Lipids

Definition of lipids:
Lipids are compounds that occur frequently in nature. They are found in places as diverse as egg yolks and the human nervous system and are an important component of plant, animal, and microbial membranes. Lipids comprise very heterogeneous group of compounds which are insoluble in water but soluble in non-polar organic solvents such as benzene, chloroform, and ether. The group includes fats, oils, waxes and related compounds.

General Functions of Lipids
i. They are efficient energy sources.
ii. Serve as thermal insulators.
iii. They are structural components of the cell membrane.
iv. Serve as precursors for hormones (steroid hormones).
v. They also dissolve the vitamins, which are fat-soluble and assist their digestion.

Classified according to their chemical nature, lipids fall into two main groups:

1- One group, which consists of open-chain compounds with polar head groups and long nonpolar tails, includes fatty acids, triacylglycerols, sphingolipids, phosphoacylglycerols, and glycolipids.

2- The second major group consists of fused-ring compounds, the steroids; an important representative of this group is cholesterol.

Chemical natures of the lipid types:

A. Fatty Acids
Fatty acids exist free (they are unesterified) in nature, and are also found as fatty acyl esters (esterified) in more complex molecules.

Structure of fatty acids

Fatty acids are building block of most lipids, made of long chain organic acids having one polar carboxyl group (head) and a non-polar hydrocarbon chain (tail) this make fatty acids are amphipathic compounds. However, for long-chain fatty acids (LCFAs), the hydrophobic portion is predominant. These molecules are highly water-insoluble, and must be transported in the circulation in association with protein. More than 90% in the plasma are in esterified form and free plasma transported in association with albumin.
Most naturally occurring fatty acids have got even number of carbons. They may be saturated or unsaturated, with one or more double bonds.

There are two types of numbering:
1. Numbering starts from carboxyl carbon. The last carbon is the "n" carbon.
2. The second carbon is the "α" and the third the "β" Carbon. The last carbon atom is omega.

The notation used for fatty acids indicates the number of carbon atoms and the number of double bonds. In this system, 18:0 denotes an 18-carbon saturated fatty acid with no double bonds, and 18:1 denotes an 18-carbon fatty acid with one double bond.

**Also fatty acids can be essential or nonessential**

**Essential fatty acids.**
Two PUFA (Polyunsaturated fatty acids): They have two or more double bonds. They are called as essential fatty acids because they are required in the body and cannot be synthesized. So they need to be include in the diet.
• Linoleic acid: precursor of omega-6 arachidonic acid, the substrate for prostaglandin synthesis.
• Linolenic acid: the precursor of omega-3 important for growth and development.

• **Arachidonic acid is semi essential fatty acid because it can be synthesized from the above two essential fatty acids.**

Functions of fatty acids:
1- Free fatty acids can be oxidized by many tissues to provide energy.
2- Fatty acids are also structural components of membrane lipids, such as phospholipids and glycolipids.
3- Fatty acids are attached to certain intracellular proteins to enhance the ability of those proteins to associate with membranes.
4- Fatty acids are precursors of the hormone-like prostaglandins.
5- Esterified fatty acids, in the form of triacylglycerols stored in adipose cells, serve as the major energy reserve of the body.

B. Triacylglycerols:
**Glycerol** is a simple compound that contains three hydroxyl groups. When all three of the alcohol groups form ester linkages with fatty acids, the resulting compound is a **triacylglycerol**; an older name for this type of compound is **triglyceride**.

Note that the three ester groups are the polar part of the molecule, whereas the tails of the fatty acids are nonpolar. It is usual for three different fatty acids to be esterified to the alcohol groups of the same glycerol molecule. Triacylglycerols accumulate in adipose tissue (primarily fat cells) and provide a means of storing fatty acids, particularly in animals. They serve as concentrated

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stores of metabolic energy. Complete oxidation of fats yields about 9 kcal/g, in contrast with 4 kcal/g for carbohydrates and proteins. When an organism uses fatty acids, the ester linkages of triacylglycerols are hydrolyzed by enzymes called lipases.

C. Phosphoacylglycerols (Phospholipids)
Phospholipids are polar, ionic compounds composed of an alcohol that is attached by a phosphodiester bridge to either diacylglycerol or sphingosine. Phospholipids are amphipathic in nature. They are the predominant lipids of cell membranes.

