METABOLISM: UNDERSTANDING THE INTERACTIONS AND TRANSFORMATIONS IN LIVING CELLS

WHAT IS METABOLISM?

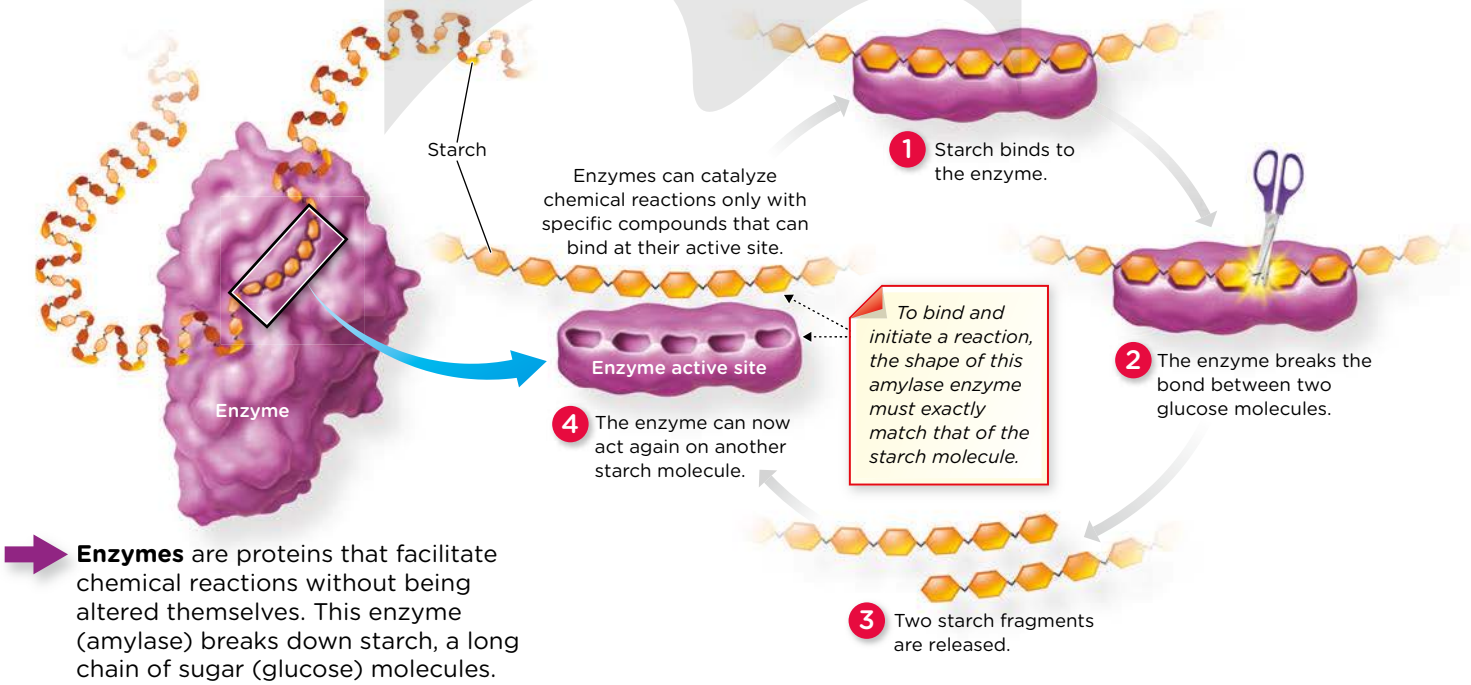
Metabolism is all the life-sustaining chemical reactions that occur in living organisms and transform one molecule into another one. The chemical reactions may rearrange atoms within a molecule, add atoms to a molecule, or remove atoms from a molecule. The vast majority of chemical reactions that occur in the body are **catalyzed** (initiated and accelerated) by **enzymes**, which are proteins that facilitate reactions without themselves being altered so they can perform the same reaction over and over again.

UNDERSTANDING METABOLISM

KEY IDEAS

- **Metabolism** is all the life-sustaining chemical reactions that occur in living organisms that convert one molecule into another molecule. Many metabolic processes fall into one of two broad categories, catabolism and anabolism.
- **Catabolism** is the breakdown of large molecules into smaller ones, and is generally accompanied by the release of energy.
- **Anabolism** is the synthesis of large molecules from smaller ones, requiring an input of energy that is often obtained from the oxidation of fuels that are provided by catabolic reactions.
- Since digestion occurs within the lumen of the gastrointestinal tract, which is fundamentally still outside the body, digestion is not considered to be metabolism.

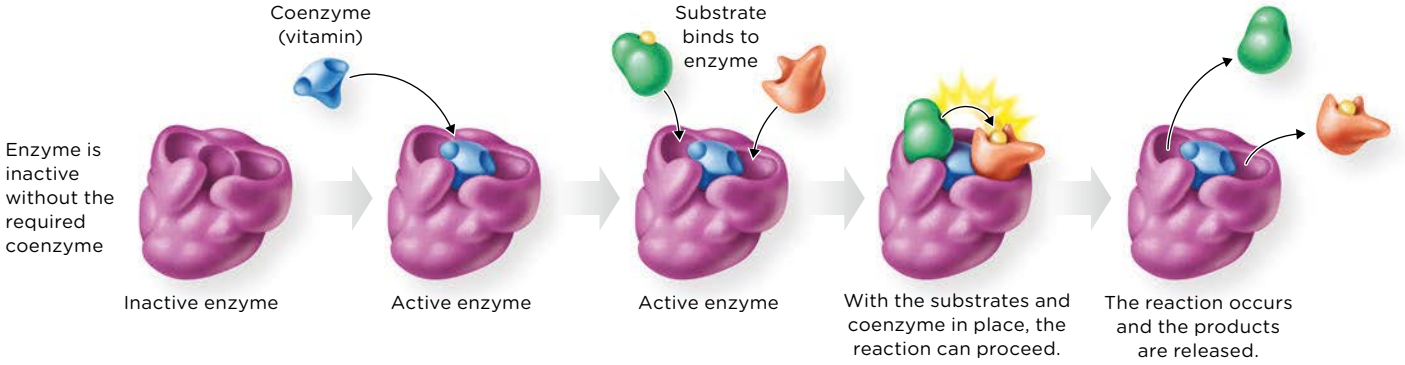
How Do Enzymes Work?



Enzymes are proteins that facilitate chemical reactions without being altered themselves. This enzyme (amylase) breaks down starch, a long chain of sugar (glucose) molecules.

? *Why won't this enzyme break down lipids or proteins?*

How Do Coenzymes Work? *Coenzymes associate with enzymes to form an active complex that is capable of catalyzing a chemical reaction. Some vitamins function as coenzymes.*



? *Describe the basic function of a coenzyme.*

The molecule that an enzyme acts on is referred to as a **substrate**, and the modified molecule that the reaction yields is called the **product**. Many enzymes require small, organic, nonprotein molecules called **coenzymes** to function. Coenzymes bind at a location on the enzyme known as the active site and form an active enzyme, which is only then capable of catalyzing its designated reaction. Vitamins C and K, and all of the B vitamins function as coenzymes.

Many of the chemical transformations that occur within cells require multiple individual reactions to be completed in a series. For this reason, cellular metabolism is typically organized into **metabolic pathways**. Each pathway transforms its original substrate into a final product or products through a sequence of linked enzyme-catalyzed reactions. At each step in the pathway the product formed in one reaction becomes the substrate for the next reaction in the pathway until the final product is formed.

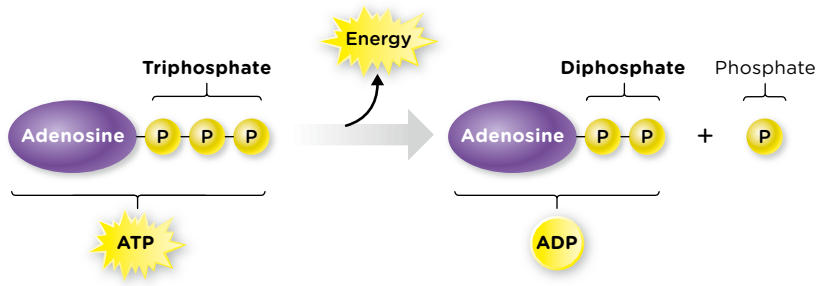
Many metabolic processes fall into one of two broad categories: **anabolism** and **catabolism**. Anabolism is the synthesis of large molecules from smaller ones, requiring an input of energy. