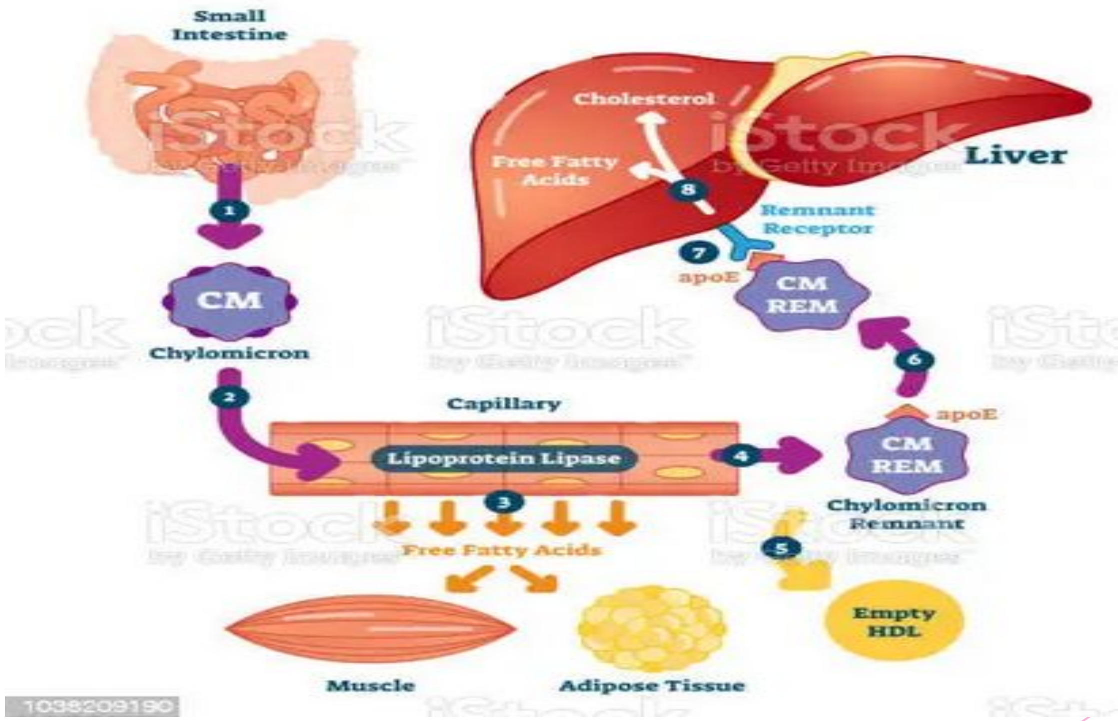
Regulation of Lipid metabolism

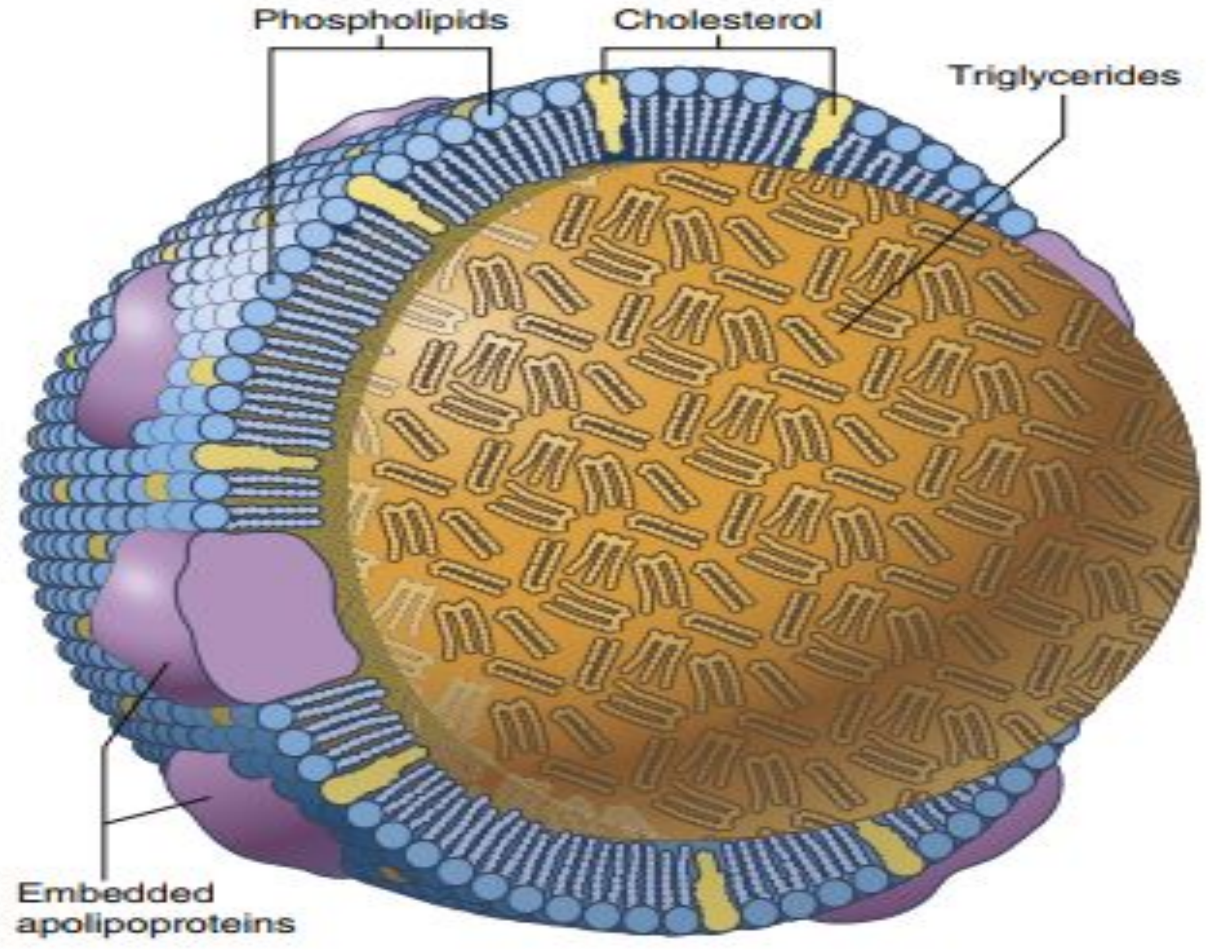
Assist. Prof. Dr. Luma Waleed Khaleel



- **Several chemical compounds in food and in the body are classified as *lipids,* including the following: (1) *neutral fat*, also known as *triglycerides;* (2) *phospholipids;* (3) *cholesterol*.**
- **Chemically, the basic lipid moiety of triglycerides and phospholipids is *fatty acids*, which are long-chain hydrocarbon organic acids.**
- **Although cholesterol does not contain fatty acid, its sterol nucleus is synthesized from portions of fatty acid molecules, thus giving it many of the physical and chemical properties of other lipids.**
- **The triglycerides are used in the body mainly to provide energy for the different metabolic processes, a function they share almost equally with carbohydrates.**
- **However, some lipids, especially cholesterol, phospholipids, and small amounts of triglycerides, are used to form the membranes of all cells of the body and to perform other essential cellular functions.**