Non-membrane bound phospholipids serve additional functions in the body, for example:
1- As components of lung surfactants.
2- Essential components of bile.
D. Glycolipids
If a carbohydrate is bound to an alcohol group of a lipid by a glycosidic linkage, the resulting compound is a **glycolipid**. In most cases, the sugar is glucose or galactose. Glycolipids are often found as markers on cell membranes and play a large role in tissue and organ specificity.

E. Steroids
Many compounds of widely differing functions are classified as **steroids** because they have the same general structure. There are many important steroids, including sex hormones. The steroid that is of most interest in our discussion of membranes is **cholesterol**. Cholesterol is widespread in biological membranes, especially in animals.

Cholesterol has a number of important biological functions, including its role as a precursor of other steroids and of vitamin D3. However, cholesterol is best known for its harmful effects on health when it is present in excess in the blood. It plays a role in the development of **atherosclerosis**, a condition in which lipid deposits block the blood vessels and lead to heart disease.

**Cholesterol is important in many ways:**
- For the synthesis of bile salts that are important in lipid digestion and absorption.
- For the synthesis of steroid hormones that are biologically important like the sex hormones estrogen and progesterone.
- For the synthesis of vitamin D3
- As a structural material in biological membranes.
- As a component of lipoproteins as transport forms of lipid based energy.
Digestion and absorption of dietary lipids:

More than 90% of dietary lipids is normally triacylglycerol (TAG, formerly called triglyceride). The remainder of the dietary lipids consists primarily of cholesterol, cholesteryl esters, phospholipids, and unesterified (“free”) fatty acids. The digestion of dietary lipids is summarized in Figure 15.2.

A. Processing of dietary lipid in the stomach
The digestion of fat begins in the stomach by **two acid stable lipases**, **lingual lipase**, which originates from glands at the back of the tongue, and **gastric lipase** secreted by gastric mucosa. TAG molecules, particularly those containing fatty acids of short- or medium-chain length (fewer than 12 carbons, such as are found in milk fat), are the primary target of this enzyme. Lingual and gastric lipases can hydrolyze fats without emulsification with bile salts.

These “acid lipases” play a particularly important role in lipid digestion in neonates, for whom milk fat is the primary source of calories. They also become important digestive enzymes in individuals with pancreatic insufficiency.

**B. Emulsification of dietary lipid in the small intestine**

The critical process of emulsification of dietary lipids occurs in the duodenum. Emulsification increases surface area of the hydrophobic lipid droplets so that the digestive enzymes, which work at the interface of the droplet and the surrounding aqueous solution, can act effectively.

*Emulsification is accomplished by two complementary mechanisms:*

1. Use of the detergent properties of the bile salts.
2. Mechanical mixing due to peristalsis.

Bile salts (emulsifying agents) interact with the dietary lipid particles and the aqueous duodenal contents, thereby stabilizing the particles as they become smaller, and preventing them from coalescing. Dietary lipids are processed by several **pancreatic lipases**, whose actions facilitate uptake by intestinal epithelial cells.

**C. Degradation of dietary lipids by pancreatic enzymes**

1. **Triacylglycerols** are hydrolyzed by pancreatic lipase at their 1 and 3 positions. The products are monoglyceride and 2 fatty acids. Monoglyceride is further hydrolyzed by another lipase. Thus 3 fatty acids and one glycerol molecule is produced from the digestion of dietary triglyceride.

2. **Phospholipids** are hydrolyzed by **phospholipases**, which remove a fatty acid from carbon 2, leaving a **lysophospholipid**, which may be further processed or absorbed. They are four in number, A (A1, A2) B, C, and D, each enzyme has a different site of action of phospholipids PL, as a result each enzyme has a different products.

3. **Cholesteryl esters** are synthesized by combining free cholesterol with a fatty acid. **Cholesteryl esterase** hydrolyses cholesterol ester to free cholesterol and one fatty acid. Cholesteryl esterase activity is greatly increased in the presence of bile salts.
D. Absorption of lipids by intestinal mucosal cells (enterocytes):

Free fatty acids, free cholesterol, and 2-monoacylglycerol are the primary products of lipid digestion in the jejunum. These, plus bile salts and fat-soluble vitamins (A, D, E, and K), form mixed micelles—disk shaped clusters of amphipathic lipids that coalesce with their hydrophobic groups on the inside and their hydrophilic groups on the outside. Mixed micelles are, therefore, soluble in the aqueous environment of the intestinal lumen (Figure 15.5).

These particles approach the primary site of lipid absorption, the brush border membrane of the enterocytes (mucosal cell). This membrane is separated from the liquid contents of the intestinal lumen by an unstirred water layer that mixes poorly with the bulk fluid. The hydrophilic surface of the micelles facilitates the transport of the hydrophobic lipids through the unstirred water layer to the brush border membrane where they are absorbed. After uptake, the micelles are dismantled and their components are modified for shipment to other organs.

Bile salts are absorbed in the ileum. [Note: Relative to other dietary lipids, cholesterol is only poorly absorbed by the enterocytes. Drug therapy (for example, with ezetimibe) can further
reduce cholesterol absorption in the small intestine.] short- and medium chain length fatty acids do not require the assistance of mixed micelles for absorption by the intestinal mucosa. Impaired secretion of lipases from the pancreas and bile salts from liver results in failure in fat absorption and causes steatorrhea (excessive passage fatty stool).

E. Resynthesis of TAG and cholesteryl esters:

The mixture of lipids absorbed by the enterocytes migrates to the endoplasmic reticulum where biosynthesis of complex lipids takes place.

Note: Virtually all long-chain fatty acids entering the enterocytes are used in this fashion to form TAGs, phospholipids, and cholesteryl esters. Short- and medium-chain length fatty acids are not converted to their CoA derivatives, and are not reesterified to 2-monoacylglycerol. Instead, they are released into the portal circulation, where they are carried by serum albumin to the liver.

F. Secretion of lipids from enterocytes

The newly resynthesized TAGs and cholesteryl esters are very hydrophobic, and aggregate in an aqueous environment. It is, therefore, necessary that they be packaged as particles of lipid droplets surrounded by a thin layer composed of phospholipids, unesterified cholesterol, and a molecule of the characteristic protein, apolipoprotein B-48. This layer stabilizes the particle and increases its solubility, thereby preventing multiple particles from coalescing.

The particles are released by exocytosis from enterocytes into the lymphatic vessels originating in the villi of the small intestine. The presence of these particles in the lymph after a lipid-rich meal gives it a milky appearance. The particles are named chylomicrons. Chylomicrons follow the lymphatic system to the thoracic duct, and are then conveyed to the left subclavian vein, where they enter the blood. The steps in the production of chylomicrons are summarized in Figure 15.6.
**Use of dietary lipids by the tissues**

Triacylglycerol contained in chylomicrons is **broken down** primarily in the **capillaries of skeletal muscle and adipose tissues, but also those of the heart, lung, kidney, and liver**. Triacylglycerol in chylomicrons is degraded to free fatty acids and glycerol by **lipoprotein lipase**. This enzyme is synthesized primarily by adipocytes and muscle cells.

1. **Fate of free fatty acids**: The free fatty acids derived from the hydrolysis of TAG may either directly enter adjacent muscle cells or adipocytes, or they may be transported in the blood in association with serum albumin until they are taken up by cells. Most cells can oxidize fatty acids to produce energy. Adipocytes can also reesterify free fatty acids to produce TAG molecules, which are stored until the fatty acids are needed by the body.

2. **Fate of glycerol**: Glycerol that is released from TAG is used almost exclusively by the liver to produce **glycerol 3-phosphate**, which can enter either glycolysis or gluconeogenesis by oxidation to dihydroxyacetone phosphate.

3. **Fate of the remaining chylomicron components**: After most of the TAG has been removed, the chylomicron remnants (which contain cholesteryl esters, phospholipids, apolipoproteins, fat-soluble vitamins, and some TAG) bind to receptors on the liver, and are then endocytosed. The remnants are then hydrolyzed to their component parts. Cholesterol and the nitrogenous bases of phospholipids can be recycled by the body.

**Lipoproteins:**
Plasma lipids contain triacylglycerols, cholesterol and other polar lipids. Lipids combined with apolipoproteins to form Lipoproteins. Based on their density they are classified into four subgroups:

A. CHYLOMICRONS:
Chylomicrons export dietary triacylglycerols and cholesterol from the intestine to other organs. The triacylglycerols and cholesteryl esters form the **hydrophobic core** of the chylomicrons, which are coated with **surface phospholipids**, free cholesterol, and **apolipoprotein B-48**. Most **plasma cholesterol** is esterified to fatty acids and is thus highly water insoluble. These **cholesteryl esters** circulate in complexes with the lipoproteins.

B. VLDL (very low density lipoproteins):
These are synthesized in the liver and used to transport triacylglycerols from the liver to extrahepatic tissues.

VLDLs have **high triacylglycerol** content and are used to distribute fatty acids throughout the body. The action of lipoprotein lipase lining the blood vessels degrades the triacylglycerols, releasing fatty acids locally for cellular uptake. In addition, triacylglycerols can be transferred to HDL particles transforming the VLDL into LDL.

C. LDL (Low density lipoproteins):
These are produced from the final stage in the catabolism of VLDL. They transport cholesterol synthesized in the liver to peripheral tissues. LDL is metabolized via the LDL receptor. Approximately 30% of the LDL is degraded in extra hepatic tissues, rest is degraded in liver.

D. HDL (High density lipoproteins):
HDL particles have several functions, but among the most important is transport of excess cholesterol scavenged from the cell membranes back to the liver, a process called **reverse cholesterol transport**.  
1. HDL particles extract cholesterol from peripheral membranes and, after esterification of cholesterol to a fatty acid, the cholesteryl esters are delivered to the liver (to make bile salts) or steroidogenic tissues (precursor of steroids).
2. In this way, **HDL particles** participate in disposal.
of cholesterol, and thus, a high HDL concentration is considered a protective factor against the development of cardiovascular disease.
Figure 18.17
Metabolism of VLDL and LDL. TAG = triacylglycerol; VLDL = very-low-density lipoprotein; LDL = low-density lipoprotein; IDL = intermediate-density lipoprotein; C = cholesterol; CE = cholesteryl esters. Apo B-100, apo C-II, and apo E are apolipoproteins found as specific components of plasma lipoproteins. Lipoproteins are not drawn to scale (see Figure 18.13 for details of the size and density of lipoproteins).
Fatty acid and triacylglycerol TAG metabolism

**Synthesis of fatty acids:**
A large proportion of the fatty acids used by the body is supplied by the diet. Carbohydrates and protein obtained from the diet in excess of the body's needs for these compounds can be converted to fatty acids, which are stored as triacylglycerols. In adult humans, fatty acids synthesis occurs primarily in the liver and lactating mammary glands and, to a lesser extent, in adipose tissue.

This cytosolic process incorporates carbons from acetyl coenzyme A (CoA) into the growing fatty acid chain, using adenosine triphosphate (ATP) and reduced NADPH.

**A. Production of cytosolic acetyl CoA**
The first step in fatty acid synthesis is the transfer of acetate units from mitochondrial acetyl CoA to the cytosol. Mitochondrial acetyl CoA produced by:
- Oxidation of pyruvate.
- Catabolism of fatty acids.
- Catabolism of certain amino acids.

The CoA portion of acetyl CoA, however, cannot cross the inner mitochondrial membrane; only the acetyl portion enters the cytosol. It does so as part of citrate produced by the condensation of oxaloacetate (OAA) and acetyl CoA. Because a large amount of ATP is needed for fatty acid synthesis, the increase in both ATP and citrate enhances this pathway.
B. Oxidation of acetyl CoA to form malonyl CoA

Malonyl-CoA:

- Starting point in fatty acid synthesis.
- This reaction catalyzed by acetyl CoA carboxylase, and requires ATP and CO2.
- The coenzyme is the vitamin, biotin.

C. Fatty acid synthase: a multifunctional enzyme in eukaryotes.

The remaining series of reactions of fatty acid synthesis in eukaryotes is catalyzed by the multifunctional, dimeric enzyme, fatty acid synthase (FAS). The biosynthesis of fatty acids involves the successive addition of two-carbon units to the growing chain.

# When the fatty acid reaches a length of 16 carbons, the synthetic process is terminated. This process releasing a fully saturated molecule of palmitate (16 C).

#Further elongation of palmitate by addition of two carbons requires a system of separate enzymes in the smooth endoplasmic reticulum. Enzymes (desaturases) also present in smooth endoplasmic reticulum are responsible for desaturating long-chain fatty acids.

D. Storage of fatty acids as components of triacylglycerols

- Synthesis of glycerol phosphate.
- Conversion of fatty acid to its activated form.
- Synthesis of TAG from fatty acyl CoA and glycerol phosphate.
- In adipose tissue TAG stored as fat droplets in the cytosol of these cells. Little TAG is stored in liver. Instead, most is exported.

Regulation of Fatty Acid Synthesis:

- High carbohydrate diet increases synthesis.
- Palmitoyl CoA inhibits synthesis
- Fasting decreases acetyl carboxylase, decreases fatty acid synthesis.
- Insulin stimulates fatty acid synthesis.
**Mobilization of stored fats and oxidation of fatty acids**

**A. Release of fatty acids from TAG**

The mobilization of stored fat requires the hydrolytic release of fatty acids and glycerol from TAG form. **Mobilization of fat stores allows fats to be burned to produce energy via fatty acid oxidation.** The initial step to release fatty acids is triacylglycerol hydrolysis catalyzed by hormone-sensitive (HS) lipase. As its name implies, the enzyme is regulated via hormones. Glucagon and epinephrine stimulate lipase activity in order to provide fatty acids and glycerol for use as fuels, while insulin inhibits lipase activity as it stimulates storage of fatty acids.

The glycerol backbone derived from lipase-mediated triacylglycerol breakdown is released into the bloodstream and taken up by the liver. Glycerol is phosphorylated on its 3 position and Glycerol 3-phosphate can then enter glycolysis or gluconeogenesis.

**B. β-Oxidation of fatty acids:**

The major pathway for catabolism of fatty acids is a mitochondrial pathway called β-oxidation, in which two-carbon fragments are successively removed from the carboxyl end of the fatty acyl CoA, producing acetyl CoA, NADH, and FADH2.

1. **Transport of long-chain fatty acids (LCFA) into the mitochondria:**

After a LCFA enters a cell, it is converted in the cytosol to its CoA derivative by long-chain fatty acyl CoA synthetase an enzyme of the outer mitochondrial membrane.

**ACTIVATION OF FATTY ACIDS:**
Because β-oxidation occurs in the mitochondrial matrix, the fatty acid must be transported across the inner mitochondrial membrane that is impermeable to CoA. Therefore, a specialized carrier transports the long chain acyl group from the cytosol into the mitochondrial matrix. This carrier is carnitine, and this rate-limiting transport process is called the carnitine shuttle.

Carnitine shuttle:
Inhibitor of the carnitine shuttle: Malonyl CoA inhibits CPT-I, thus preventing the entry of long-chain acyl groups into the mitochondrial matrix. Therefore, when fatty acid synthesis is occurring in the cytosol (as indicated by the presence of malonyl CoA), the newly made palmitate cannot be transferred into the mitochondria and degraded.

Sources of carnitine: Carnitine can be obtained from the diet, where it is found primarily in meat products. Carnitine can also be synthesized from the amino acids lysine and methionine by an enzymatic pathway found in the liver and kidney but not in skeletal or heart muscle. Therefore, these latter tissues are totally dependent on uptake of carnitine provided by endogenous synthesis or the diet, and distributed by the blood. [Note: Skeletal muscle contains about 97% of all carnitine in the body.]

Carnitine deficiencies: Such deficiencies result in a decreased ability of tissues to use LCFA as a metabolic fuel. Secondary carnitine deficiency occurs in many situations, including:
1) In patients with liver disease causing decreased synthesis of carnitine.
2) In individuals suffering from malnutrition or those on strictly vegetarian diets.
3) In those with an increased requirement for carnitine as a result of, for example, pregnancy, severe infections, burns, or trauma.
4) In those undergoing hemodialysis, which removes carnitine from the blood.

Congenital deficiencies in one of the components of the carnitine palmitoyltransferase system, in renal tubular reabsorption of carnitine, or in carnitine uptake by cells cause primary carnitine deficiency.

2. Entry of short- and medium-chain fatty acids into the mitochondria:
Fatty acids shorter than 12 carbons can cross the inner mitochondrial membrane without the aid of carnitine or the CPT system. Once inside the mitochondria, they are activated to their CoA derivatives by matrix enzymes, and are oxidized.
3. Reactions of β-oxidation:
The first cycle of β-oxidation is shown in the figure below. It consists of a sequence of four reactions involving the β-carbon (carbon 3) that results in shortening the fatty acid chain by two carbons. The steps include an oxidation that produces FADH2, a hydration step, a second oxidation that produces NADH, and a thiolytic cleavage that releases a molecule of acetyl CoA. Each step is catalyzed by enzymes with chain-length specificity.

These four steps are repeated for saturated fatty acids of even-numbered carbon chains \( \frac{n}{2} - 1 \) times (where \( n \) is the number of carbons), each cycle producing an acetyl group plus one NADH and one FADH2. The final thiolytic cleavage produces two acetyl groups. [Note: Acetyl CoA is a positive allosteric effector of pyruvate carboxylase, thus linking fatty acid oxidation and gluconeogenesis.]

4. Energy yield from fatty acid oxidation:
The energy yield from the β-oxidation pathway is high. For example, the oxidation of a molecule of palmitoyl CoA to CO2 and H2O produces 8 acetyl CoA, 7 NADH, and 7 FADH2, from which 131 ATP can be generated; however, activation of the fatty acid requires 2 ATP. Thus, the net yield from palmitate is 129 ATP.

- There are two sources of ATP to keep in mind when calculating the overall yield of ATP.
The first source is the reoxidation of the NADH and FADH2 produced by the oxidation of the fatty acid to acetyl-CoA.

The second source is ATP production from the processing of the acetyl-CoA through the citric acid cycle and oxidative phosphorylation.

A comparison of the processes of synthesis and degradation of long-chain saturated fatty acids with an even number of carbon atoms is provided in figure 16.9

<table>
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<th>SYNTHESIS</th>
<th>DEGRADATION</th>
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<tr>
<td>Greatest flux through pathway</td>
<td>After carbohydrate-rich meal</td>
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<tr>
<td>Hormonal state favoring pathway</td>
<td>High insulin/glucagon ratio</td>
</tr>
<tr>
<td>Major tissue site</td>
<td>Primarily liver</td>
</tr>
<tr>
<td>Subcellular location</td>
<td>Primarily cytosol</td>
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<tr>
<td>Carriers of acyl/acyetyl groups between mitochondria and cytosol</td>
<td>Citrate (mitochondria to cytosol)</td>
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<tr>
<td>Phosphopantotheine-containing active carriers</td>
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<td>Oxidation/reduction coenzymers</td>
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<td>Two-carbon donor/product</td>
<td>Malonyl CoA: donor of one acetyl group</td>
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<tr>
<td>Activator</td>
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<tr>
<td>Inhibitor</td>
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<td>Product of pathway</td>
<td>Palmitate</td>
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<tr>
<td>Repetitive four-step process</td>
<td>Condensation, reduction dehydration, reduction</td>
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<td></td>
<td>Dehydrogenation, hydration dehydrogenation, thiolysis</td>
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**Figure 16.19**
Comparison of the synthesis and degradation of long-chain, even-numbered, saturated fatty acids.

5. Oxidation of unsaturated fatty acids:

Done by Dr.Du'a Al-Zou'bi
The Oxidation of unsaturated fatty acids provides less energy than that of saturated fatty acids.

6. Oxidation of fatty acids with an odd number of carbons:
The β-oxidation of a saturated fatty acid with an odd number of carbon atoms proceeds by the same reaction steps as that of fatty acids with an even number, until the final three carbons are reached. This compound, propionyl CoA, is metabolized by a three-step pathway.

**KETONE BODIES: AN ALTERNATE FUEL FOR CELLS**

Done by Dr. Du'a Al-Zou'bi
Liver mitochondria have the capacity to convert acetyl CoA derived from fatty acid oxidation into ketone bodies. The compounds categorized as ketone bodies are acetoacetate, 3-hydroxybutyrate (also called β-hydroxybutyrate), and acetone.

Acetoacetate and 3-hydroxybutyrate are transported in the blood to the peripheral tissues. There they can be reconverted to acetyl CoA, which can be oxidized by the TCA cycle. Ketone bodies are important sources of energy for the peripheral tissues because:

1) They are soluble in aqueous solution and, therefore, do not need to be incorporated into lipoproteins or carried by albumin as do the other lipids.
2) They are produced in the liver during periods when the amount of acetyl CoA present exceeds the oxidative capacity of the liver.
3) They are used in proportion to their concentration in the blood by extrahepatic tissues, such as the skeletal and cardiac muscle and renal cortex.

Even the brain can use ketone bodies to help meet its energy needs if the blood levels rise sufficiently; thus, ketone bodies spare glucose. This is particularly important during prolonged periods of fasting.

A. Synthesis of ketone bodies by the liver: ketogenesis
During a fast, the liver is flooded with fatty acids mobilized from adipose tissue. The resulting elevated hepatic acetyl CoA produced primarily by fatty acid degradation inhibits pyruvate dehydrogenase, and activates pyruvate carboxylase. The OAA thus produced is used by the liver for gluconeogenesis rather than for the TCA cycle. Therefore, acetyl CoA is channeled into ketone body synthesis.

B. Excessive production of ketone bodies in diabetes mellitus
When the rate of formation of ketone bodies is greater than the rate of their use, their levels begin to rise in the blood (ketonemia) and, eventually, in the urine (ketonuria). This is seen most often in cases of uncontrolled, type 1 diabetes mellitus. In diabetic individuals with severe ketosis.

A frequent symptom of diabetic ketoacidosis is a fruity odor on the breath, which results from increased production of acetone. An elevation of the ketone body concentration in the blood results in acidemia.

C. Excessive production of ketone bodies in diabetes mellitus:
When the rate of formation of ketone bodies is greater than the rate of their use, their levels begin to rise in the blood and eventually in urine (ketonuria). This is seen most often in cases of uncontrolled type one diabetes mellitus. A frequent symptom of ketoacidosis is a fruity odor which results from increased production of acetone. An elevation of the ketone body concentration in the blood results in acidemia. Ketoacidosis may also be seen in cases of fasting.
Figure 16.24
Mechanism of diabetic ketoacidosis seen in type 1 diabetes.
Biosynthesis of Cholesterol

Cholesterol is synthesized in the cell cytosol and smooth endoplasmic reticulum from acetylCoA. Cholesterol synthesized in all tissues in humans, although Liver, intestine, adrenal cortex, and reproductive tissues, make the largest contributions to the body's cholesterol pool. The synthesis follows five major steps which include:

- Acetyl CoA is converted to HMG CoA. HMG CoA is reduced to Mevalonate by a reductase.
- Mevalonate is converted to 5- pyrophospho mevalonate.
- Dephosphorylation, decarboxylation converts it to Isopentenyl pyrophosphate( isoprene unit) five carbon.
- It is isomerised to dimethyl allyl pyrophosphate by isomeras.
- Isopentenyl pyrophosphate and dimethyl allyl pyrophosphate form Geranyl PP(10C).
- Geranyl PP and one more molecule of Isopentenyl PP→ Farnesyl PP(15C).
- Two of Farnesyl PP join to form Squalene (30C).

Squalene undergoes cyclization, loses three carbon atoms,aquire a double bond,forms Cholesterol

Done by Dr.Du'a Al-Zou'bi
Regulation of Cholesterol Synthesis:

The reduction of HMG CoA to mevalonate. It catalyzed by HMG CoA reductase and it is the committed step in the synthesis of cholesterol. HMG CoA reductase is the key regulatory enzyme.

1. Dietary cholesterol inhibits endogenous synthesis.
2. Fasting leads to low levels of the key enzyme.
3. Insulin activates protein phosphatase which converts it to active enzyme. Glucagon decreases its activity through cAMP dependent protein kinase.
4. Whenever ATP levels are low, the enzyme is switched off by AMP activated protein kinase.
5. mRNA for HMG CoA reductase is under the control of sterols. High concentration of sterols inhibits the synthesis of mRNA, thereby the synthesis of enzyme.
6. High levels of degradation products lead to rapid degradation of HMG CoA reductase.