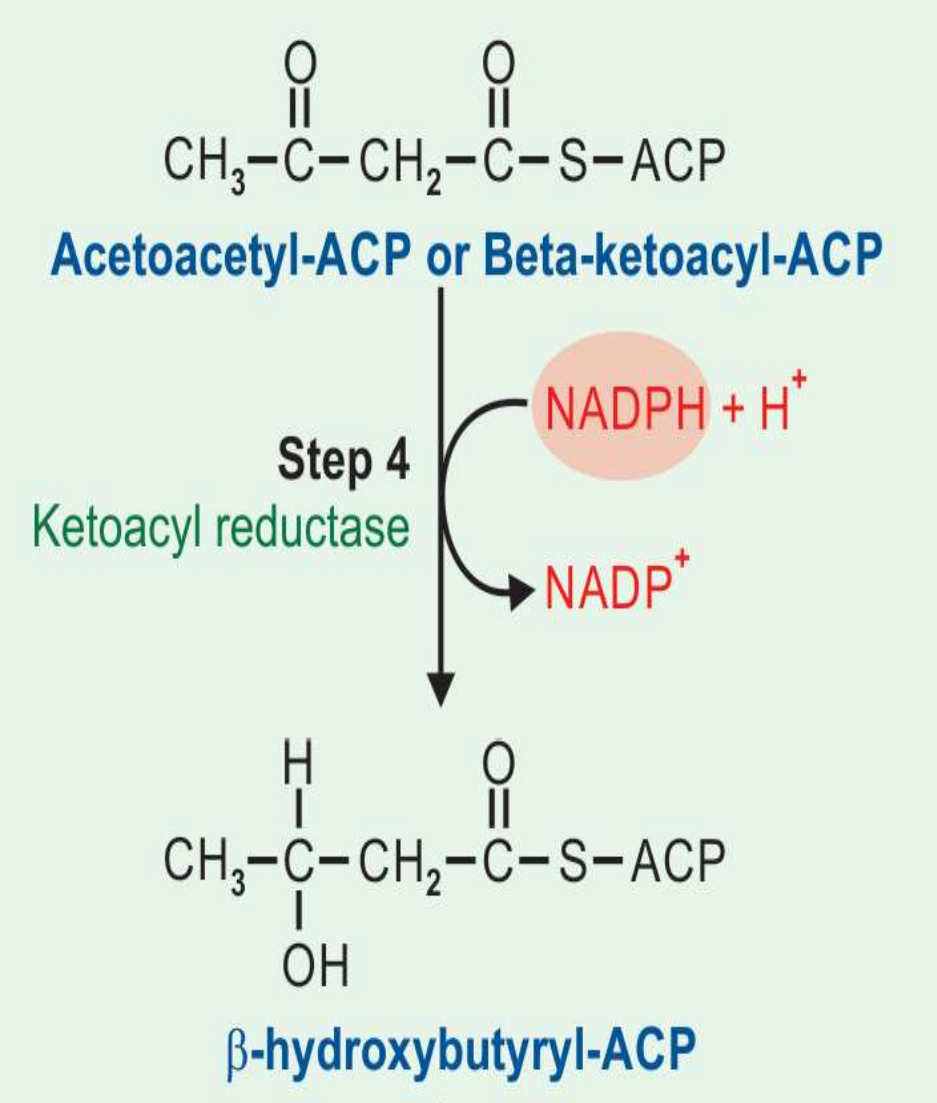
- Acetyl (2C) and malonyl (3C) units are condensed to form aceto acetyl ACP (4C).
- During this process one carbon is lost as CO2 (Step 3).
- The enzyme is called **condensing enzyme** (CE).



Step 3: Condensation



Step 4: Reduction



Acetoacetyl ACP is reduced by

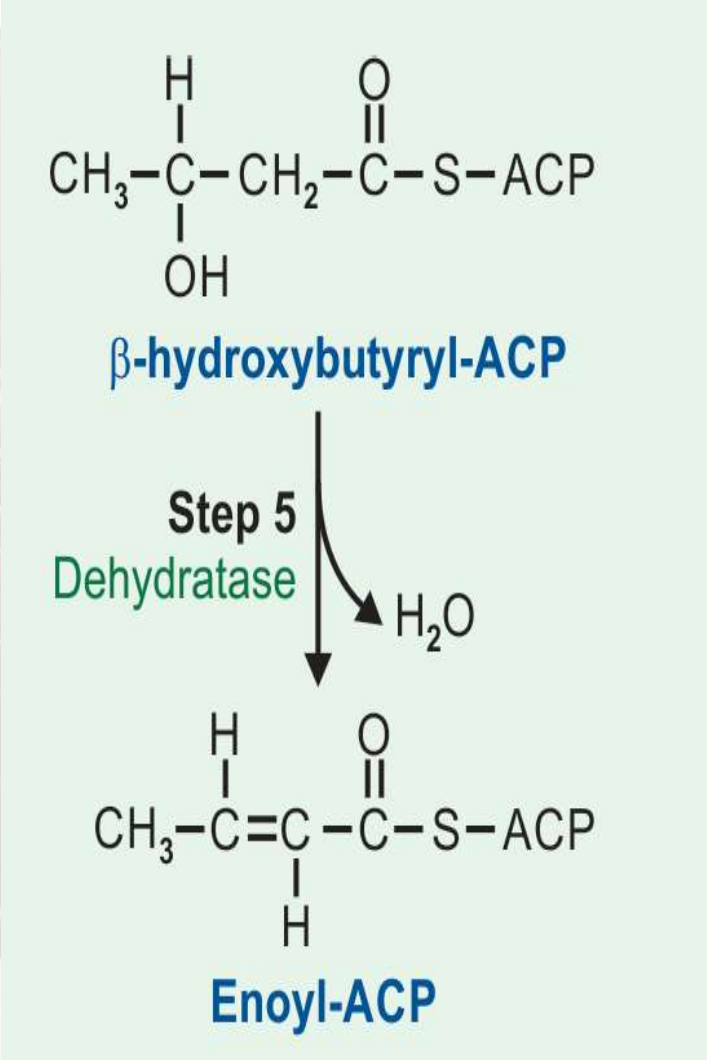
NADPH dependent **reductase** (KR)

to form beta-hydroxy fatty acyl ACP

(Step 4).

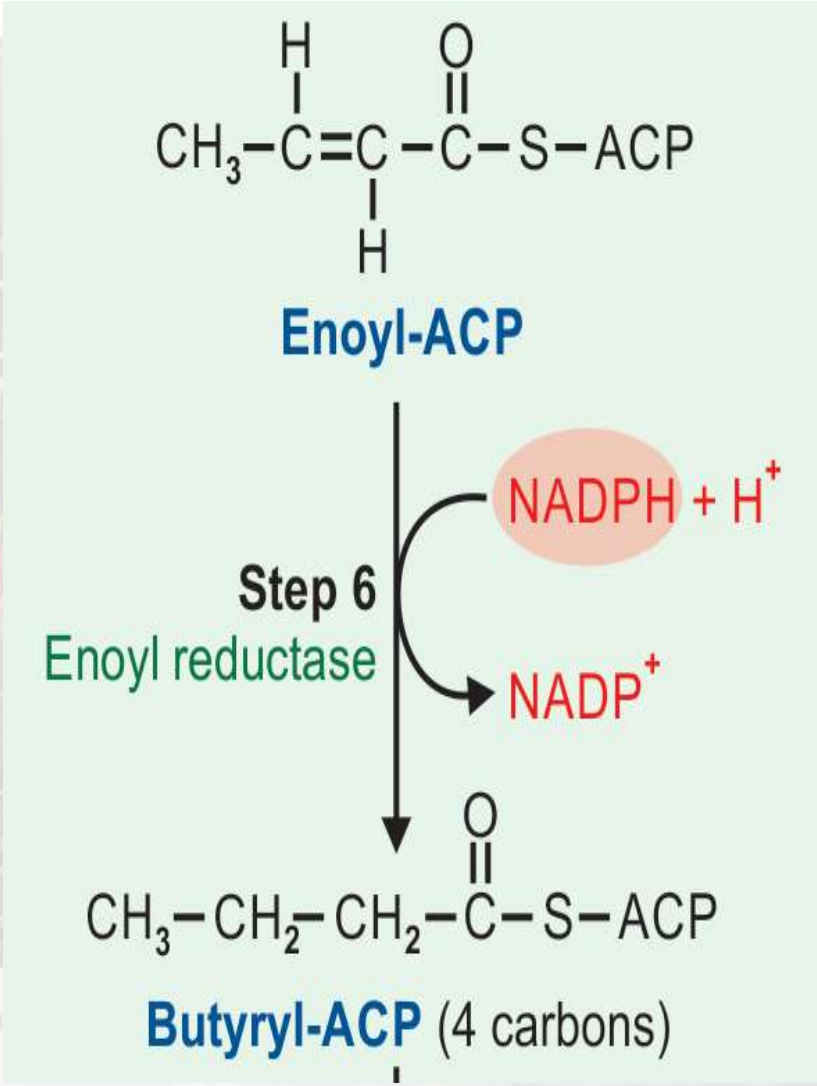
Step 5: Dehydration

- It is then dehydrated by a **dehydratase** (DH) to form enoyl ACP (unsaturated acyl ACP) (Step 5).



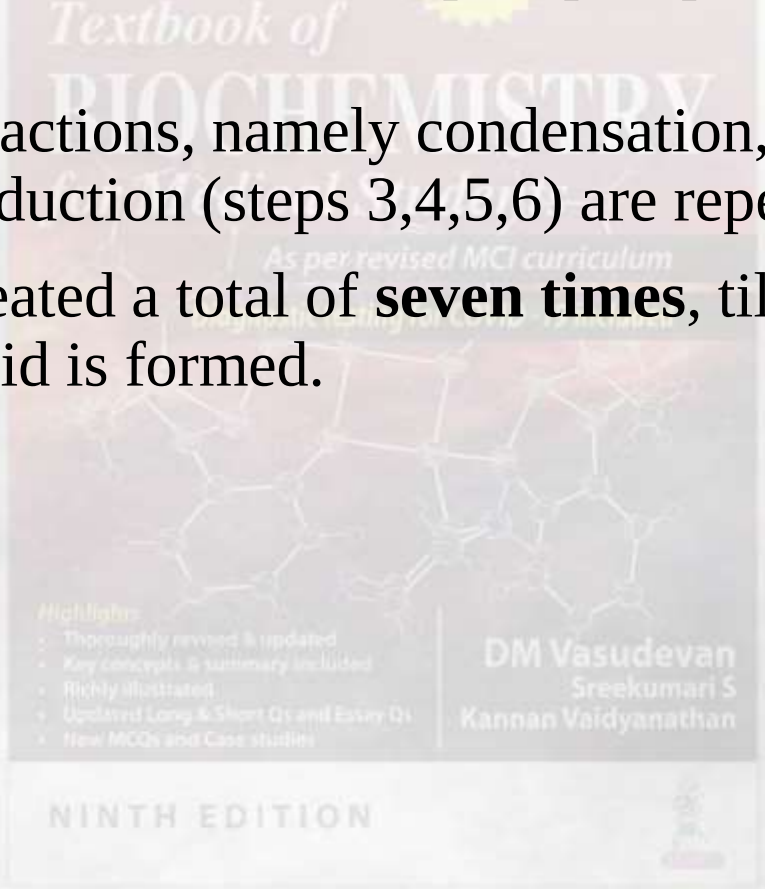
Step 6: Second Reduction

- The enoyl ACP is again reduced by enoyl reductase (ER) utilizing a 2nd molecule of **NADPH** to form butyryl ACP (Step 6).



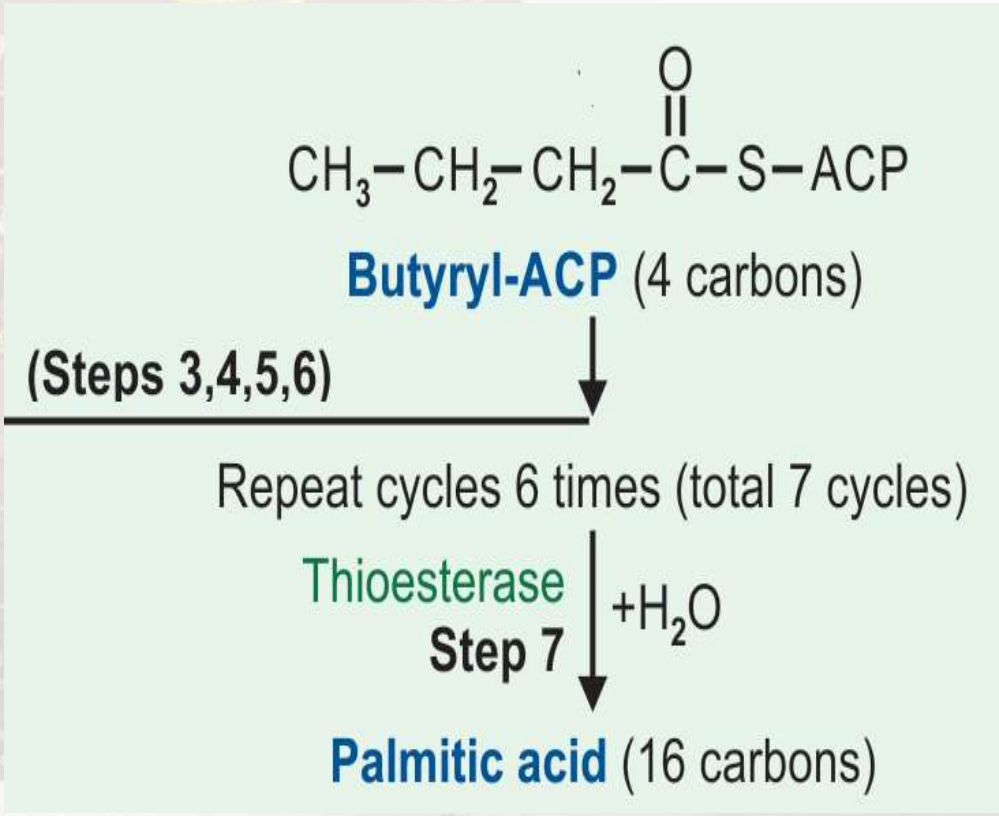
Cycling of Reactions

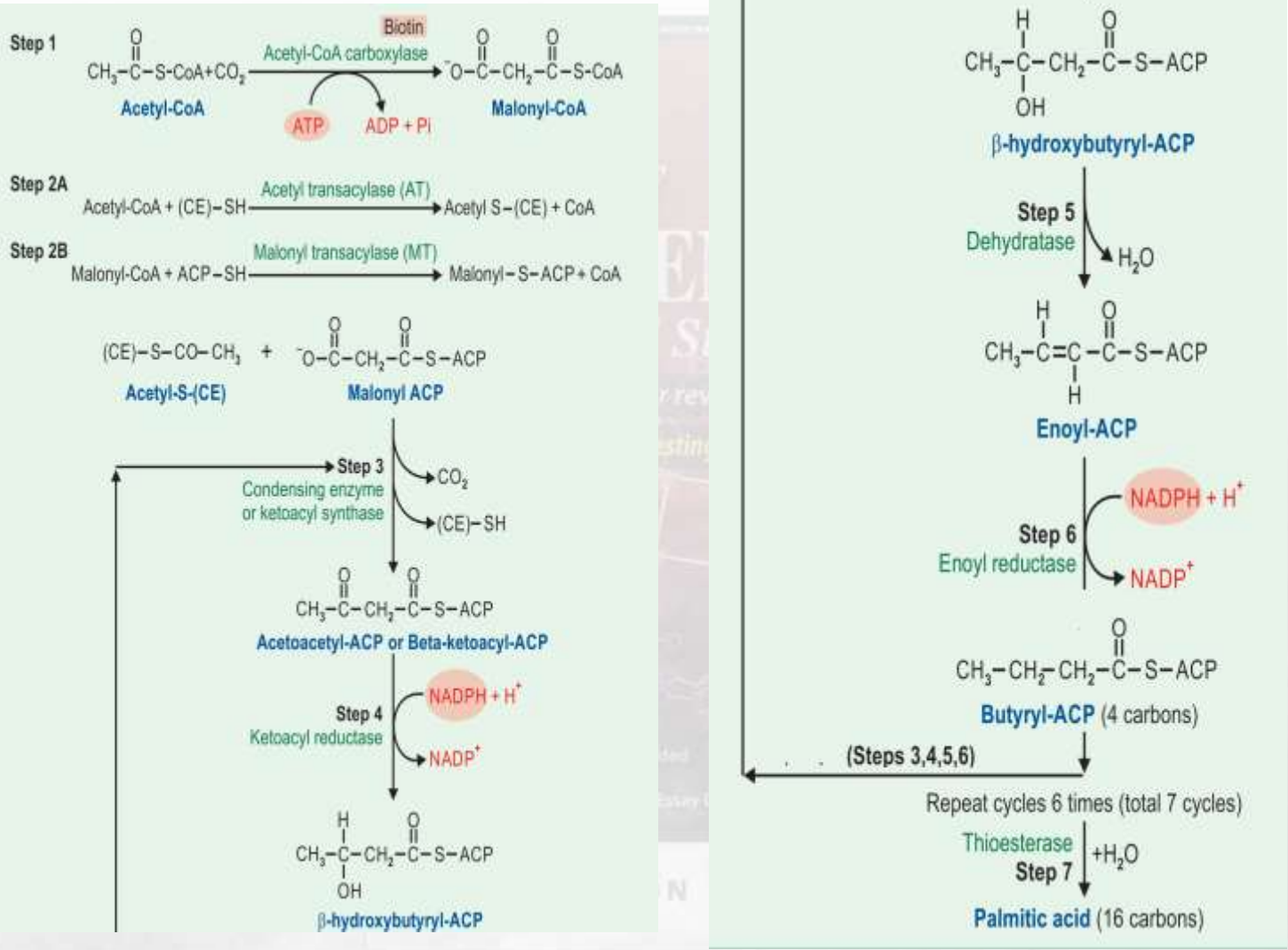
- The butyryl group (4C) is now transferred to the SH group of the condensing enzyme on the other monomer and a 2nd malonyl-CoA molecule binds to the phospho-pantothenyl SH group.
- The sequence of reactions, namely condensation, reduction, dehydration and reduction (steps 3,4,5,6) are repeated.
- The cycles are repeated a total of **seven times**, till the 16-Carbon palmitic acid is formed.



Step 7: Palmitic acid is Released

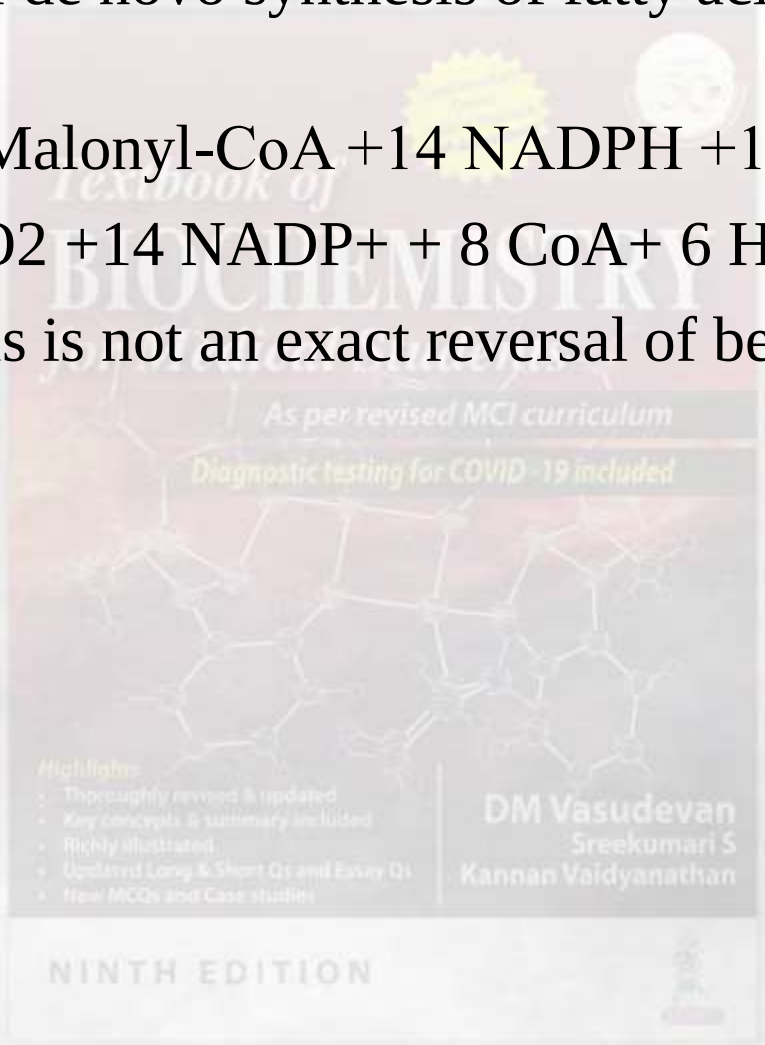
- Thio-esterase or deacylase activity (TE) releases palmitate from the multi-enzyme complex (Step 7).
- The end point is Palmitic acid (16 C) in liver and adipose tissue.
- But in lactating mammary gland, the end products are Capric (10 C) and Lauric (12 C) acids.
- Mother's milk contains these medium-chain fatty acids.
- Cow's milk contains odd numbered fatty acids.




Step 1
Biotin
Acetyl-CoA carboxylase
Acetyl-CoA
ATP
ADP + Pi
Malonyl-CoA
Step 2A
Acetyl transacylase (AT)
Acetyl-CoA + (CE)–SH
Acetyl S–(CE) + CoA
Step 2B
Malonyl transacylase (MT)
Malonyl-CoA + ACP–SH
Malonyl–S–ACP + CoA
Acetyl-S-(CE)
Malonyl ACP
Step 3
Condensing enzyme
or ketoacyl synthase
CO2
(CE)–SH
Acetoacetyl-ACP or Beta-ketoacyl-ACP
Step 4
Ketoacyl reductase
NADPH + H+
NADP+
β-hydroxybutyryl-ACP
Step 5
Dehydratase
H2O
Enoyl-ACP
Step 6
Enoyl reductase
NADPH + H+
NADP+
Butyryl-ACP (4 carbons)
(Steps 3,4,5,6)
Repeat cycles 6 times (total 7 cycles)
Thioesterase
Step 7
+H2O
Palmitic acid (16 carbons)

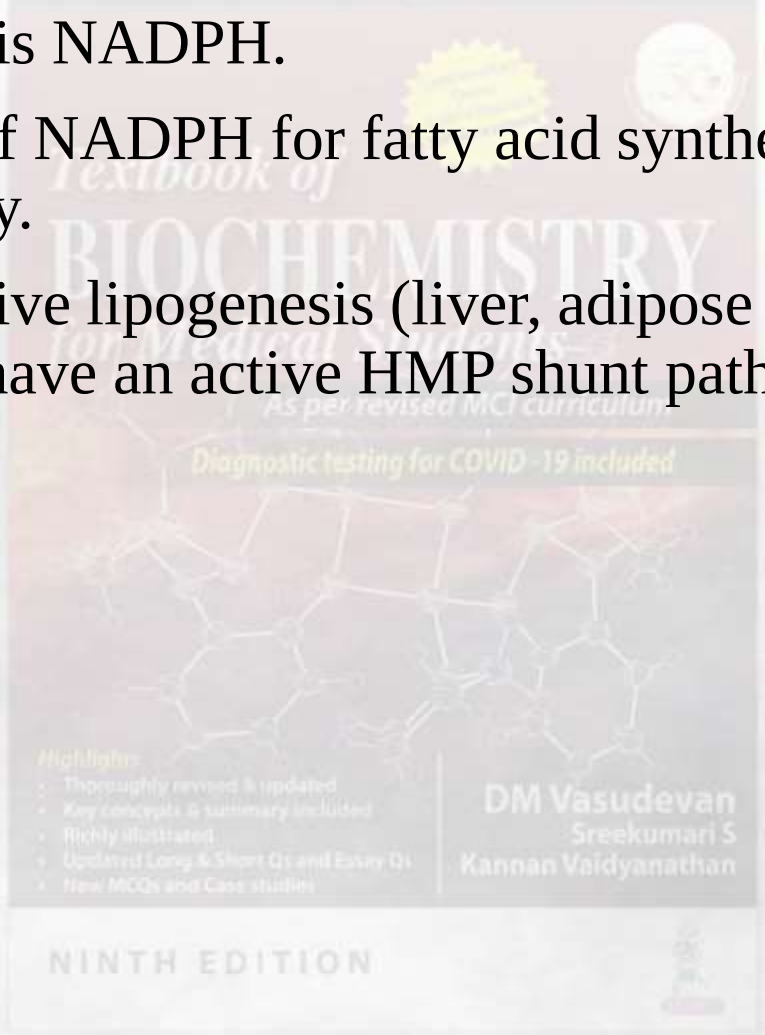
Summary of De Novo Synthesis

- The net reaction of de novo synthesis of fatty acid may be summarized as:
- 1 Acetyl-CoA +7 Malonyl-CoA +14 NADPH +14 H+ →
- 1 Palmitate + 7 CO2 +14 NADP+ + 8 CoA+ 6 H2O.
- Fatty acid synthesis is not an exact reversal of beta oxidation.



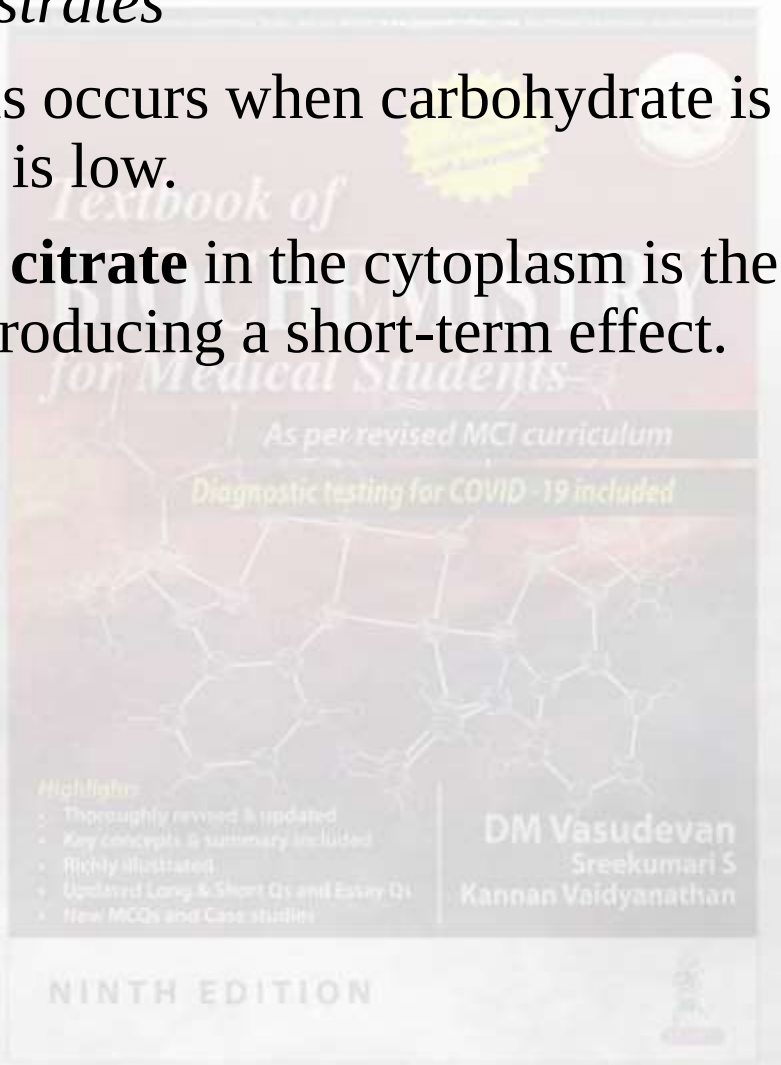
Coenzymes of Fatty Acid Synthesis

- An important point to remember is that the coenzyme utilized for de novo synthesis is NADPH.
- The main source of NADPH for fatty acid synthesis is Pentose Phosphate Pathway.
- Tissues having active lipogenesis (liver, adipose tissue, lactating mammary gland) have an active HMP shunt pathway also.



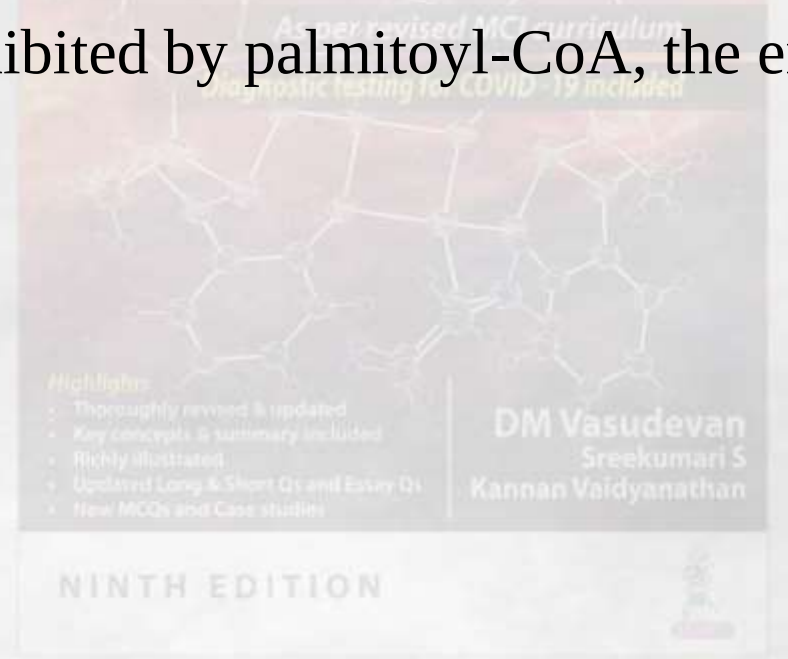
Regulation of Fatty Acid Synthesis

- *Availability of Substrates*
- Fatty acid synthesis occurs when carbohydrate is abundant and the level of fatty acids is low.
- The availability of **citrate** in the cytoplasm is the most important regulatory factor producing a short-term effect.



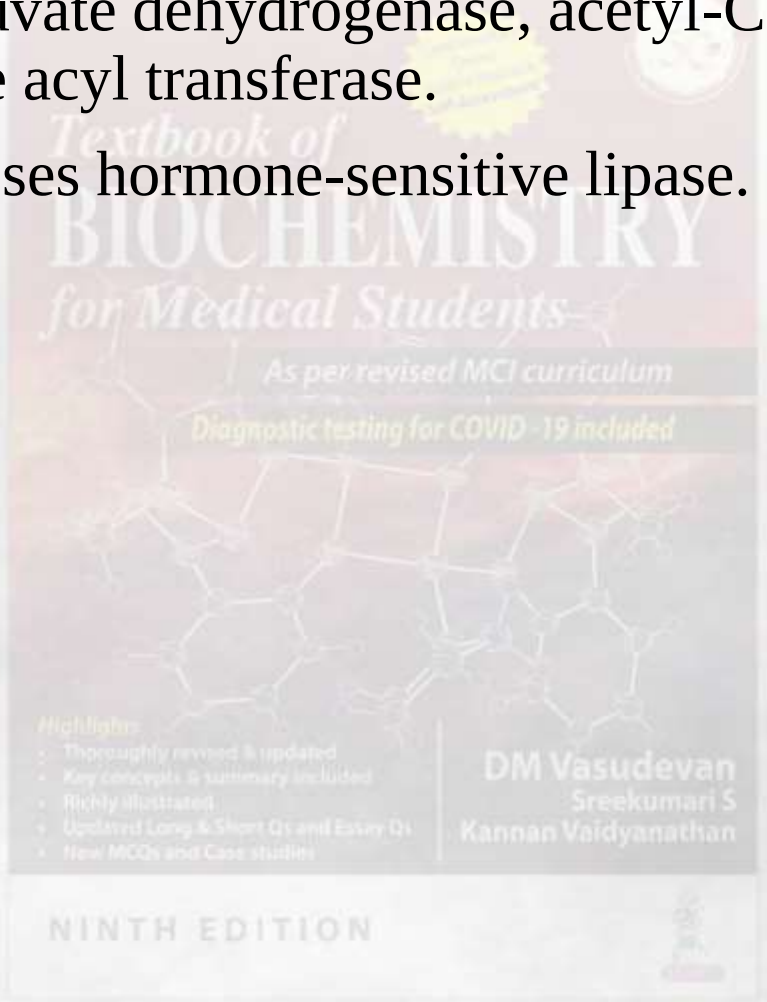
Acetyl-CoA Carboxylase

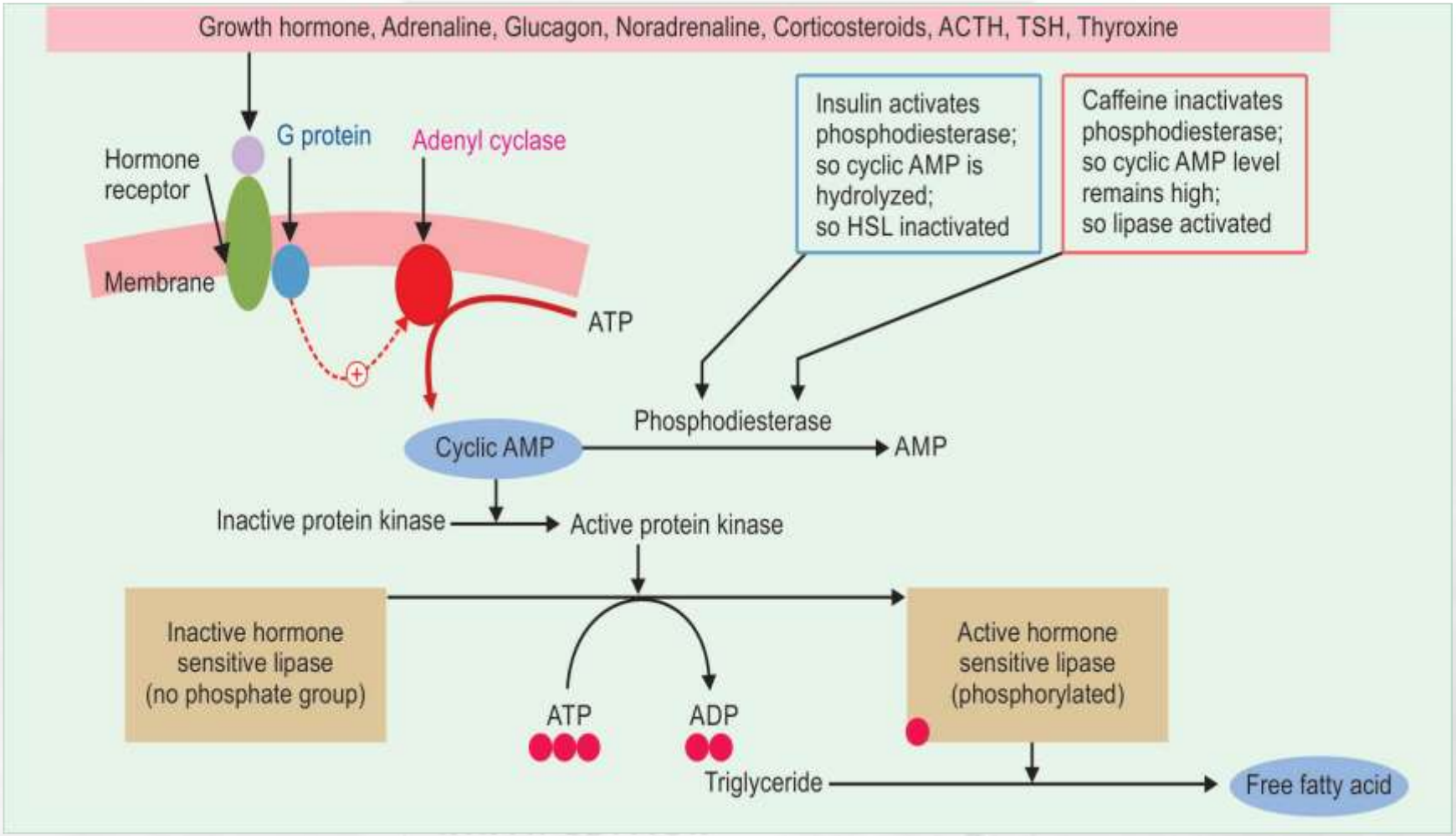
- Phosphorylation inactivates acetyl-CoA carboxylase.
- AMP activates this phosphorylation, while ATP inhibits it.
- So, fatty acid synthesis is enhanced when energy charge is high.
- Fatty acid synthesis decreases when glucose level and energy charge is low.
- The enzyme is inhibited by palmitoyl-CoA, the end product.



Insulin Favors Lipogenesis

- Insulin enhances the uptake of glucose by adipocytes and increases the activity of pyruvate dehydrogenase, acetyl-CoA carboxylase and glycerol phosphate acyl transferase.
- Insulin also depresses hormone-sensitive lipase.