TRANSPORT OF LIPIDS IN THE BODY FLUIDS

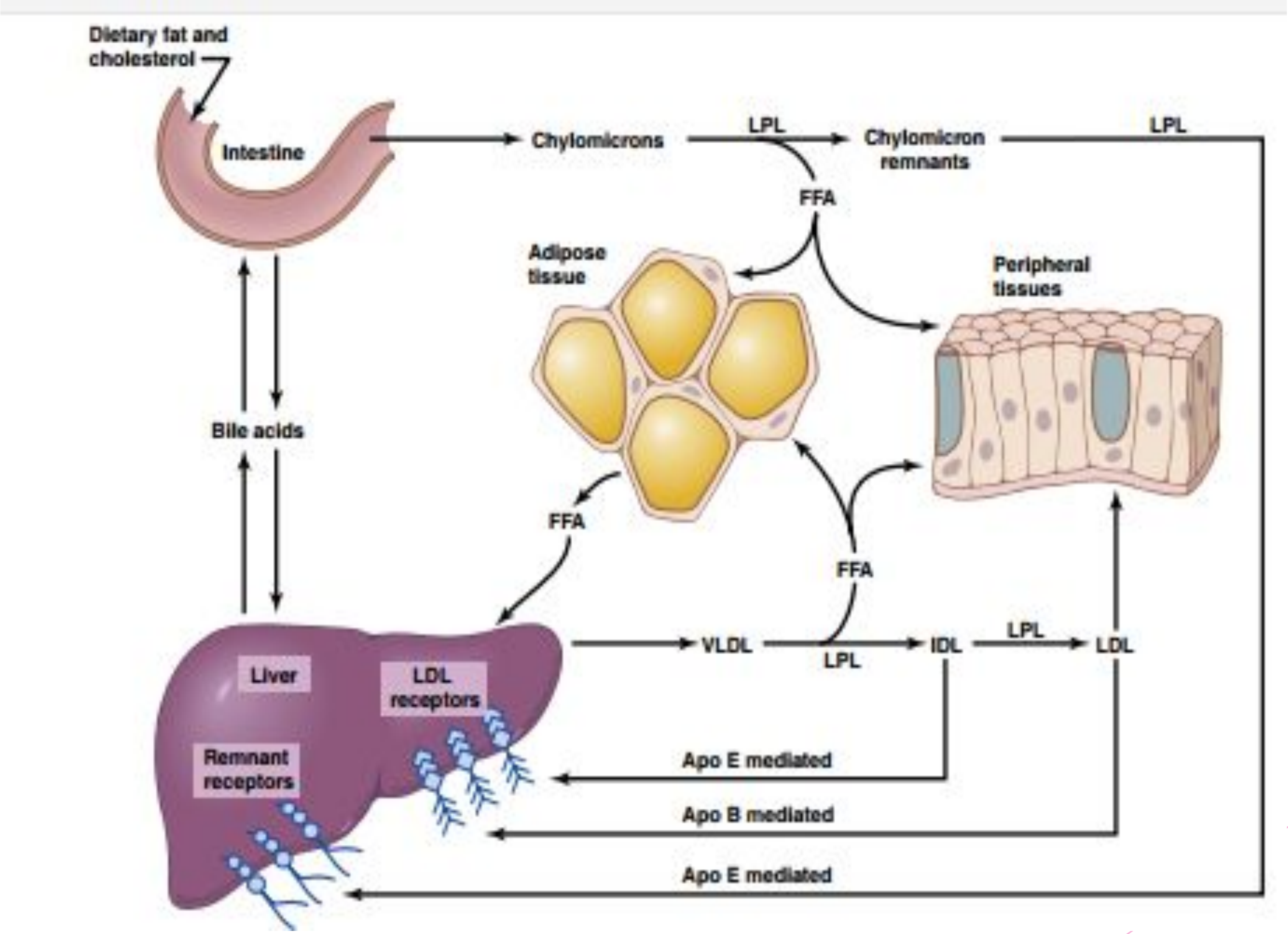
- **TRANSPORT OF TRIGLYCERIDES AND OTHER LIPIDS FROM THE GASTROINTESTINAL TRACT BY LYMPH—THE CHYLOMICRON:**
- Almost all the fats in the diet, with the principal exception of a few short-chain fatty
acids, are absorbed from the intestines into the intestinal lymph. During digestion, most triglycerides are split into monoglycerides and fatty acids. Then, while passing through the intestinal epithelial cells, the monoglycerides and fatty acids are resynthesized into new molecules of triglycerides that enter the lymph as minute, dispersed droplets called *chylomicrons*. A small amount of *apolipoprotein*, mainly *apolipoprotein B,* is adsorbed to the outer surfaces of the chylomicrons.
- The remainder of the protein molecules project into the surrounding water and thereby increase the suspension stability of the chylomicrons in the lymph fluid and prevent their adherence to the lymphatic vessel walls.
Most of the cholesterol and phospholipids absorbed from the gastrointestinal tract enter the chylomicrons.
- Thus, although the chylomicrons are composed principally of triglycerides, they also contain about 9% phospholipids, 3% cholesterol, and 1% apolipoproteins. The chylomicrons are then transported upward through the thoracic duct and emptied into the circulating venous blood at the juncture of the jugular and subclavian veins.


Phospholipids
Cholesterol
Triglycerides
Embedded
apolipoproteins

REMOVAL OF THE CHYLOMICRONS FROM THE BLOOD

- About 1 hour after a meal containing large quantities of fat, the chylomicron concentration in the plasma may rise to 1% to 2% of the total plasma, and because of the large size of the chylomicrons.
- However, the chylomicrons have a half-life of less than 1 hour, so the plasma becomes clear again within a few hours. The fat of the chylomicrons is removed mainly in the following way:
- Most of the chylomicrons are removed from the circulating blood as they pass through the capillaries of various tissues, especially adipose tissue, skeletal muscle, and heart. These tissues synthesize the enzyme lipoprotein lipase, which is transported to the surface of capillary endothelial cells,
- where it hydrolyzes the triglycerides of chylomicrons as they come in contact with the endothelial wall, thus releasing fatty acids and glycerol.

- The fatty acids released from the chylomicrons, being highly miscible with the membranes of the cells, diffuse into the fat cells of the adipose tissue and muscle cells. Once inside these cells, the fatty acids can be used for fuel or again synthesized into triglycerides, with new glycerol being supplied by the metabolic processes of the storage cells.
- The lipase also causes hydrolysis of phospholipids, which also releases fatty acids to be stored in the cells in the same way After the triglycerides are removed from the chylomicrons, the cholesterol-enriched chylomicron remnants are rapidly cleared from the plasma. The chylomicron remnants bind to receptors on endothelial cells in the liver sinusoids. Apolipoprotein-E on the surface of the chylomicron remnants and secreted by liver cells also plays an important role in initiating clearance of these plasma lipoproteins.
- "Free Fatty Acids" Are Transported in the Blood in Combination With Albumin:
- **When fat that has been stored in the adipose tissue is to be used elsewhere in the body to provide energy, it must first be transported from the adipose tissue to the other tissue.**
- **It is transported mainly in the form of free fatty acids. This transport is achieved by hydrolysis of the triglycerides back into fatty acids and glycerol.**


Dietary fat and cholesterol
Intestine
Chylomicrons
LPL
Chylomicron remnants
LPL
FFA
Adipose tissue
Peripheral tissues
Bile acids
FFA
FFA
Liver
LDL receptors
VLDL
LPL
IDL
LPL
LDL
Remnant receptors
Apo E mediated
Apo B mediated
Apo E mediated

- At least two classes of stimuli play important roles in promoting this hydrolysis. First, when the amount of glucose available to the fat cell is inadequate, one of the glucose breakdown products, α-glycerophosphate, Because this substance is required to maintain the glycerol portion of triglycerides, the result is hydrolysis of triglycerides.
- Second, a hormone-sensitive cellular lipase can be activated by several hormones from the endocrine glands, and this also promotes rapid hydrolysis of triglycerides.
- Upon leaving fat cells, fatty acids ionize strongly in the plasma and the ionic portion combines immediately with albumin molecules of the plasma proteins. Fatty acids bound in this manner are called free fatty acids or non-esterified fatty acids, to distinguish them from other fatty acids in the plasma.

Lipoproteins—Their Special Function in Transporting Cholesterol and Phospholipids

- In the postabsorptive state, after all the chylomicrons have been removed from the blood, more than 95% of all the lipids in the plasma are in the form of lipoprotein. Containing triglycerides, cholesterol, phospholipids, and protein.
- Types of Lipoproteins.
- Aside from the chylomicrons, which are very large lipoproteins, there are four major types of lipoproteins, classified by their densities as:
- (1) very low density lipoproteins (VLDLs) with high cholesterol and phospholipids(2) intermediate-density lipoproteins (IDLs), which are VLDLs from it. (3) low density lipoproteins (LDLs) high concentration of cholesterol and a moderately high concentration of phospholipids; .
- (4) high-density lipoproteins (HDLs), which contain a high concentration of protein but much smaller concentrations of cholesterol and phospholipids.

- Formation and Function of Lipoproteins.
- Almost all the lipoproteins are formed in the liver, which is also where most of the plasma cholesterol, phospholipids, and triglycerides are synthesized. In addition, small quantities of HDLs are synthesized in the intestinal epithelium during absorption of fatty acids from the intestines.
- The primary function of the lipoproteins is to transport their lipid components in the blood. The VLDLs transport triglycerides synthesized in the liver mainly to the adipose tissue. The other lipoproteins are especially important in different stages of phospholipid and cholesterol transport from the liver to the peripheral tissues or from the periphery back to the liver.

Adipose Tissue

- A major function of adipose tissue is storage of triglycerides until they are needed to provide energy. Additional functions are to provide heat insulation for the body, and secretion of hormones, such as leptin and adiponectin, which affect multiple body functions, including appetite and energy expenditure.
- Tissue Lipases Permit Exchange of Fat Between Adipose Tissue and the Blood.
- large quantities of lipases are present in adipose tissue. Some of these enzymes catalyze the deposition of cell triglycerides from the chylomicrons and lipoproteins. Others, when activated by hormones, cause splitting of the triglycerides of the fat cells to release free fatty acids.

Liver Lipids:

- The principal functions of the liver in lipid metabolism are to (1) degrade fatty acids into small compounds that can be used for energy; (2) synthesize triglycerides, mainly from carbohydrates, but to a lesser extent from proteins as well; and (3) synthesize other lipids from fatty acids, especially cholesterol and phospholipids.
- Large quantities of triglycerides appear in the liver during (1) the early stages of starvation, (2) in diabetes mellitus, and (3) in any other condition in which fat instead of carbohydrates is being used for energy. In these conditions, large quantities of triglycerides are mobilized from the adipose tissue, transported as free fatty acids in the blood, and redeposited as triglycerides in the liver, where the initial stages of much of fat degradation begin.
- Thus, under normal physiological conditions, the total amount of triglycerides in the liver is determined to a great extent by the overall rate at which lipids are being used for energy.

- **The liver cells, in addition to containing triglycerides, contain large quantities of phospholipids and cholesterol, which are continually synthesized by the liver. Also, the liver cells are much more capable of desaturating fatty acids than are other tissues, and thus liver triglycerides normally are much more unsaturated than the triglycerides of adipose tissue.**
- **This capability of the liver to desaturate fatty acids is functionally important to all tissues of the body because many structural elements of all cells contain reasonable quantities of unsaturated fats, and their principal source is the liver. This desaturation is accomplished by a dehydrogenase in the liver cells.**
- **Hydrolysis of Triglycerides Into Fatty Acids and Glycerol:**
- The first stage in using triglycerides for energy is their hydrolysis into fatty acids and glycerol. Then, both the fatty acids and the glycerol are transported in the blood to the active tissues, where they will be oxidized to give energy.
- Almost all cells—with some exceptions, such as brain tissue and red blood cells—can use fatty acids for energy.
- Glycerol, upon entering the active tissue, is immediately changed by intracellular enzymes into glycerol-3- phosphate, which enters the glycolytic pathway for glucose breakdown and is thus used for energy. Before the fatty acids can be used for energy, they must be processed further in the mitochondria.

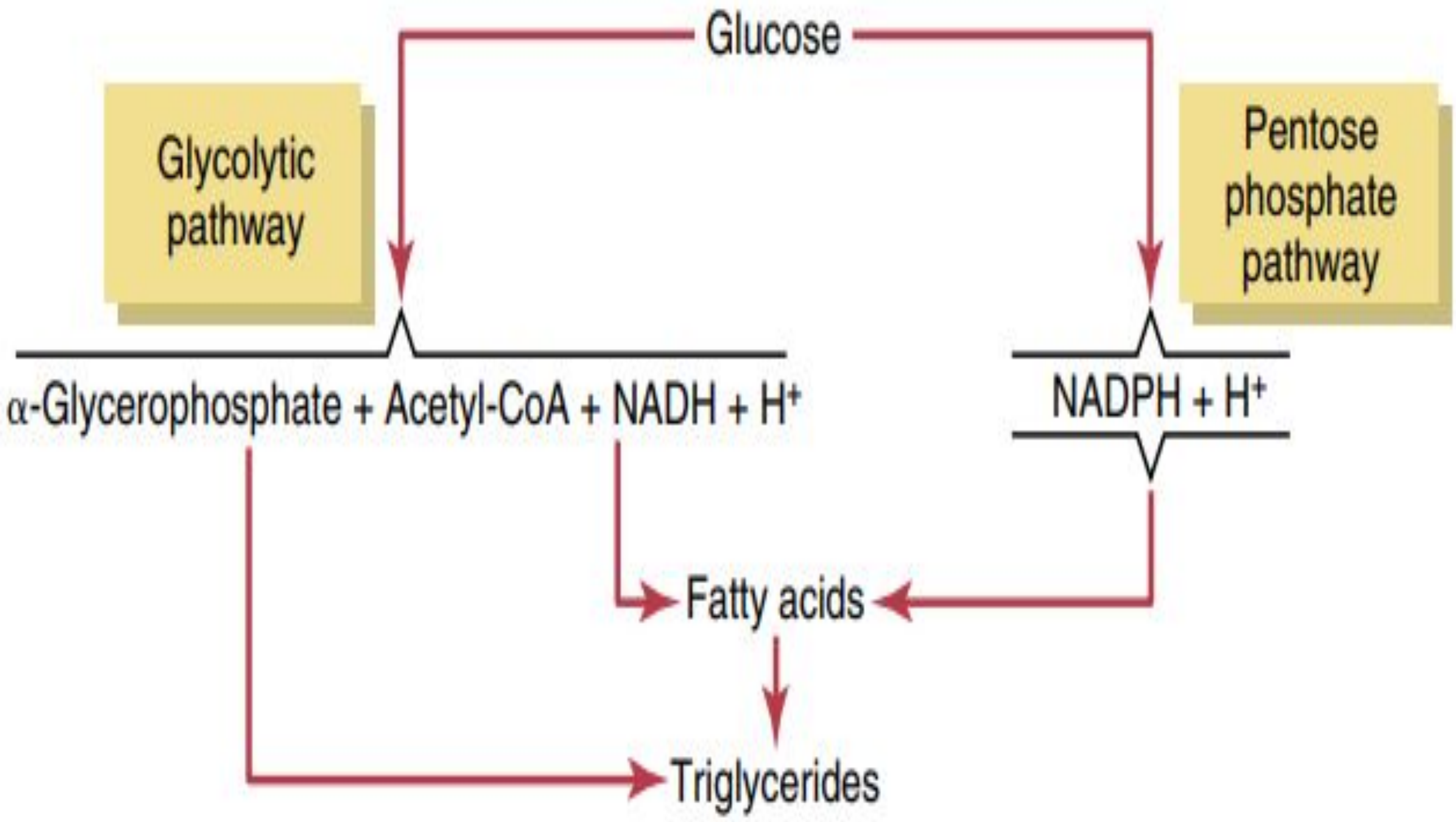
- ## Entry of Fatty Acids Into Mitochondria
- Degradation and oxidation of fatty acids occur only in the mitochondria. Therefore, the first step for the use of fatty acids is their transport into the mitochondria using carnitine as a carrier. Once inside the mitochondria, fatty acids split away from carnitine and are degraded and oxidized.
- ### Degradation of Fatty Acids to Acetyl Coenzyme A by Beta-Oxidation
- Fatty acids are degraded in the mitochondria by progressive release acetyl coenzyme A (acetyl-CoA). This degradation process, which is called beta-oxidation of fatty acids.
- **Oxidation of Acetyl-CoA.** The acetyl-CoA molecules formed by beta-oxidation of fatty acids in the mitochondria enter immediately into the citric acid cycle, combining first with oxaloacetic acid to form citric acid, which then is degraded into carbon dioxide and hydrogen atoms. The hydrogen is subsequently oxidized by the chemiosmotic oxidative system of the mitochondria.

- Thus, after initial degradation of fatty acids to acetylCoA, their final breakdown is precisely the same as that of the acetyl-CoA formed from pyruvic acid during the metabolism of glucose. The extra hydrogen atoms are also oxidized by the same chemiosmotic oxidative system of the mitochondria that is used in carbohydrate oxidation, liberating large amounts of adenosine triphosphate (ATP).
- **Formation of Acetoacetic Acid in the Liver and Its Transport in the Blood:**
- A large share of the initial degradation of fatty acids occurs in the liver, especially when large amounts of lipids are being used for energy. However, the liver uses only a small proportion of the fatty acids for its own intrinsic metabolic processes. Instead, when the fatty acid chains have been split into acetyl-CoA, two molecules of acetyl-CoA condense to form one molecule of acetoacetic acid, which is then transported in the blood to the other cells throughout the body, where it is used for energy.
- 2Acetyl-CoA------- → **Acetoacetate ------→Acetone or β-Hydroxybutyrate**

- **Ketosis in Starvation, Diabetes, and Other Diseases.**
- The concentrations of acetoacetic acid, β-hydroxybutyric acid, and acetone occasionally rise to levels many times normal in the blood and interstitial fluids; this condition is called ketosis because acetoacetic acid is a keto acid.
- The three compounds are called ketone bodies. Ketosis occurs especially as a consequence of starvation, in persons with diabetes mellitus, and sometimes even when a person's diet is composed almost entirely of fat. In all these states, essentially no carbohydrates are metabolized—in starvation and with a high-fat diet because carbohydrates are not available, and in diabetes because insulin is not available to cause glucose transport into the cells.
- In addition, several hormonal factors—such as increased secretion of glucocorticoids by the adrenal cortex, increased secretion of glucagon by the pancreas, and decreased secretion of insulin by the pancreas—further enhance removal of fatty acids from the fat tissues. As a result, large quantities of fatty acids become available (1) to the peripheral tissue cells to be used for energy and (2) to the liver cells, where much of the fatty acid is converted to ketone bodies.

- Combination of Fatty Acids With α-Glycerophosphate to Form Triglycerides:
- Once the synthesized fatty acid chains have grown to contain 14 to 18 carbon atoms, they bind with glycerol to form triglycerides. The glycerol portion of triglycerides is furnished by α-glycerophosphate, which is another product derived from the glycolytic scheme of glucose degradation.
- Efficiency of Carbohydrate Conversion Into Fat: During triglyceride synthesis, only about 15% of the original energy in the glucose is lost in the form of heat; the remaining 85% is transferred to the stored triglycerides.

- # Importance of Fat Synthesis and Storage:
- Fat synthesis from carbohydrates is especially important for two reasons:
- 1. The ability of the different cells of the body to store carbohydrates in the form of glycogen is generally slight; a maximum of only a few hundred grams of glycogen can be stored in the liver, the skeletal muscles, and all other tissues of the body put together. In contrast, many kilograms of fat can be stored in adipose tissue.
- 2. Each gram of fat contains almost two and a half times the calories of energy contained by each gram of glycogen.
- **Failure to Synthesize Fats From Carbohydrates in the Absence of Insulin.**
- When insufficient insulin is available, as occurs in diabetes mellitus, fats are poorly synthesized. First, when insulin is not available, glucose does not enter the fat and liver cells, so little of the acetyl-CoA and NADPH needed for fat synthesis can be derived from glucose.
- Second, lack of glucose in the fat cells greatly reduces the availability of α-glycerophosphate, which also makes it difficult for the tissues to form triglycerides.


Glucose
Glycolytic pathway
Pentose phosphate pathway
α-Glycerophosphate + Acetyl-CoA + NADH + H+
NADPH + H+
Fatty acids
Triglycerides

- ## Synthesis of Triglycerides From Proteins:
- Many amino acids can be converted into acetyl-CoA. The acetyl-CoA can then be synthesized into triglycerides. Therefore, when people have more proteins in their diets than their tissues can use as proteins, a large share of the excess is stored as fat.
- ## Hormonal Regulation of Fat Utilization:
- At least seven of the hormones secreted by the endocrine glands have significant effects on fat utilization. Some important hormonal effects on fat metabolism, in addition to lack of insulin.
- Probably the most dramatic increase that occurs in fat utilization is that observed during heavy exercise. This increase results almost entirely from release of epinephrine and norepinephrine by the adrenal medullae during exercise, as a result of sympathetic stimulation.
- These two hormones directly activate hormone-sensitive triglyceride lipase, which is present in abundance in the fat cells, and this activation causes rapid breakdown of triglycerides and mobilization of fatty acids.

- Stress also causes large quantities of adrenocorticotropic hormone (ACTH) to be released by the anterior pituitary gland, which causes the adrenal cortex to secrete extra quantities of glucocorticoids. Both ACTH and glucocorticoids activate either the same hormone-sensitive triglyceride lipase as that activated by epinephrine and norepinephrine or a similar lipase.
- When ACTH and glucocorticoids are secreted in excessive amounts for long periods, as occurs in the endocrine condition called Cushing's syndrome, fats are frequently mobilized to such a great extent that ketosis results. ACTH and glucocorticoids are then said to have a ketogenic effect.
- Growth hormone has an effect similar to but weaker than that of ACTH and glucocorticoids in activating hormone-sensitive lipase. Therefore, growth hormone can also have a mild ketogenic effect.
- Thyroid hormone indirectly causes rapid mobilization of fat by increasing overall rate of energy metabolism in all cells of the body under the influence of this hormone. The resulting reduction in acetyl-CoA and other intermediates of both fat and carbohydrate metabolism in the cells is a stimulus to fat mobilization.

Phospholipids and Cholesterol
Phospholipids

- The major types of body phospholipids are lecithins, cephalins, and sphingomyelin; their typical chemical formulas are Phospholipids always contain one or more fatty acid molecules and one phosphoric acid radical, and they usually contain a nitrogenous base.
- Formation of Cholesterol:
- The basic structure of cholesterol is a sterol nucleus, which is synthesized entirely from multiple molecules of acetyl-CoA. In turn, the sterol nucleus can be modified by various side chains to form (1) cholesterol; (2) cholic acid, which is the basis of the bile acids formed in the liver; and (3) many important steroid hormones secreted by the adrenal cortex, the ovaries, and the testes.

- Factors That Affect Plasma Cholesterol Concentration, Feedback Control of body Cholesterol:
- **1. An increase in the amount of cholesterol ingested each day may increase the plasma concentration slightly. However, when cholesterol is ingested, the rising concentration of cholesterol inhibits the most essential enzyme for endogenous synthesis of cholesterol, 3-hydroxy-3-methylglutaryl CoA reductase, thus providing an intrinsic feedback control system to prevent an excessive increase in plasma cholesterol concentration.**
- **2.**A diet high in saturated fat increases blood cholesterol concentration. This increase in blood cholesterol results from increased fat deposition in the liver, which then provides increased quantities of acetyl-CoA in the liver cells for the production of cholesterol.
- 3.Ingestion of fat containing highly unsaturated fatty acids usually depresses the blood cholesterol concentration a slight to moderate amount.
- 4. Lack of insulin or thyroid hormone increases the blood cholesterol concentration, whereas excess thyroid hormone decreases the concentration. These effects are probably caused mainly by changes in the degree of activation of specific enzymes responsible for the metabolism of lipids and overall metabolic rate.

- 5.Genetic disorders of cholesterol metabolism may greatly increase plasma cholesterol levels. For example, mutations of the LDL receptor gene prevent the liver from adequately removing the cholesterol-rich LDLs from plasma. This phenomenon causes the liver to produce excessive amounts of cholesterol. Mutations of the gene that encodes apolipoprotein B, the part of the LDL that binds to the receptor, also cause excessive cholesterol production by the liver.