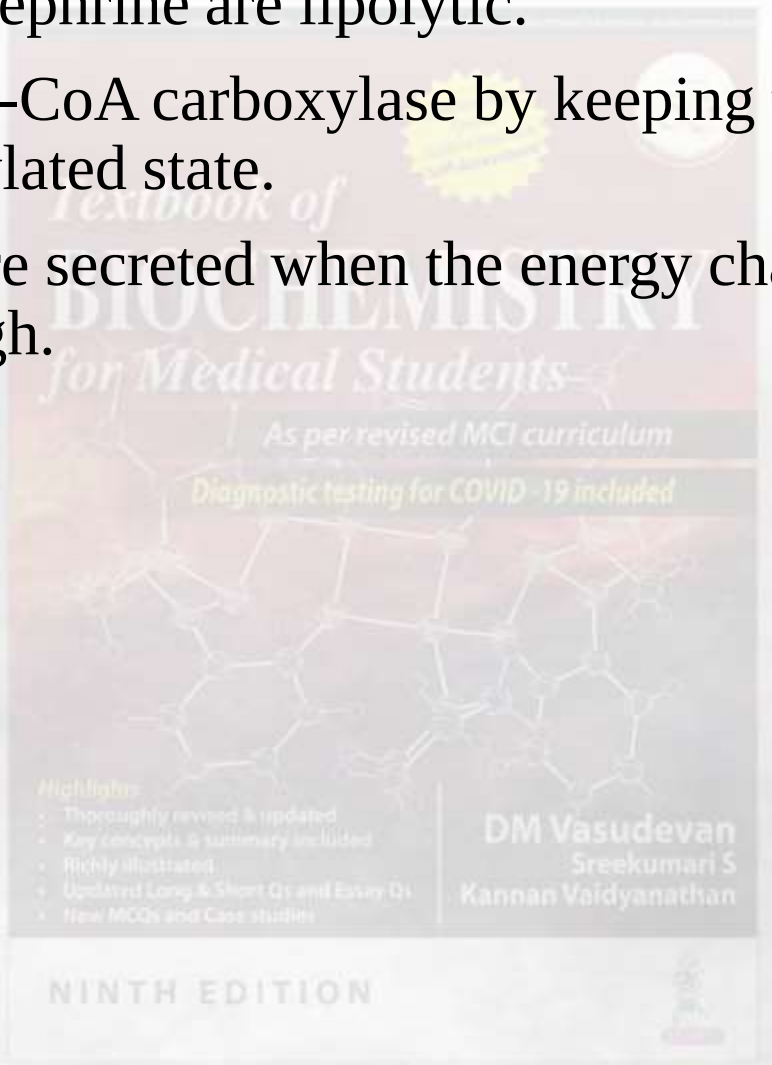




Cascade activation of hormone sensitive lipase

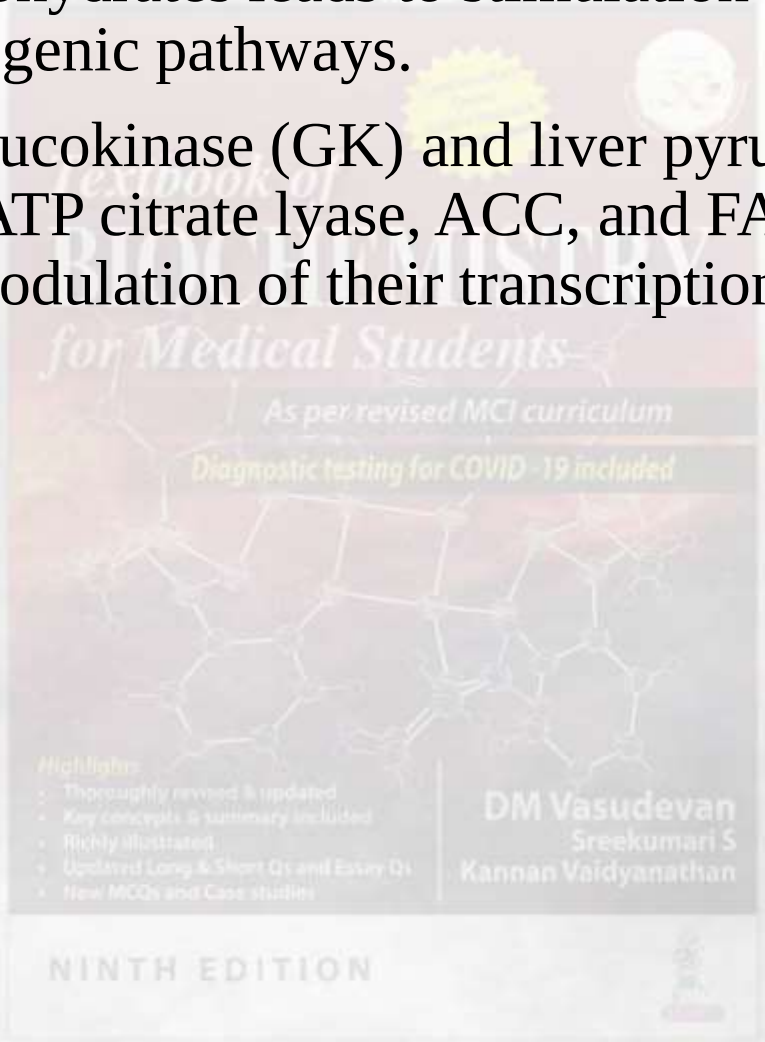
Glucagon Inhibits Lipogenesis

- Glucagon and epinephrine are lipolytic.
- They inhibit acetyl-CoA carboxylase by keeping the enzyme in the inactive phosphorylated state.
- These hormones are secreted when the energy charge is low and AMP levels are high.



Regulation at the Gene Level

- A diet rich in carbohydrates leads to stimulation of both the glycolytic and lipogenic pathways.
- Genes encoding glucokinase (GK) and liver pyruvate kinase (L-PK) of glycolysis and ATP citrate lyase, ACC, and FAS of lipogenesis are regulated by modulation of their transcription rates.

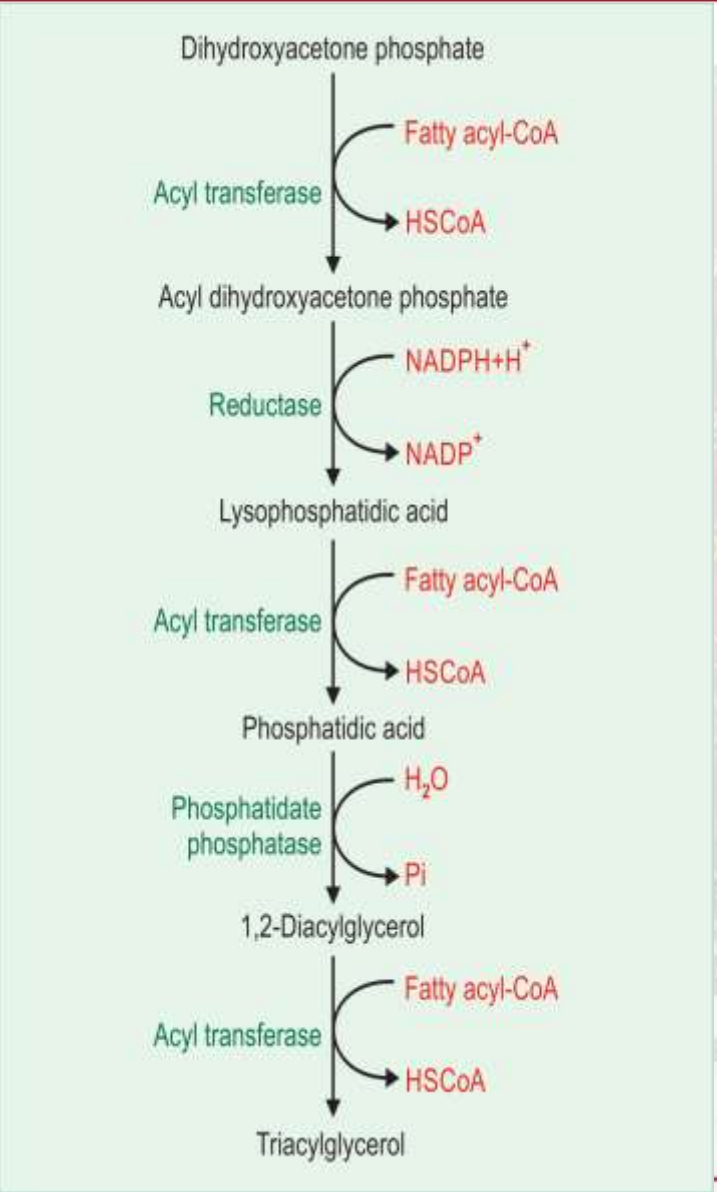


Synthesis of Triacylglycerols

- Liver and adipose tissue are the major sites of triacylglycerol (TAG) synthesis.
- The TAG synthesis in adipose tissue is for storage of energy.
- But liver TAG is secreted as VLDL and is transported.
- The TAG is synthesized by esterification of fatty acyl-CoA with either glycerol-3-phosphate or dihydroxy acetone phosphate (DHAP).
- The glycerol part of the fat is derived from the metabolism of glucose.
- DHAP is an intermediate of glycolysis.
- Glycerol-3-phosphate may be formed by phosphorylation of glycerol or by reduction of dihydroxy acetone phosphate (DHAP).

Synthesis of Triacylglycerols, Continues

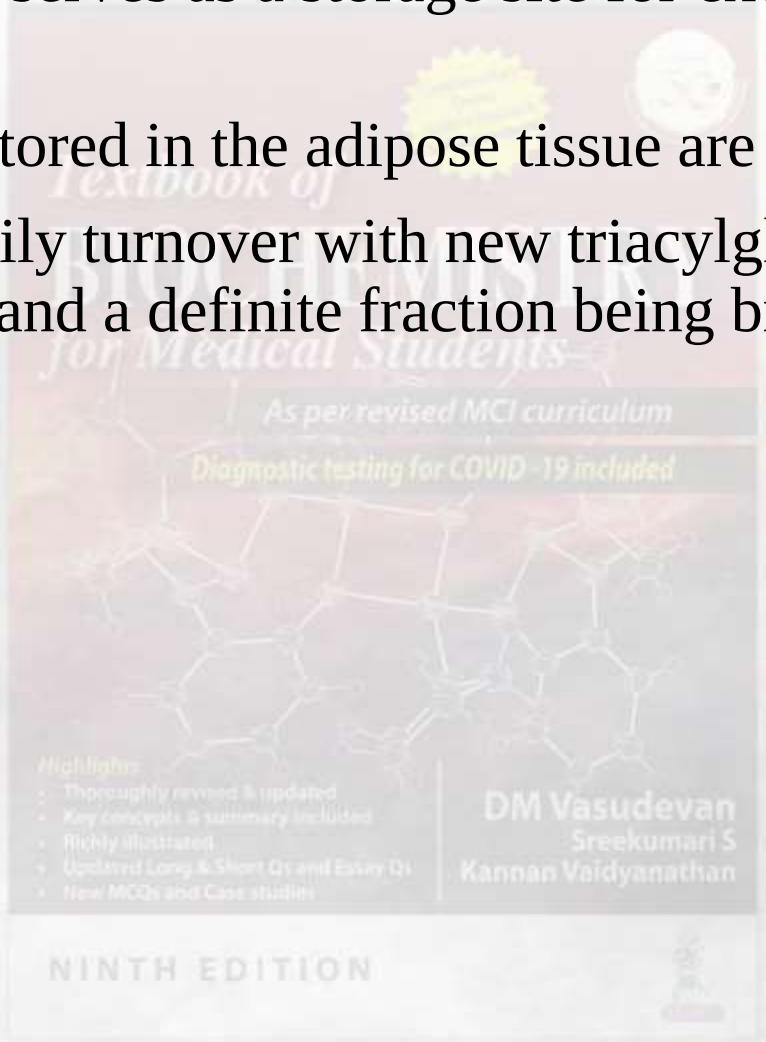
- **In adipose tissue, glycerol kinase is deficient and the major source is DHAP derived from glycolysis.**
- However in liver, glycerol kinase is active.
- The fatty acyl-CoA molecules transfer the fatty acid to the hydroxyl groups of glycerol by specific acyl transferases.
- In addition to these two pathways, in the intestinal mucosal cells the TAG synthesis occurs by the MAG pathway.
- The 2-MAG absorbed is re-esterified with fatty acyl-CoA to form TAG.



Triacylglycerol synthesis

Metabolism of Adipose Tissue

- The adipose tissue serves as a storage site for excess calories ingested.
- The triglycerides stored in the adipose tissue are not inert.
- They undergo a daily turnover with new triacylglycerol molecules being synthesized and a definite fraction being broken down.



Adipose Tissue in Well-fed Condition

- Under well-fed conditions, active lipogenesis occurs in the adipose tissue.
- The dietary triglycerides are transported by chylomicrons.
- Liver endogenously synthesize triglycerides which are secreted as VLDL.
- Both chylomicrons and VLDL are taken up by adipose tissue and stored as TAG.
- The lipoprotein molecules are broken down by the **lipoprotein lipase** present on the capillary wall.

- In well fed condition, glucose and insulin levels are increased.
- GluT4 in adipose tissue is insulin-dependent.
- Insulin increases the activity of key glycolytic enzymes as well as pyruvate dehydrogenase, acetyl-CoA carboxylase and glycerol phosphate acyl transferase.
- The stimulant effect of insulin on HMP pathway also enhances lipogenesis.
- Insulin also causes inhibition of hormone-sensitive lipase, and so lipolysis is decreased.

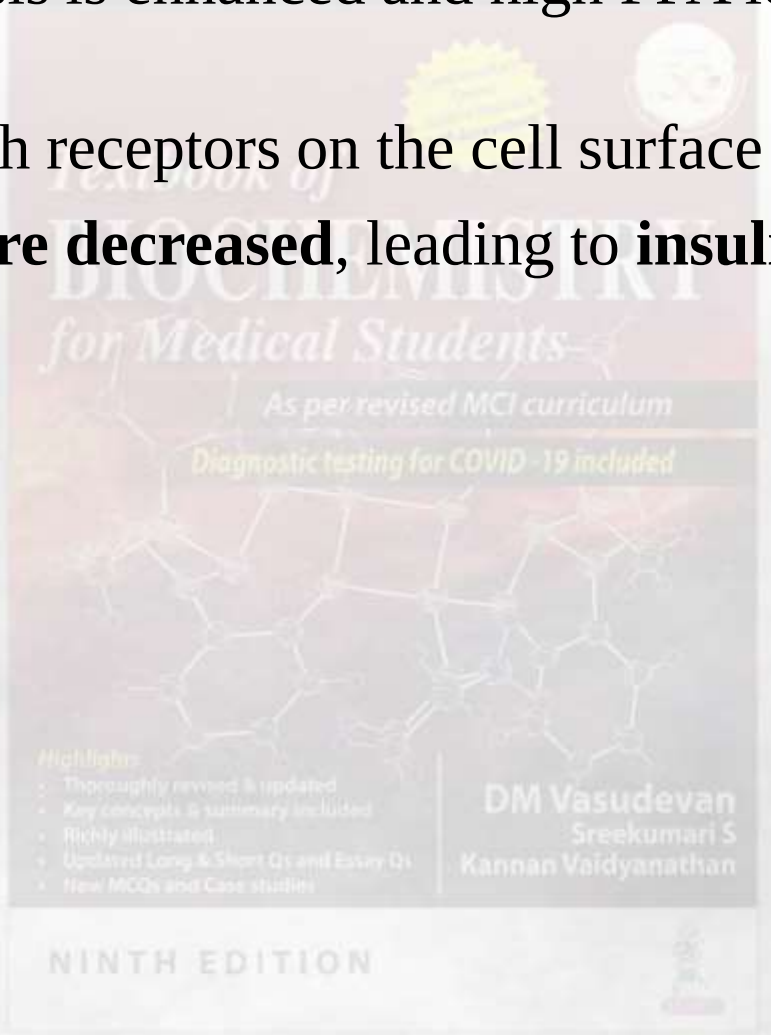
Adipose Tissue in Fasting Condition

- The metabolic pattern totally changes under conditions of fasting.
- TAG from the adipose tissue is mobilized under the effect of the hormones, **glucagon and epinephrine**.
- The cyclic AMP mediated activation cascade enhances the intracellular hormone-sensitive lipase.
- This acts on TAG and liberates fatty acids.
- Under conditions of starvation, a high glucagon, ACTH, glucocorticoids and thyroxine have lipolytic effect.
- The released free fatty acids (FFA) are taken up by peripheral tissues as a fuel.

Changes in adipose tissue	
Well-fed state	During fasting
Lipogenesis increased	Lipogenesis inhibited
Lipolysis inhibited	Lipolysis increased
Insulin inhibits HS-lipase	Glucagon activates HS-lipase
Lipoprotein lipase active	FFA in blood increased

Adipose Tissue and Diabetes Mellitus

- In diabetes, lipolysis is enhanced and high FFA level in plasma is noticed.
- Insulin acts through receptors on the cell surface of adipocytes.
- These **receptors are decreased**, leading to **insulin insensitivity** in diabetes.

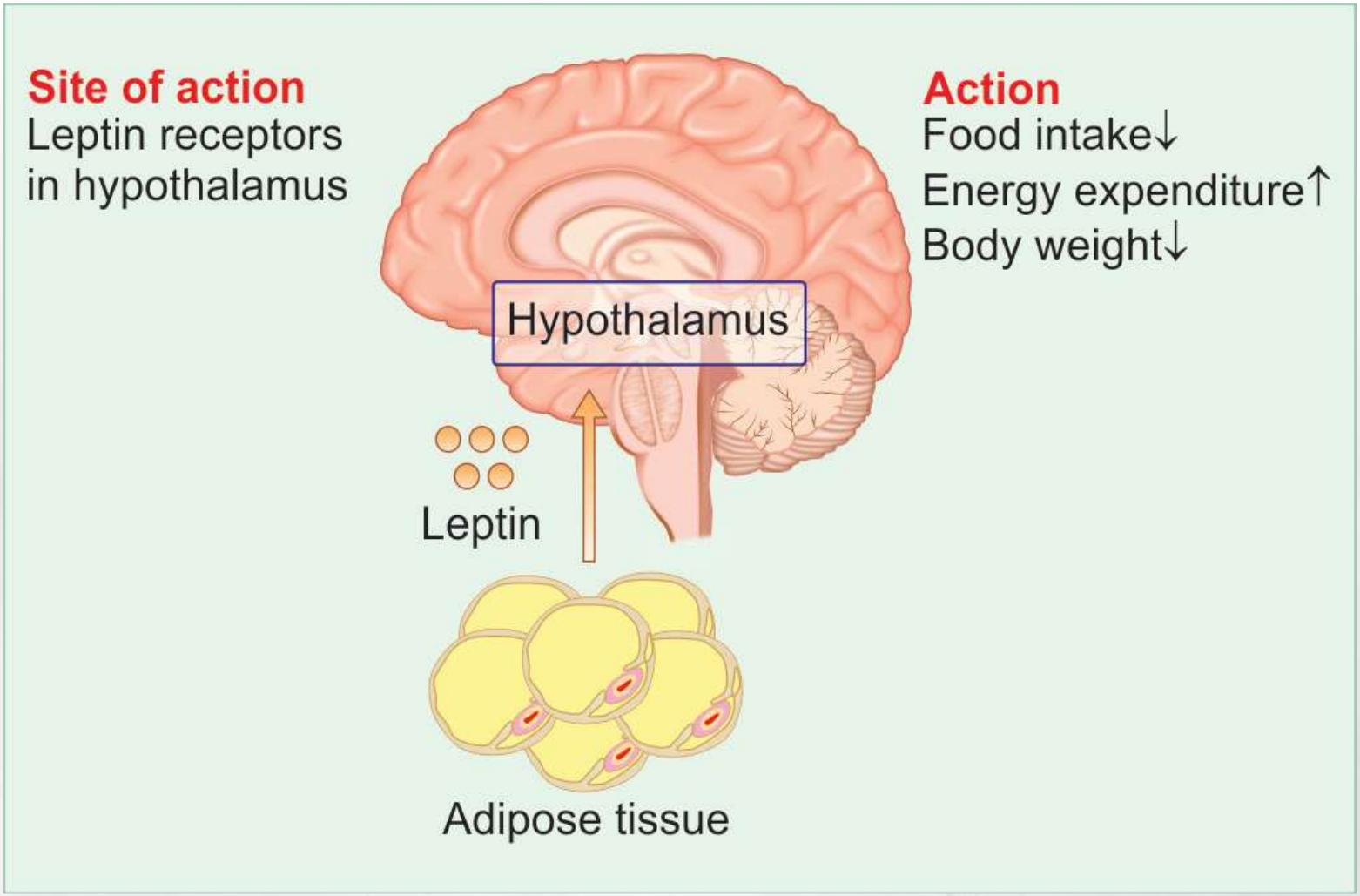


Adipose Tissue and Obesity

- The fat content of the adipose tissue can increase to unlimited amounts, depending on the amount of **excess calories** taken in. This leads to obesity.
- A high level of plasma insulin level is noticed.
- But the **insulin receptors are decreased**; and there is peripheral resistance against insulin action.
- When fat droplets are overloaded, the nucleus of adipose tissue cell is degraded, cell is destroyed, and TAG becomes extracellular.
- Such TAG cannot be metabolically reutilized and forms the dead bulk in obese individuals.

Adipokines

- Adipokines are adipose tissue dervived hormones.
- The important adipokines are leptin, adiponectin, resistin, TNF-alpha (tumor necrosis factor) and IL-6 (interleukin-6).
- **Leptin** is a small peptide, produced by adipocytes.
- Leptin receptors are present in specific regions of the brain.
- The feeding behavior is regulated by leptin.
- A defect in leptin or its receptor, can lead to obesity.
- Decreased level of leptin increases the chances of obesity.
- **Adiponectin** is another polypeptide, which increases the insulin sensitivity of muscle and liver.
- Low levels of adiponectin will accelerate atherosclerosis.
- Low levels are also observed in patients with metabolic syndrome.

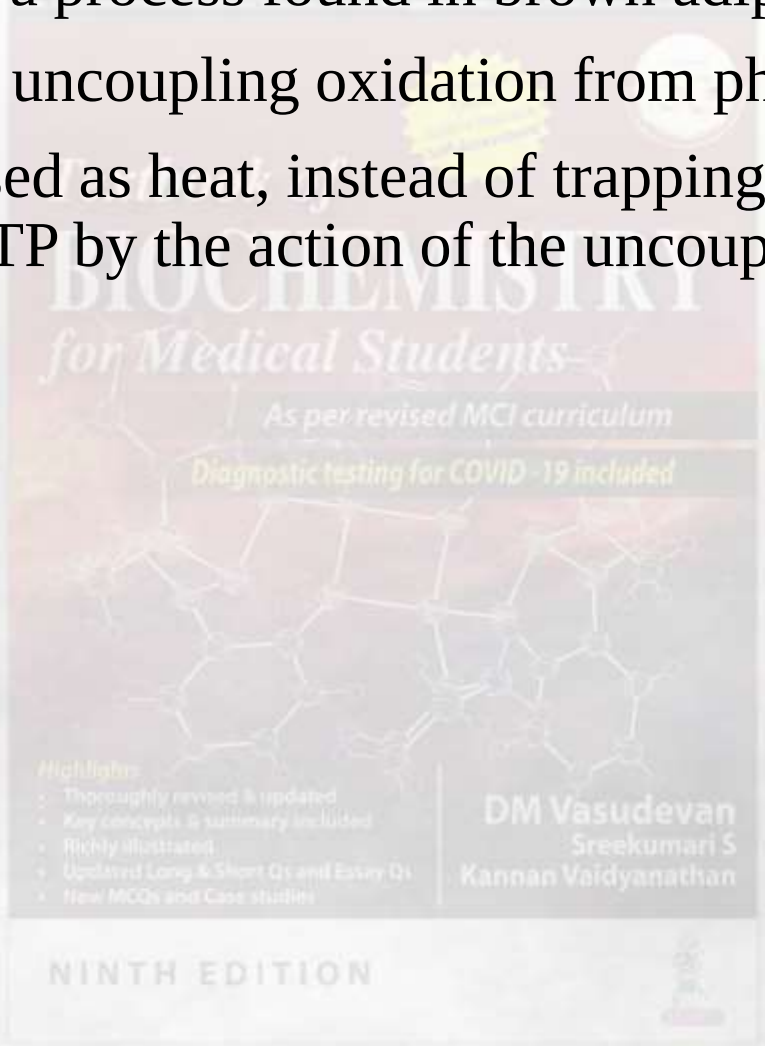


Leptin regulates food intake and energy expenditure

White Adipose Tissue

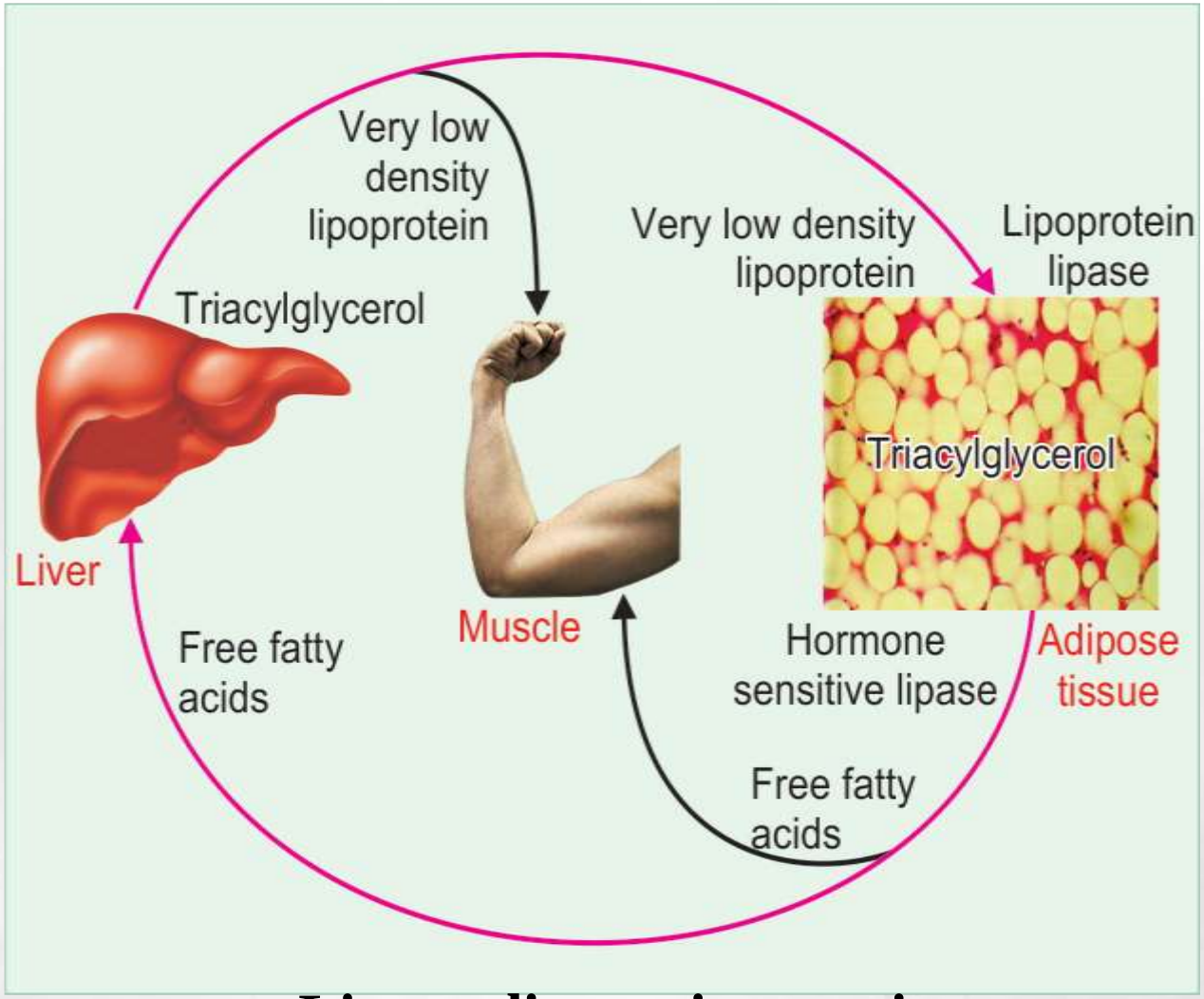
- It is mainly concerned with energy storage.
- It is made up of spherical cells, with very few mitochondria.
- The triglycerides form the major component of white adipose tissue (about 80%) with oleic acid being the most abundant fatty acid (50%).
- **Brown adipose tissue** is involved in thermogenesis.
- The brown color is due to the presence of numerous mitochondria.
- It is primarily important in new born human beings and adult hibernating animals.

- **Thermogenesis** is a process found in brown adipose tissue.
- It liberates heat by uncoupling oxidation from phosphorylation.
- So energy is released as heat, instead of trapping it in the high energy bonds of ATP by the action of the uncoupling protein, thermogenin.



Liver-Adipose Tissue Axis

- Liver produces fatty acid and TAG (triacylglycerol), which is transported as VLDL (very low density lipoprotein) in the blood.
- The fatty acids from VLDL are taken up by adipose tissue with the help of lipoprotein lipase, and stored as TAG.
- This neutral fat is hydrolysed by hormone-sensitive lipase into NEFA (FFA), which in the blood is carried by albumin.
- The NEFA is utilized by the peripheral tissues, excess of which can be taken up by liver cells.
- Thus there is a constant flux of fat molecules from liver to adipose tissue and back.



Liver-adipose tissue axis

Role of liver in fat metabolism

Secretion of bile salts.

Synthesis of fatty acid, triacylglycerol and phospholipids.

Oxidation of fatty acids.

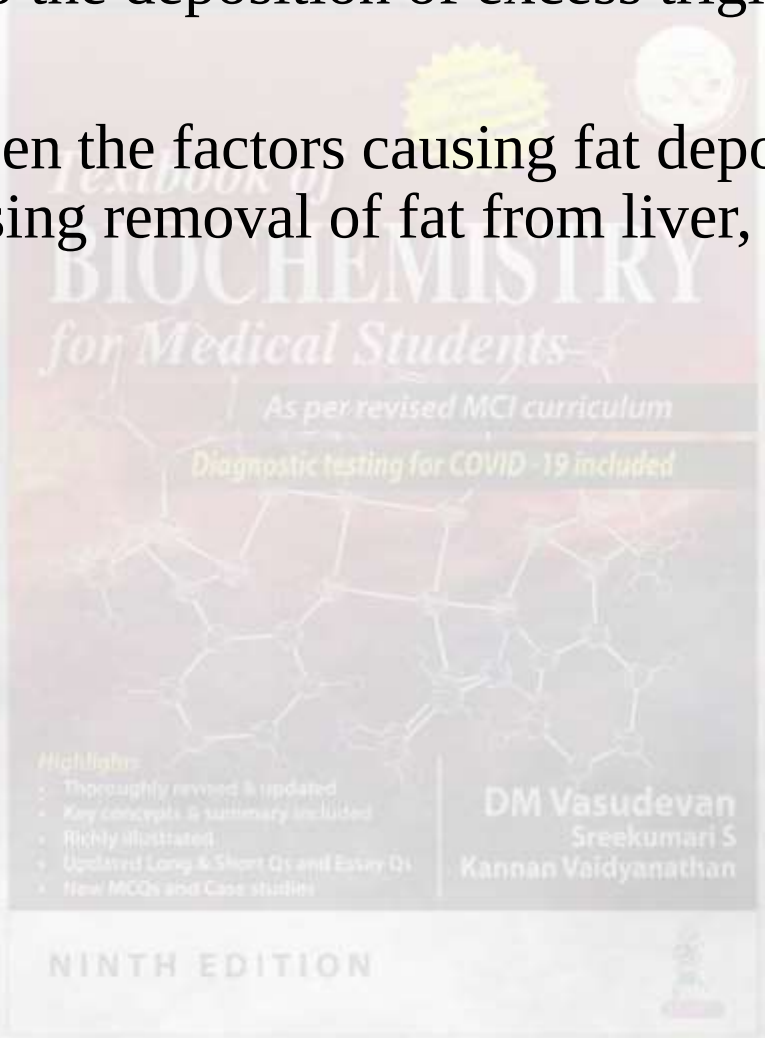
Production of lipoproteins.

Production of ketone bodies.

Synthesis and excretion of cholesterol.

Fatty Liver and Lipotropic Factors

- Fatty liver refers to the deposition of excess triglycerides in the liver cells.
- The balance between the factors causing fat deposition in liver versus factors causing removal of fat from liver, determines the outcome.



Causes of Fatty Liver

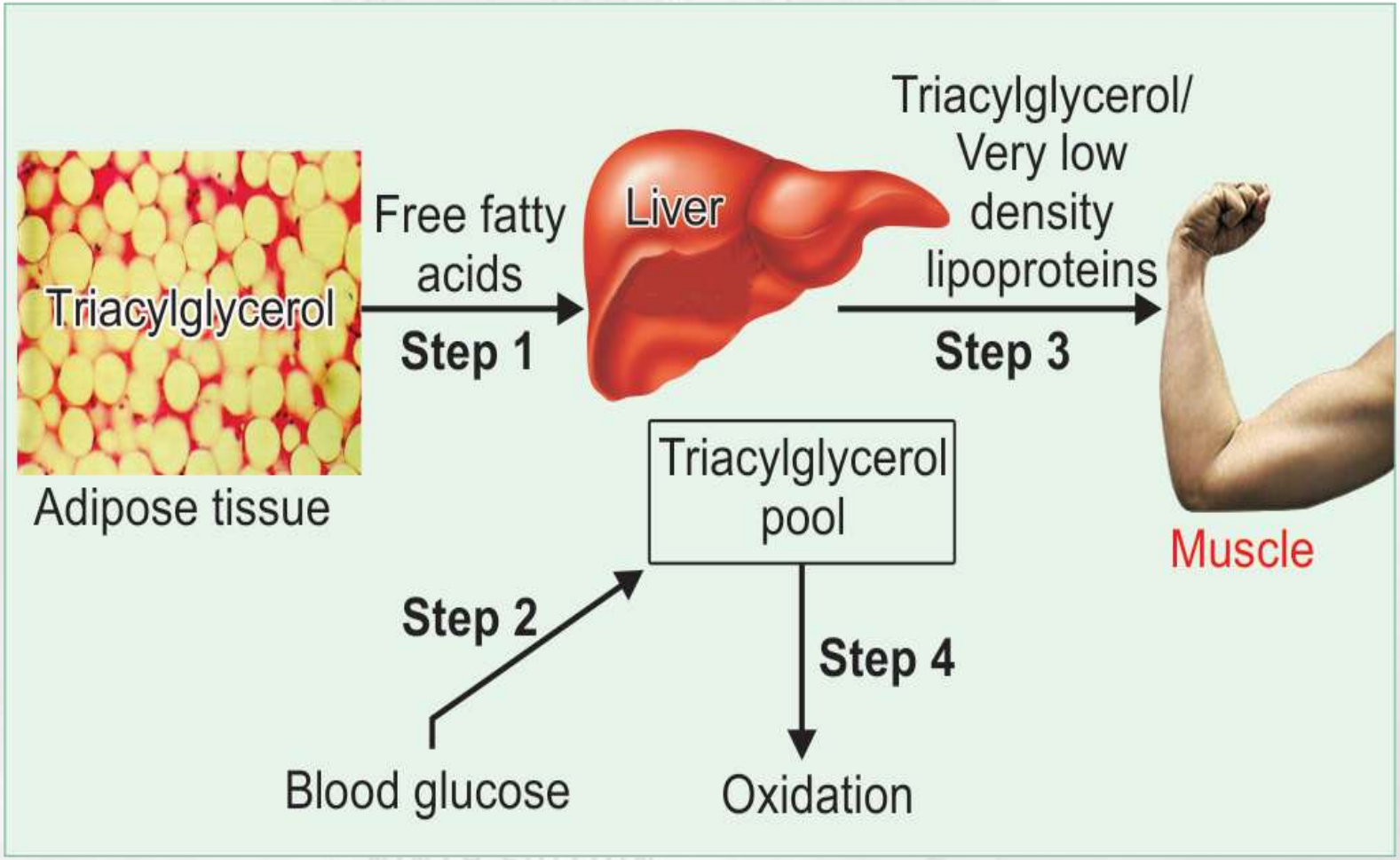
A. Causes of fat deposition in liver

1. Mobilization of fatty acids (FFA or NEFA) from adipose tissue.
2. More synthesis of fatty acid from glucose.

B. Reduced removal of fat from liver

3. Toxic injury to liver. Secretion of VLDL needs synthesis of Apo B-100 and Apo C.
4. Decreased oxidation of fat by hepatic cells.

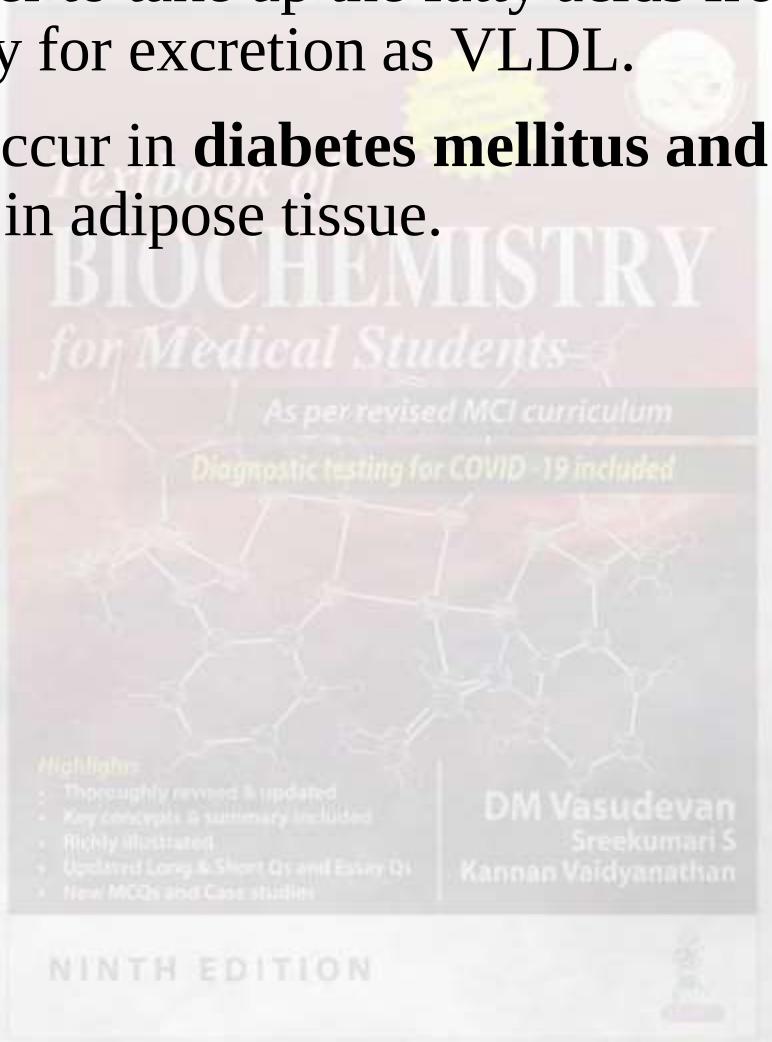
- An increase in factors (1) and (2) or a decrease in factors (3) and (4) will cause excessive accumulation, leading to fatty liver.



Causes of fatty liver

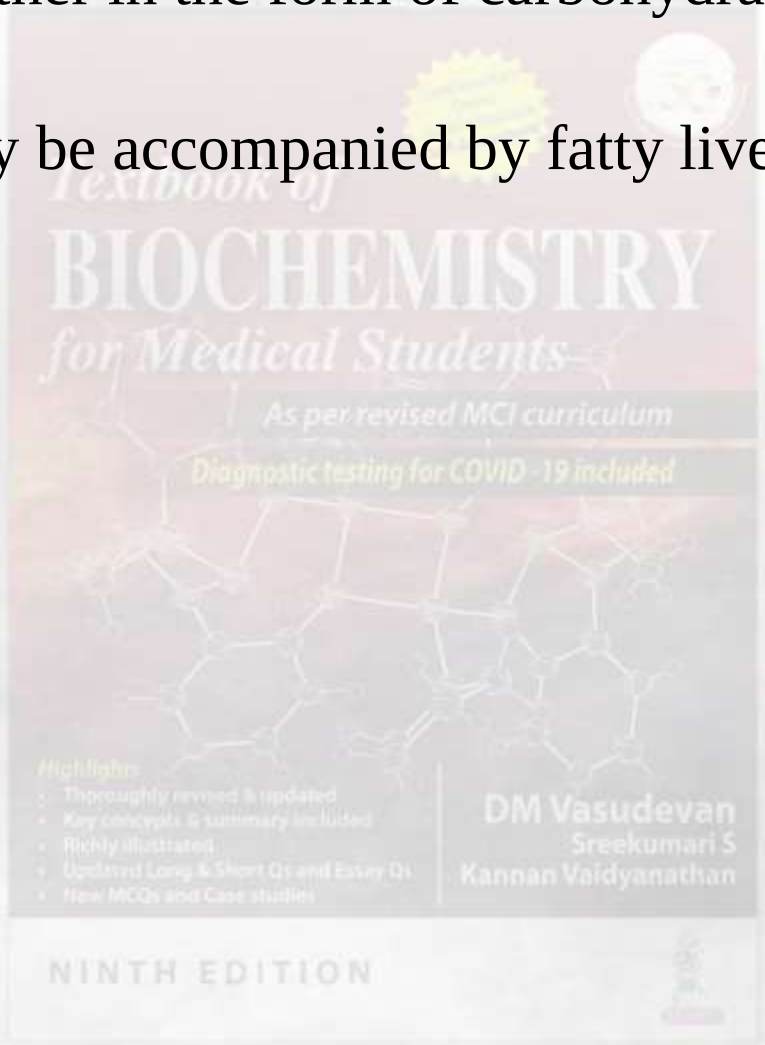
Excessive Mobilization of Fat

- The capacity of liver to take up the fatty acids from blood far exceeds its capacity for excretion as VLDL.
- So fatty liver can occur in **diabetes mellitus and starvation** due to increased lipolysis in adipose tissue.



Excess Calorie Intake

- Excess calories, either in the form of carbohydrates or as fats, are deposited as fat.
- Hence **obesity** may be accompanied by fatty liver.

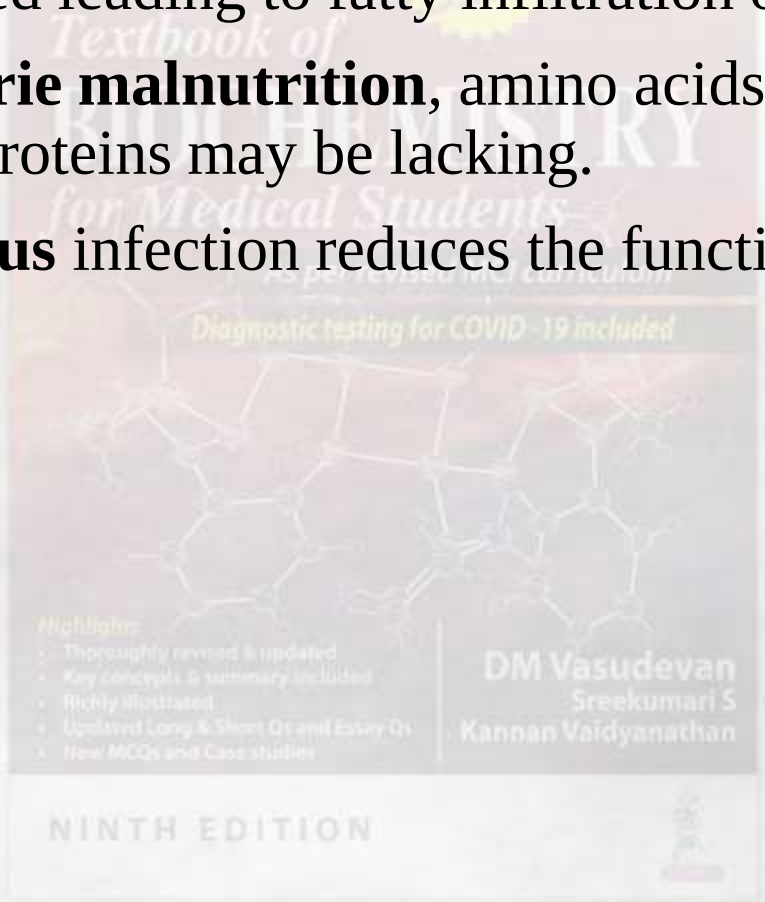


Toxic Injury to Liver

i. In toxic injury to the liver due to **poisoning** by compounds like carbon tetrachloride, arsenic, lead, etc., the capacity to synthesize VLDL is affected leading to fatty infiltration of liver.

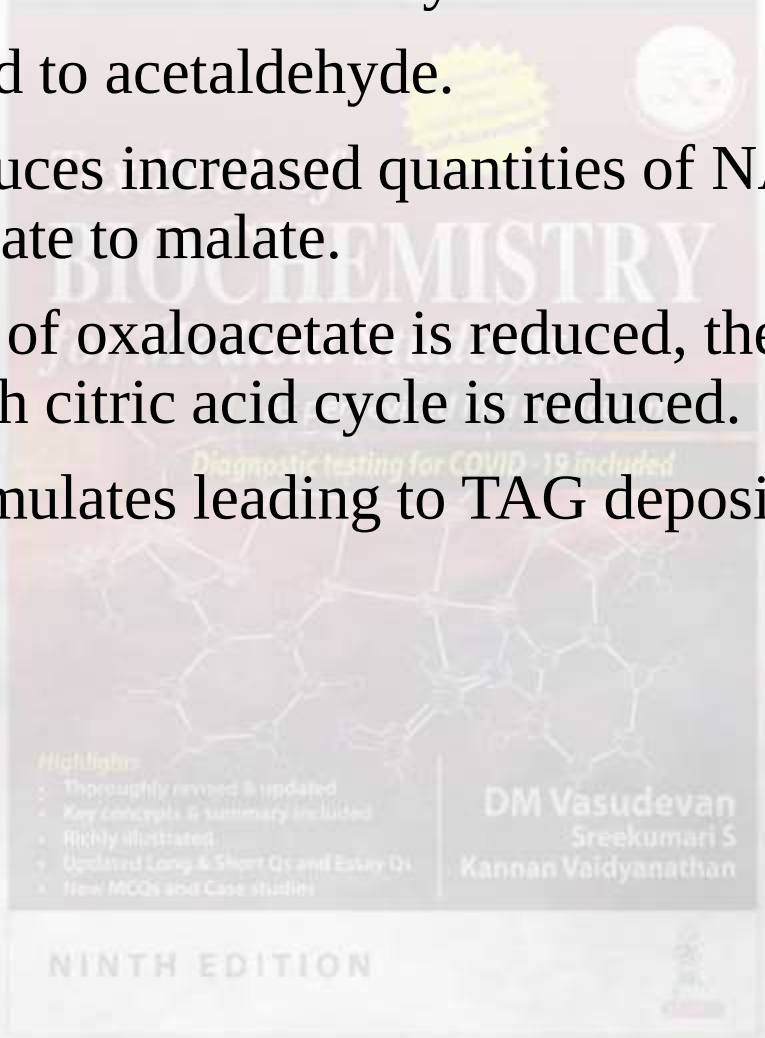
ii. In **protein calorie malnutrition**, amino acids required to synthesise apoproteins may be lacking.

iii. **Hepatitis B virus** infection reduces the function of hepatic cells.



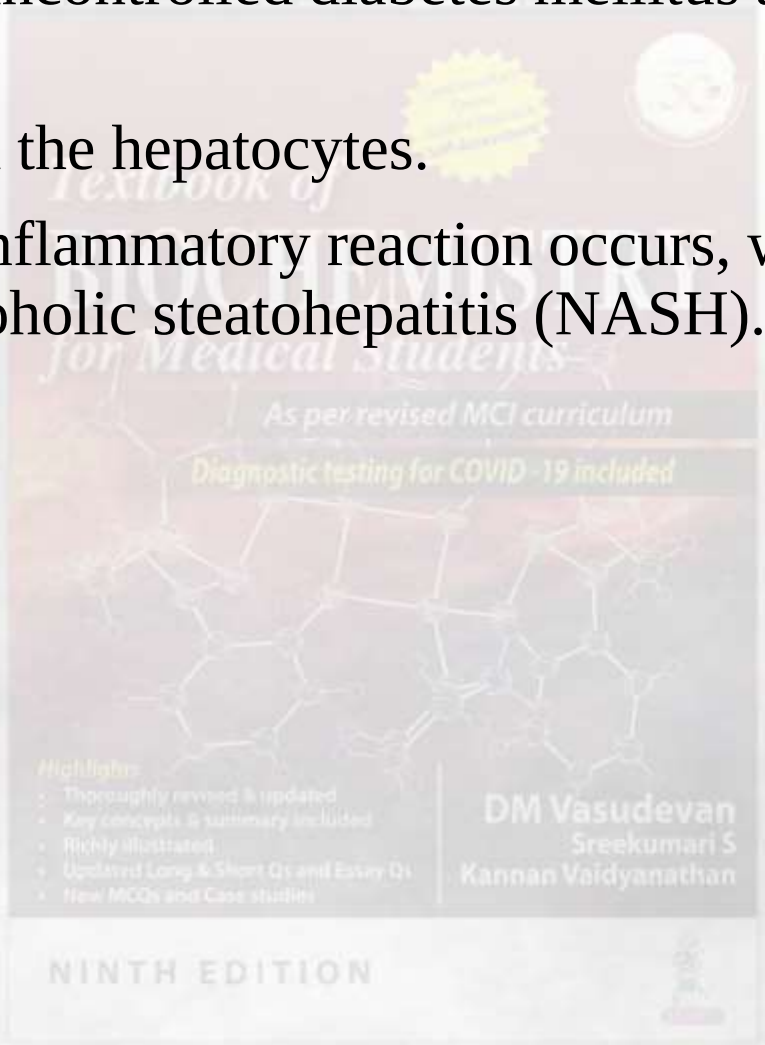
Alcoholism

- It is the most common cause of fatty liver and cirrhosis in India.
- Alcohol is oxidized to acetaldehyde.
- This reaction produces increased quantities of NADH, which converts oxaloacetate to malate.
- As the availability of oxaloacetate is reduced, the oxidation of acetyl-CoA through citric acid cycle is reduced.
- So fatty acid accumulates leading to TAG deposits in liver.



Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH)

- High fat diet and uncontrolled diabetes mellitus are the most common causes.
- Fat accumulates in the hepatocytes.
- As it progresses, inflammatory reaction occurs, which is then termed as non-alcoholic steatohepatitis (NASH).



Fatty Liver Progresses to Cirrhosis

- Fat molecules infiltrate the cytoplasm of the cell (**fatty infiltration**).
- These are seen as fat droplets, which are merged together so that most of the cytoplasm becomes laden with fat.
- The nucleus is pushed to a side of the cell, nucleus further disintegrated **(karyorrhexis)**, and ultimately the hepatic cell is lysed.
- As a healing process, fibrous tissue is laid down, causing **fibrosis** of liver, otherwise known as **cirrhosis.**
- *Liver function tests* will show abnormal values.

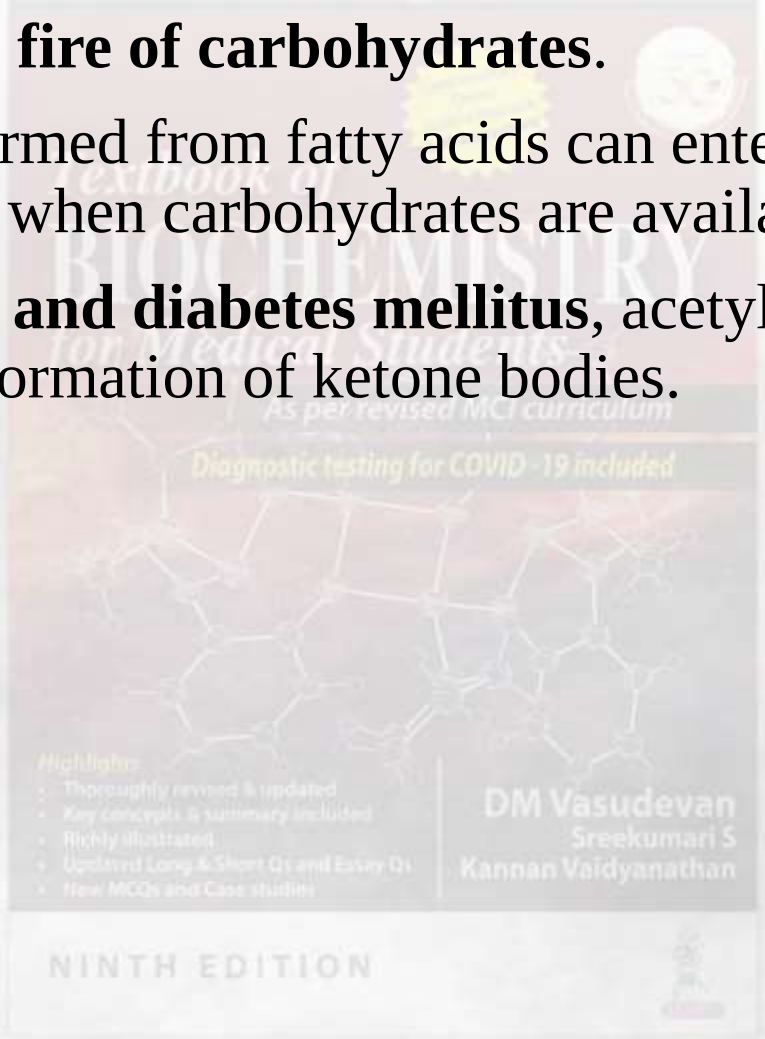
Lipotropic Factors

- They are **required for the normal mobilization** of fat from liver.
- Therefore deficiency of these factors may result in fatty liver.
- They can afford protection against the development of fatty liver.

1. **Choline**
2. **Lecithin and methionine:** They help in synthesis of apoprotein and choline formation. The deficiency of methyl groups for carnitine synthesis may also hinder fatty acid oxidation.
3. **Vitamin E and selenium** give protection due to their antioxidant effect.
4. **Omega-3 fatty acids** present in marine oils have a protective effect against fatty liver.

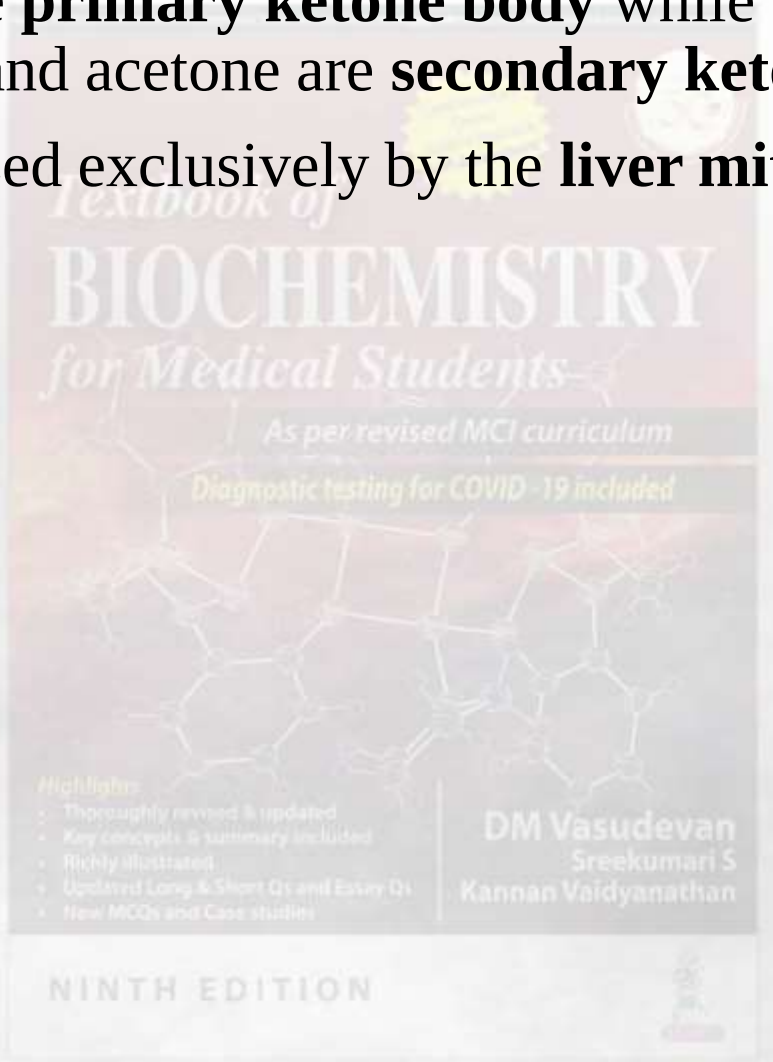
Metabolism of Ketone Bodies

- Carbohydrates are essential for the metabolism of fat or **fat is burned under the fire of carbohydrates**.
- The acetyl-CoA formed from fatty acids can enter and get oxidized in TCA cycle only when carbohydrates are available.
- During **starvation and diabetes mellitus**, acetyl-CoA takes the alternate route of formation of ketone bodies.



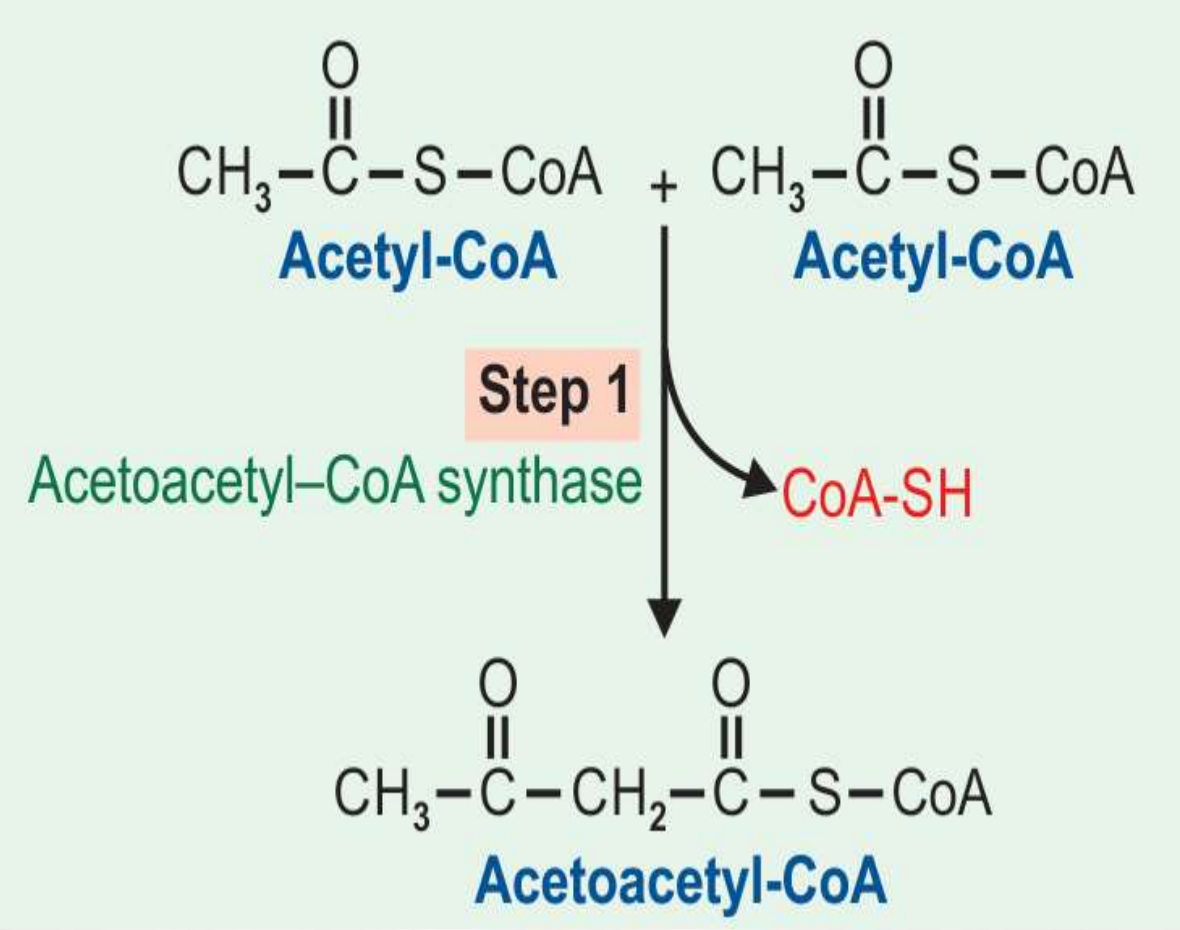
Ketogenesis

- Acetoacetate is the **primary ketone body** while beta hydroxy butyrate and acetone are **secondary ketone** bodies.
- They are synthesized exclusively by the **liver mitochondria**.

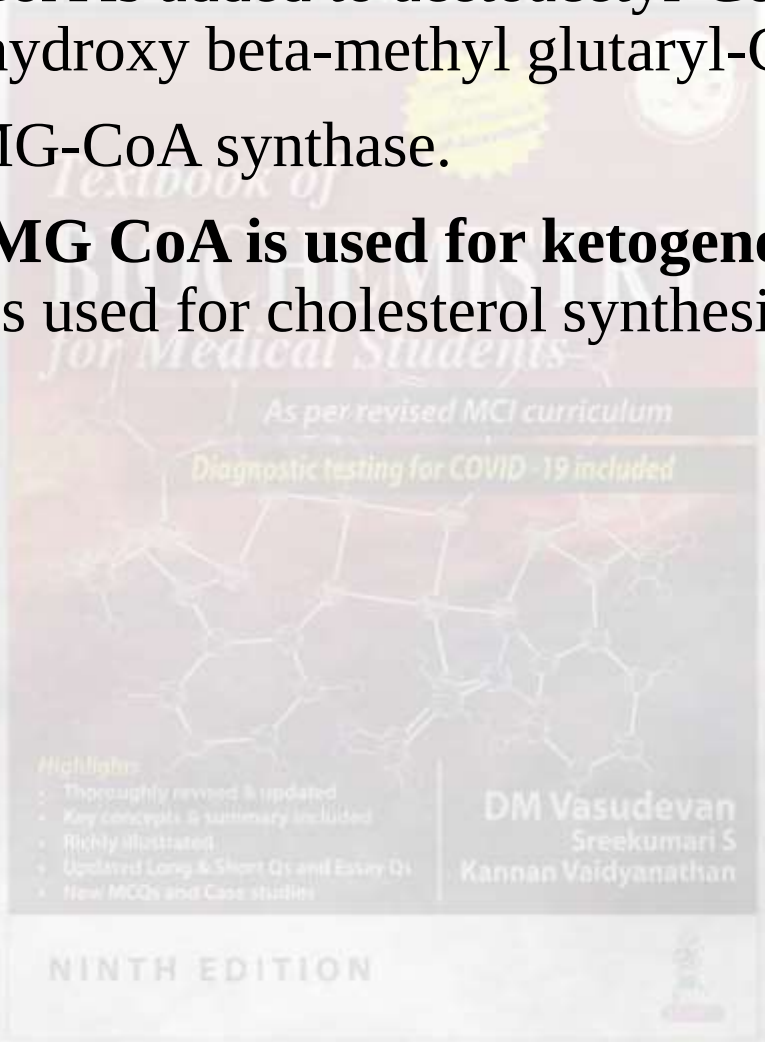


Step 1: Condensation

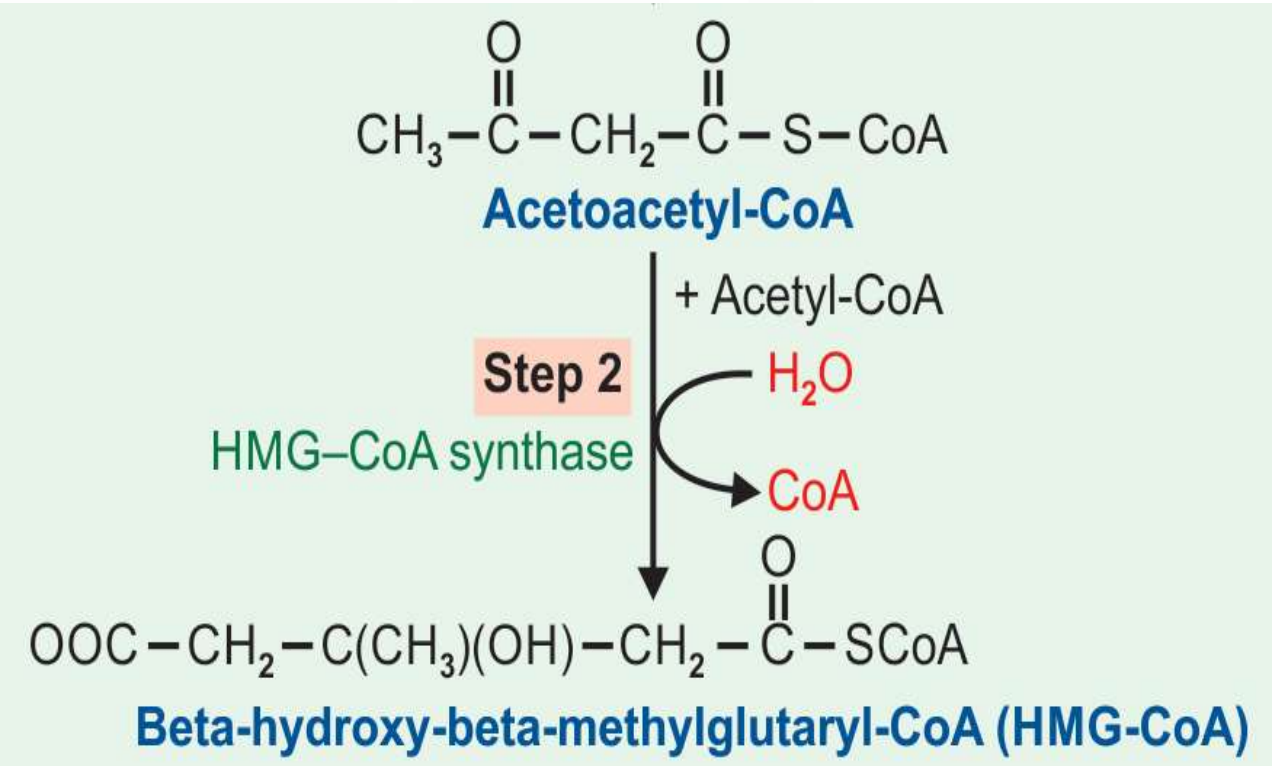
- Two molecules of acetyl-CoA are condensed to form acetoacetyl-CoA.



- One more acetyl-CoA is added to acetoacetyl-CoA to form HMG-CoA (beta-hydroxy beta-methyl glutaryl-CoA).
- The enzyme is HMG-CoA synthase.
- **Mitochondrial HMG CoA is used for ketogenesis**, while cytosolic fraction is used for cholesterol synthesis.



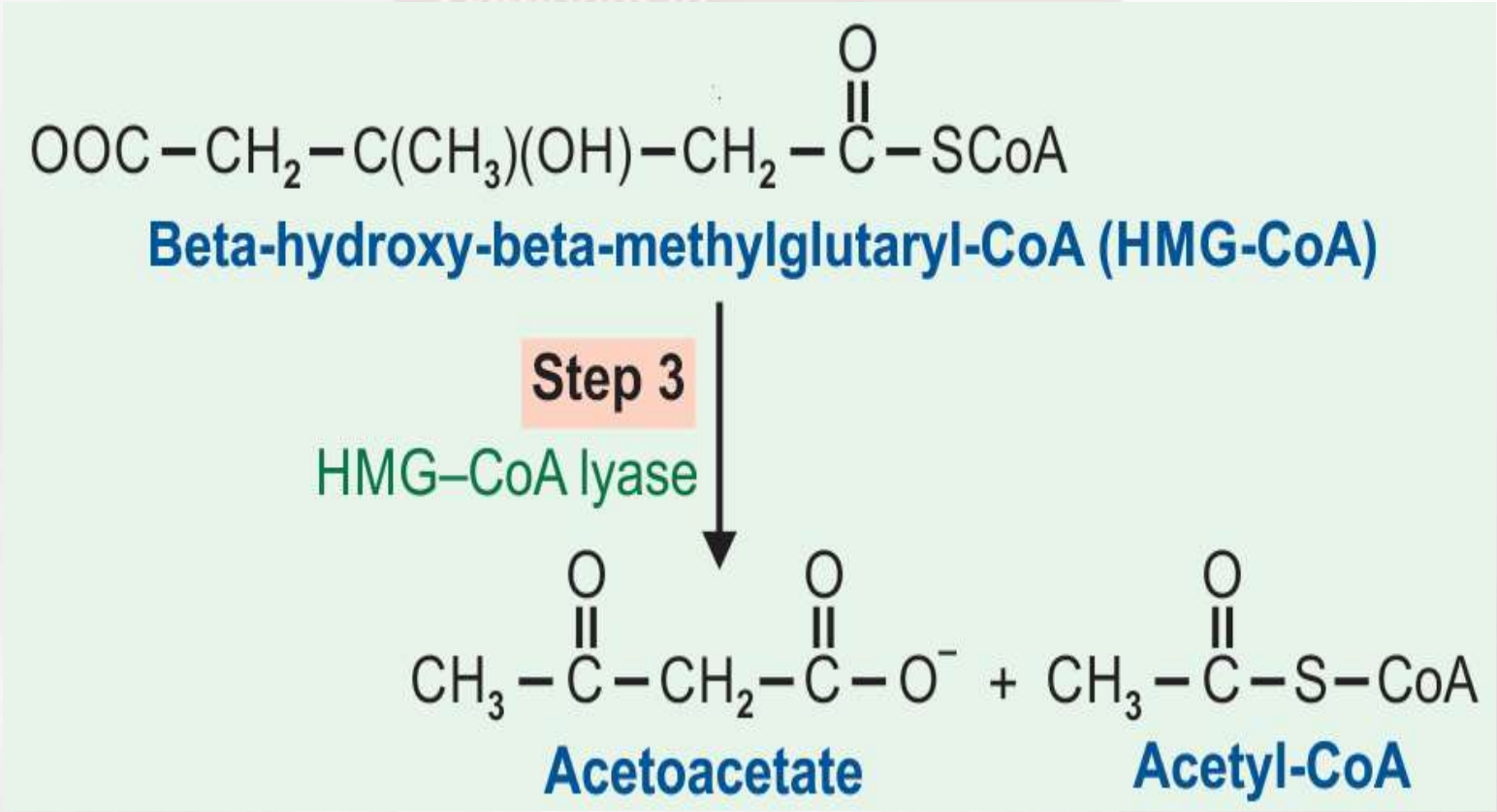
Step 2: Production of HMG-CoA



One more acetyl-CoA is added to acetoacetyl-CoA to form HMG-CoA (beta-hydroxy beta-methyl glutaryl-CoA). The enzyme is HMG-CoA synthase. **Mitochondrial HMG CoA is used for ketogenesis**, while cytosolic fraction is used for cholesterol synthesis

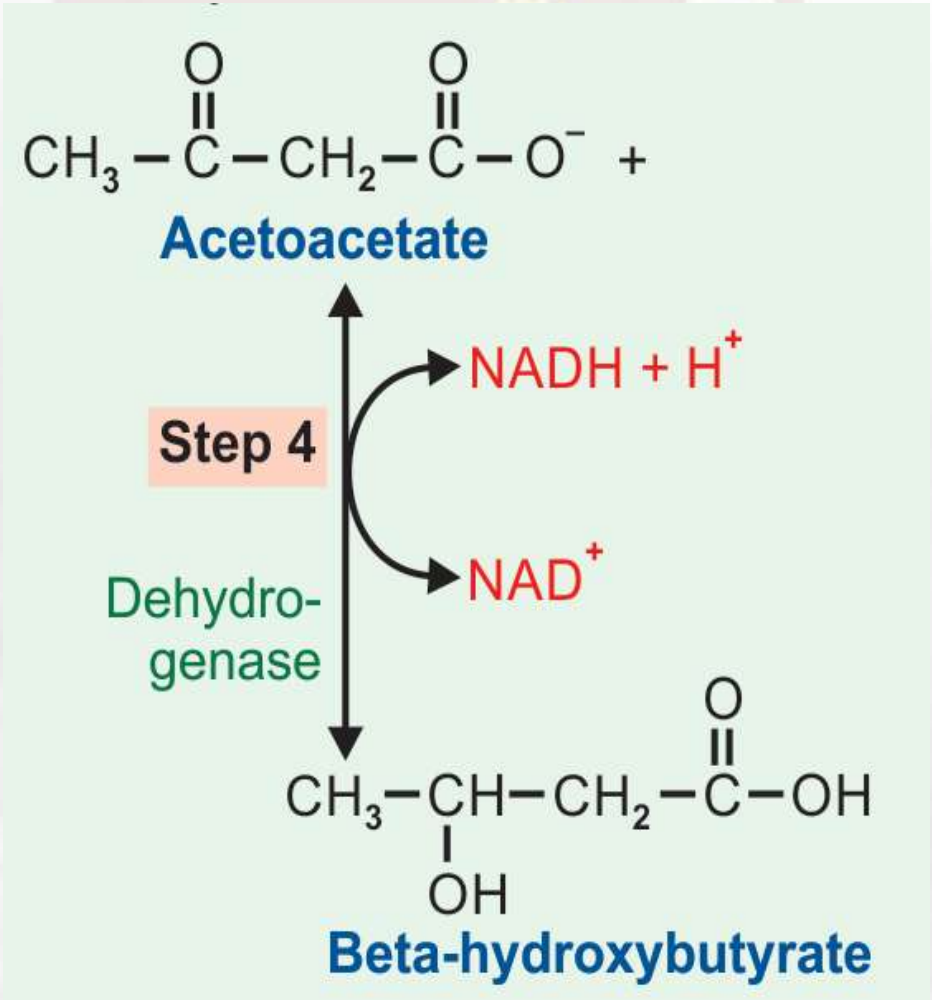
Step 3: Lysis

- Then HMG-CoA is lysed to form acetoacetate.
- HMG CoA lyase is present **only in liver**.



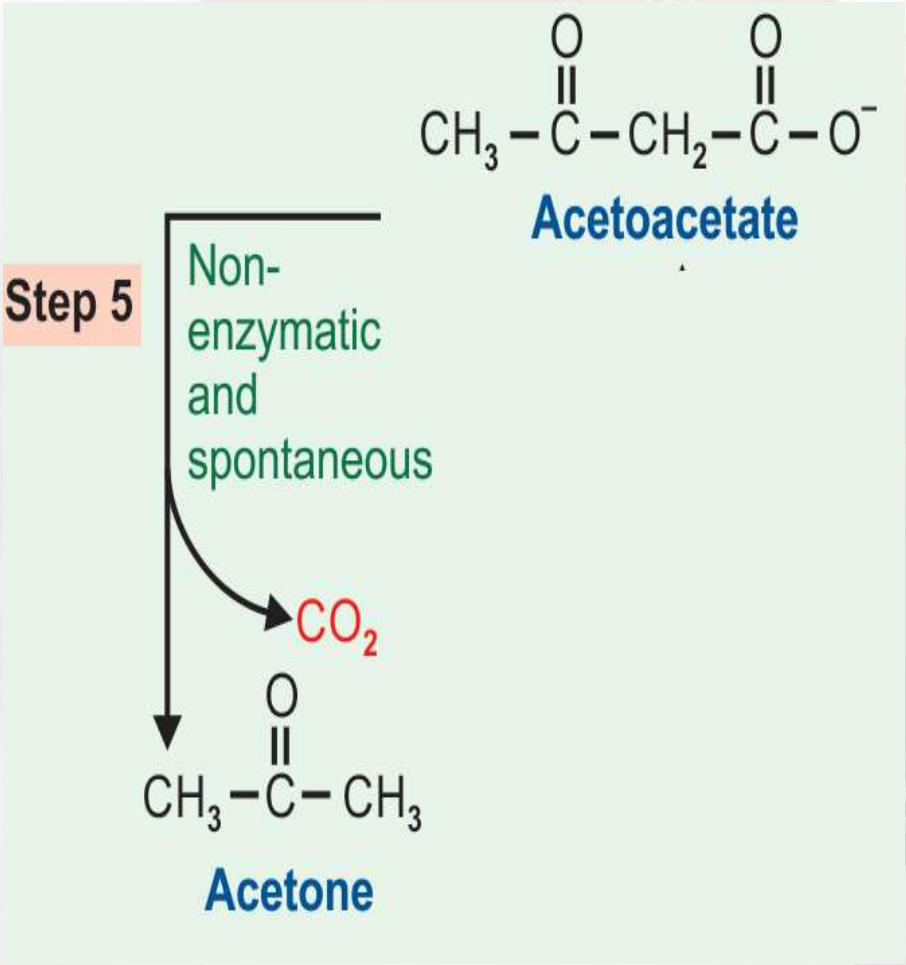
Step 4: Reduction

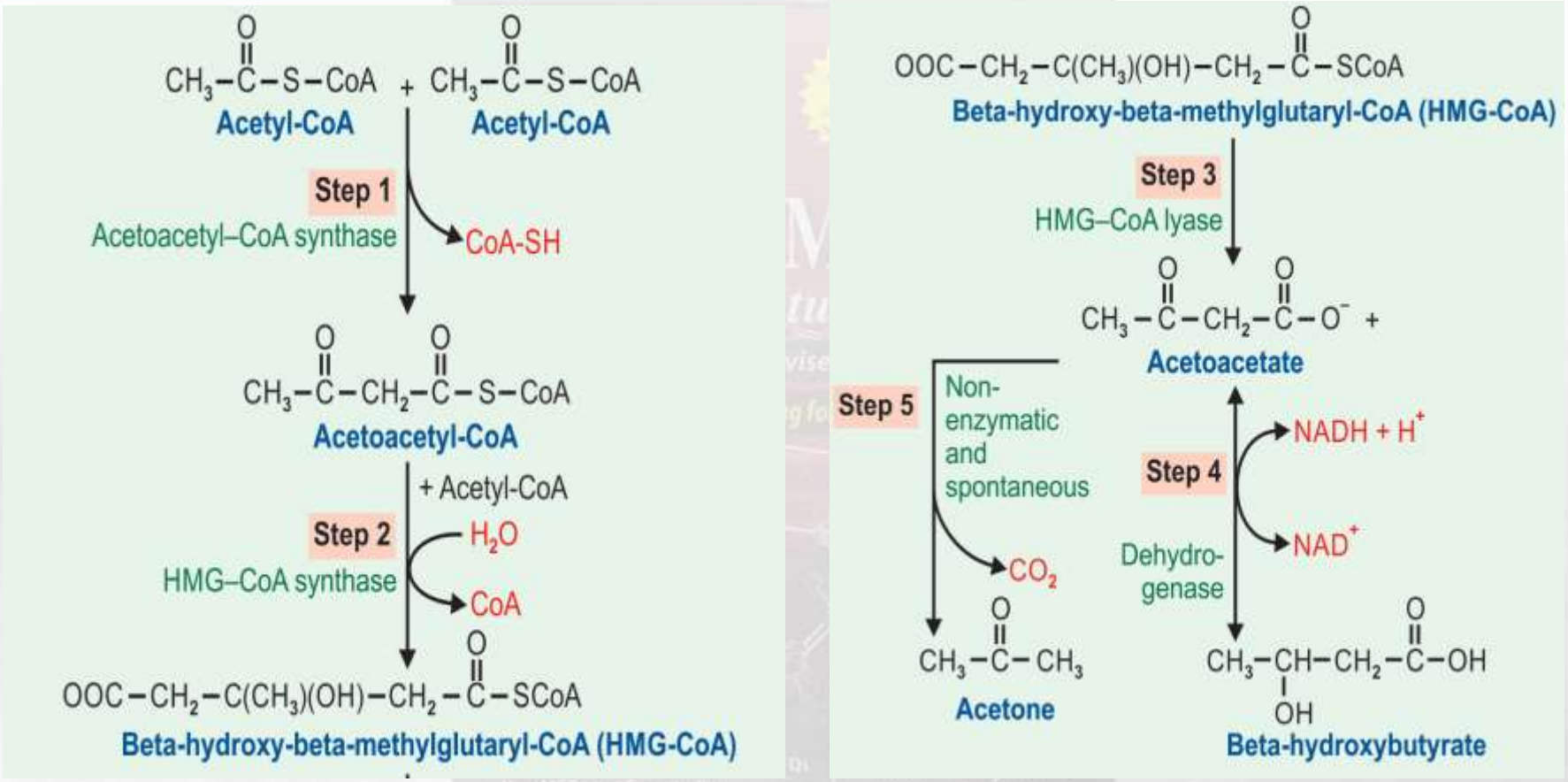
- Beta-hydroxy butyrate is formed by reduction of acetoacetate.



Step 5: Spontaneous Decarboxylation

- Acetone is formed.





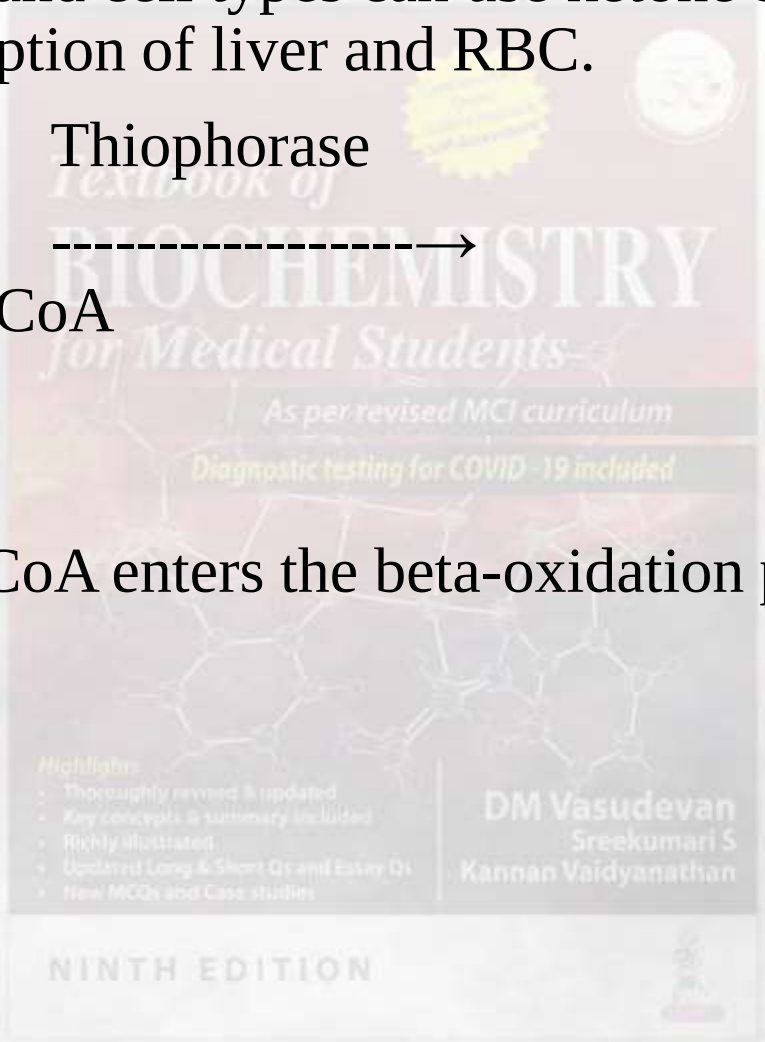
Ketone body formation (ketogenesis)

Ketolysis

- The ketone bodies are formed in the liver; but they are utilized by **extrahepatic tissues**.
- The heart muscle and renal cortex prefer the ketone bodies to glucose as fuel.
- Tissues like skeletal muscle and brain can also utilize the ketone bodies as alternate sources of energy, if glucose is not available.
- Acetoacetate is activated to acetoacetyl-CoA by **thiophorase** enzyme.

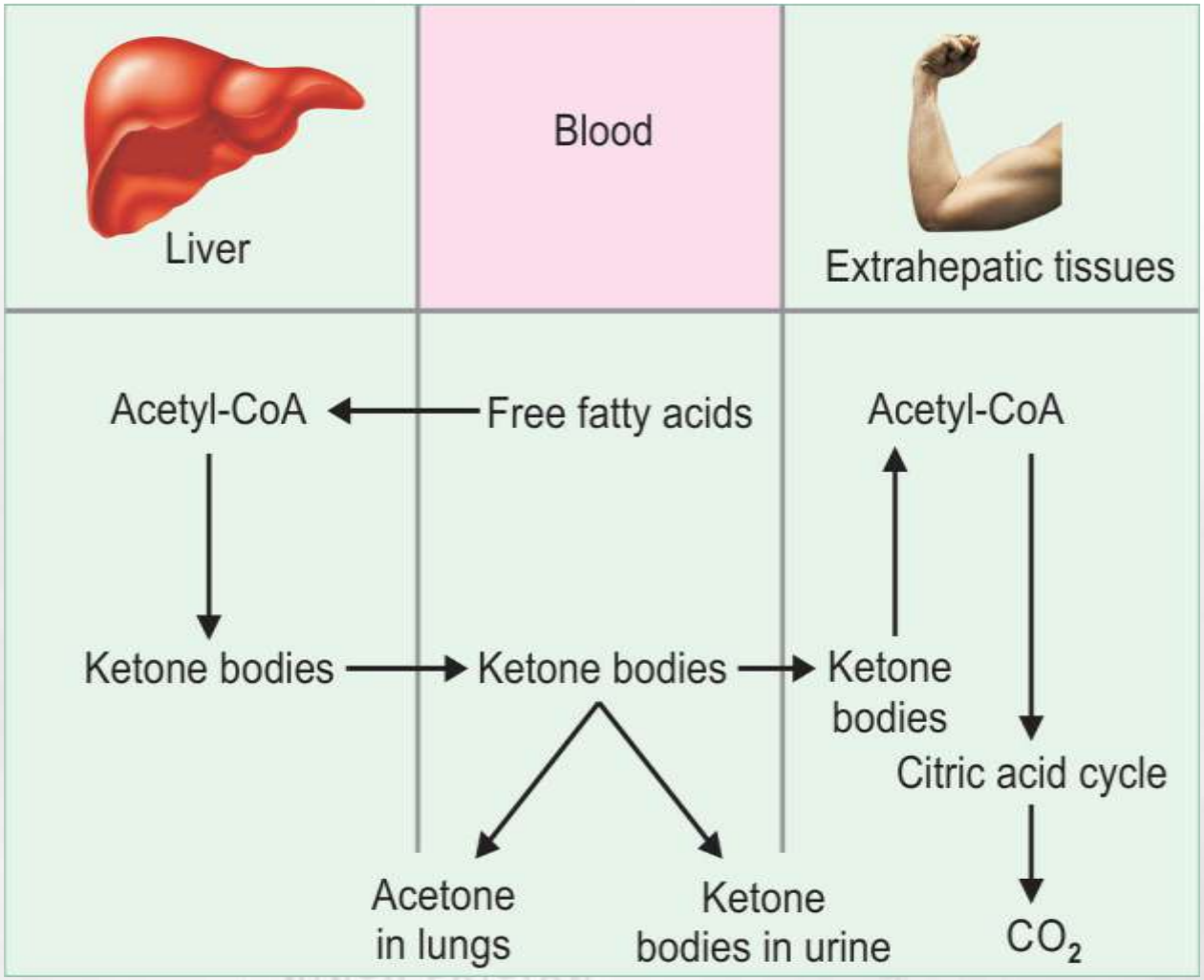
- Almost all tissues and cell types can use ketone bodies as fuel, with the exception of liver and RBC.

- Acetoacetate ---Thiophorase---→ Acetoacetyl-CoA
- + Succinyl-CoA + Succinate
- Then acetoacetyl-CoA enters the beta-oxidation pathway to produce energy.



Ketosis

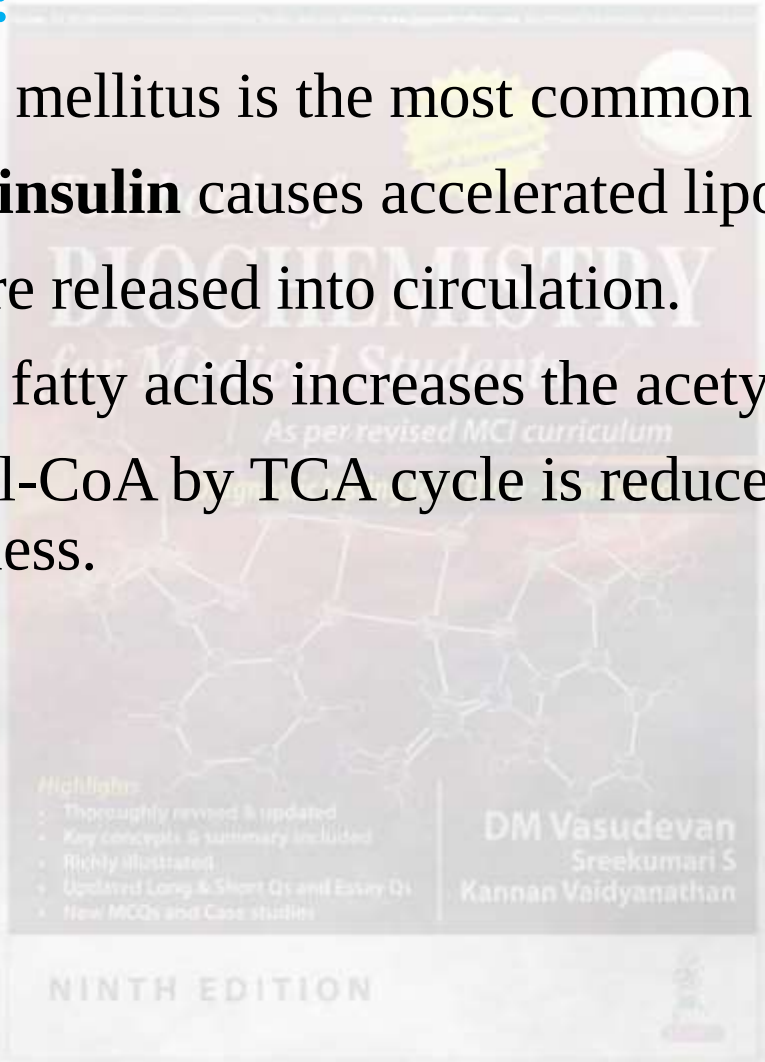
- Normally the rate of synthesis of ketone bodies by the liver is minimal.
- So they can be easily metabolized by the extrahepatic tissues.
- Hence, the blood level of ketone bodies is less than 1 mg/dL.
- Ketone bodies are not detected in urine.
- But when the rate of synthesis exceeds the ability of extrahepatic tissues to utilize them, there will be accumulation of ketone bodies in blood.
- This leads to **ketonemia**, excretion in urine (**ketonuria**) and smell of **acetone** in breath.
- All these three together constitute the condition known as ketosis.



Formation, utilization and excretion of ketone bodies

Causes for Ketosis

- **Diabetes mellitus:**
- Untreated diabetes mellitus is the most common cause for ketosis.
- The **deficiency of insulin** causes accelerated lipolysis.
- More fatty acids are released into circulation.
- Oxidation of these fatty acids increases the acetyl-CoA pool.
- Oxidation of acetyl-CoA by TCA cycle is reduced, since availability of oxaloacetate is less.



- **Starvation:**
- In starvation, the dietary supply of glucose is decreased.
- Available oxaloacetate is channelled to gluconeogenesis.
- The increased rate of lipolysis is to provide alternate source of fuel.
- The excess acetyl-CoA is converted to ketone bodies.
- The high **glucagon** favors ketogenesis.
- The brain derives 75% of energy from ketone bodies under conditions of fasting.
- **Hyperemesis** (vomiting) in early pregnancy may also lead to starvation-like condition and may lead to ketosis.

Explanation for Ketogenesis

i. During starvation and diabetes mellitus, the blood level of **glucagon** is increased.

Glucagon inhibits glycolysis, activates gluconeogenesis, activates lipolysis, and stimulates ketogenesis.

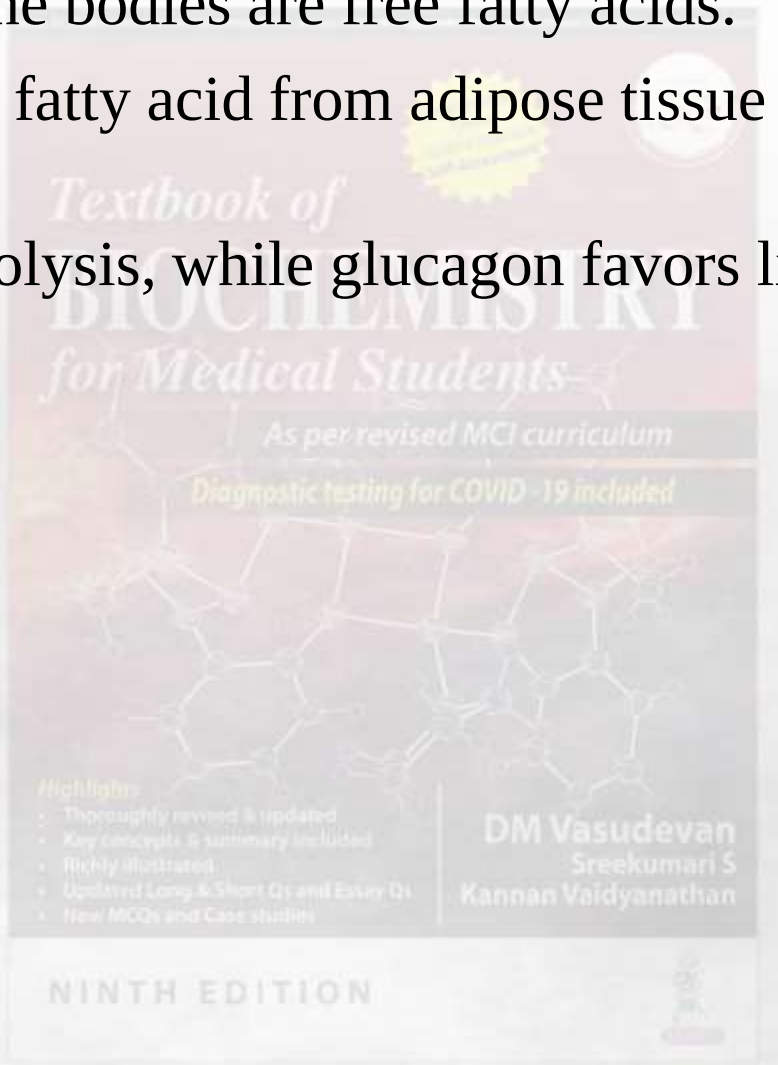
High glucagon-insulin ratio is potentially ketogenic.

ii. **Insulin** has the opposite effect; it favors glycolysis, inhibits gluconeogenesis, depresses lipolysis, and decreases ketogenesis.

- **The ketone body formation is regulated at the following 3 levels:**

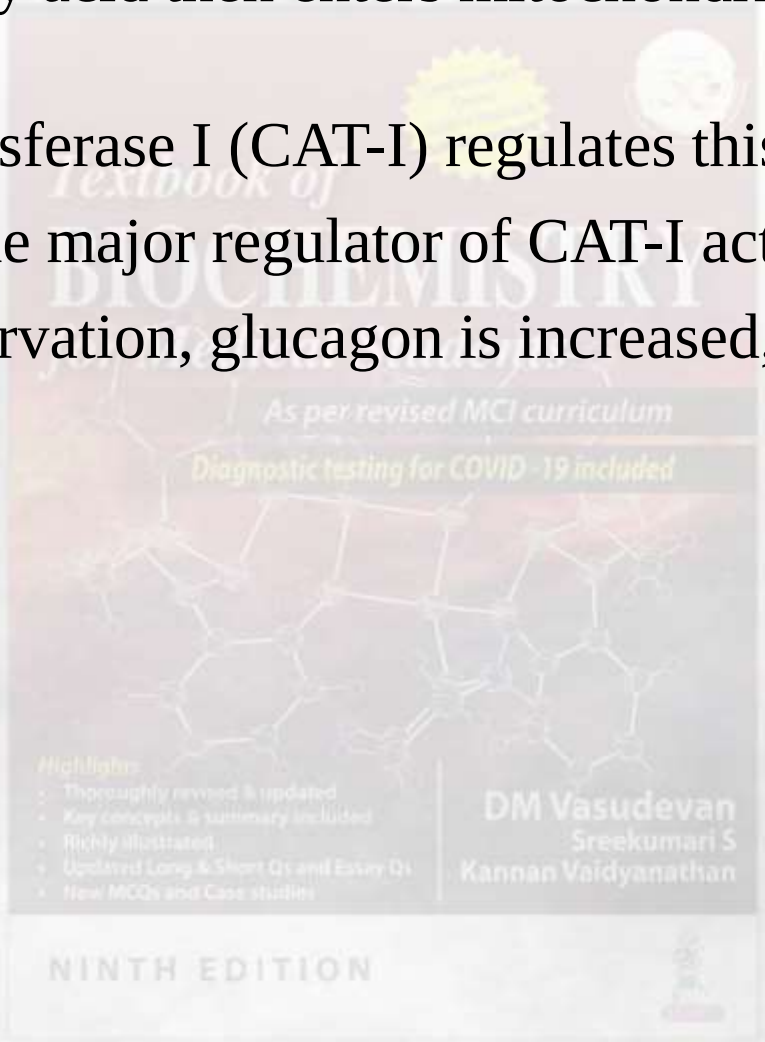
Level 1: Lipolysis

- Precursors of ketone bodies are free fatty acids.
- So mobilization of fatty acid from adipose tissue will influence ketogenesis.
- Insulin inhibits lipolysis, while glucagon favors lipolysis.



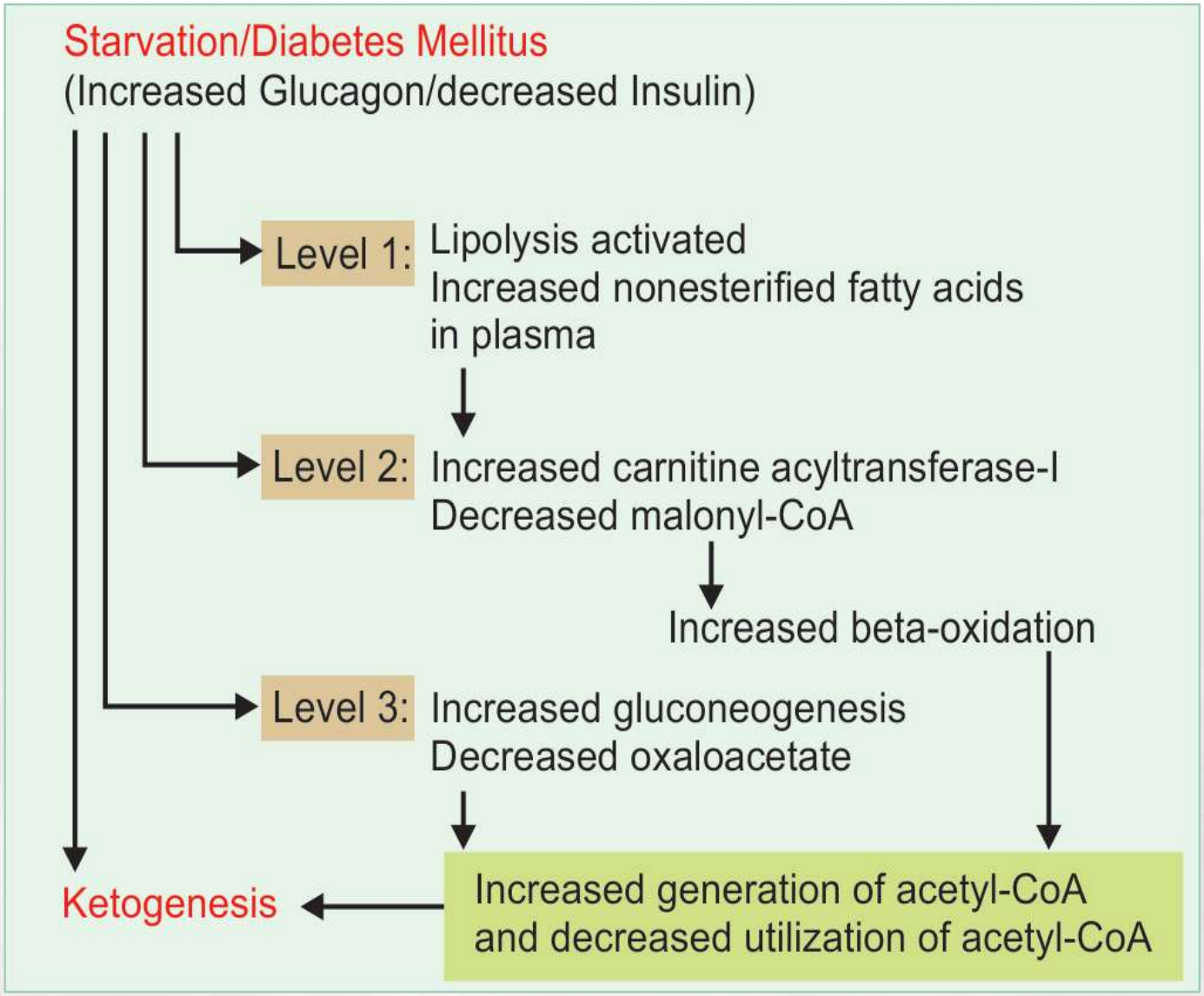
Level 2: Entry of Fatty Acid to Mitochondria

- The mobilized fatty acid then enters mitochondria for beta-oxidation.
- Carnitine acyl transferase I (CAT-I) regulates this entry.
- Malonyl-CoA is the major regulator of CAT-I activity.
- In diabetes and starvation, glucagon is increased, which decreases malonyl-CoA.



Level 3: Oxidation of Acetyl-CoA

- When the above two steps are increased, more acetyl-CoA is produced.
- Normally, acetyl-CoA is completely oxidized in the citric acid cycle.
- In both diabetes mellitus and starvation, the oxaloacetate is channelled to gluconeogenesis; so the availability of oxaloacetate is decreased.
- Hence acetyl-CoA cannot be fully oxidised in the TCA cycle.
- **When oxaloacetate is diverted for gluconeogenesis**; citric acid cycle cannot function optimally.
- Thus, on the one hand, acetyl-CoA is generated in excess, on the other hand, its utilization is reduced.
- This excess acetyl-CoA is channelled into ketogenic pathway.


Starvation/Diabetes Mellitus
(Increased Glucagon/decreased Insulin)
Level 1:
Lipolysis activated
Increased nonesterified fatty acids
in plasma
Level 2:
Increased carnitine acyltransferase-I
Decreased malonyl-CoA
Increased beta-oxidation
Level 3:
Increased gluconeogenesis
Decreased oxaloacetate
Increased generation of acetyl-CoA
and decreased utilization of acetyl-CoA
Ketogenesis

Salient Features of Ketosis

1. **Metabolic acidosis.** Acetoacetate and beta-hydroxy butyrate are acids. When they accumulate, metabolic acidosis results.
2. **Reduced buffers.** The plasma bicarbonate is used up for buffering of these acids.
3. **Kussmaul's respiration.** Patients will have typical acidotic breathing due to compensatory hyperventilation.
4. **Smell of acetone** in patient's breath.
5. **Osmotic diuresis** induced by ketonuria may lead to dehydration.
6. **Sodium loss.** The ketone bodies are excreted in urine as their sodium salt, leading to loss of cations from the body.
7. **Dehydration.** The sodium loss further aggravates the dehydration.
8. **Coma.** Dehydration and acidosis are contributing for the lethal effect of ketosis.

Diagnosis of Ketosis

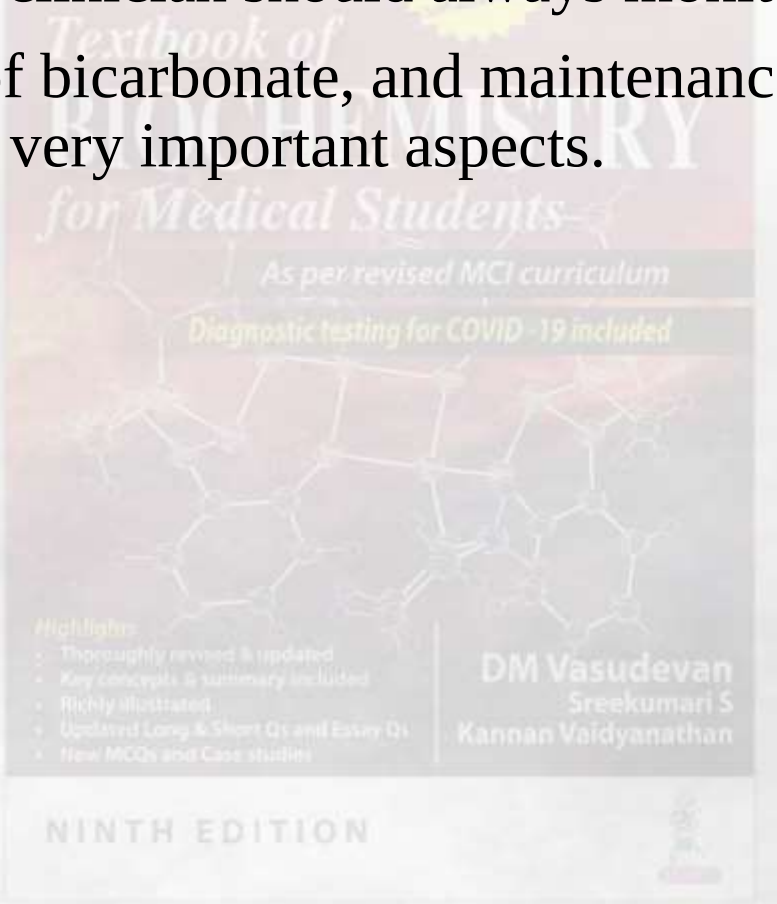
- The presence of ketosis can be established by the detection of ketone bodies in urine by **Rothera's test.**
- Supportive evidence may be derived from estimation of serum electrolytes, acid-base parameters, glucose and urea estimation.

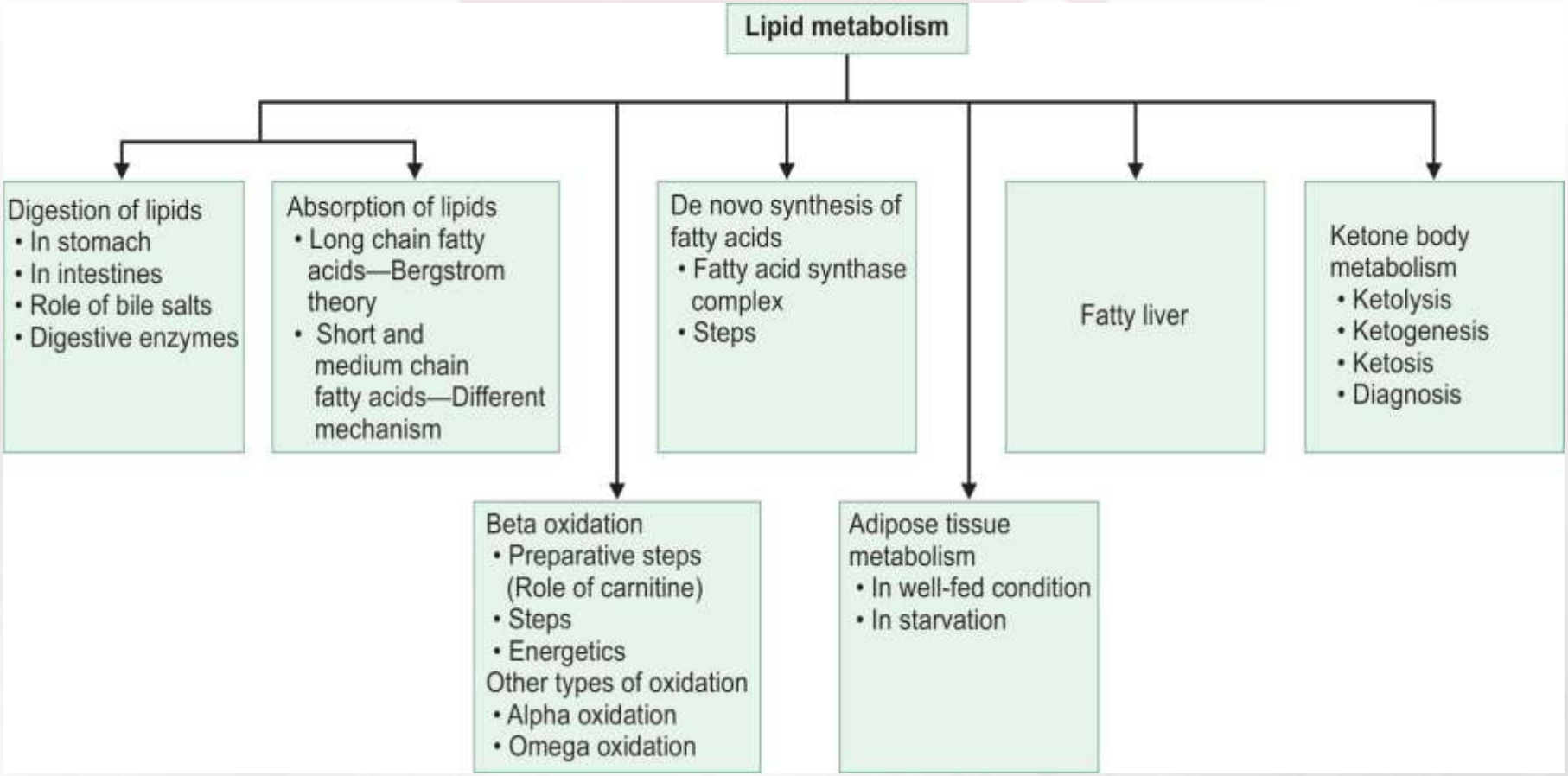
- **Differential Diagnosis**
- The urine of a patient with **diabetic** ketoacidosis will give positive Benedict's test as well as Rothera's test.
- But in **starvation** ketosis, Benedict's test is negative, but Rothera's test will be positive.

Management of Ketoacidosis

i. Treatment is to give insulin and glucose. When glucose and insulin are given intravenously, potassium is trapped within the cells. Hence, the clinician should always monitor the electrolytes.

ii. Administration of bicarbonate, and maintenance of electrolyte and fluid balance are very important aspects.




Lipid metabolism
Digestion of lipids
• In stomach
• In intestines
• Role of bile salts
• Digestive enzymes
Absorption of lipids
• Long chain fatty acids—Bergstrom theory
• Short and medium chain fatty acids—Different mechanism
De novo synthesis of fatty acids
• Fatty acid synthase complex
• Steps
Fatty liver
Ketone body metabolism
• Ketolysis
• Ketogenesis
• Ketosis
• Diagnosis
Beta oxidation
• Preparative steps (Role of carnitine)
• Steps
• Energetics
Other types of oxidation
• Alpha oxidation
• Omega oxidation
Adipose tissue metabolism
• In well-fed condition
• In starvation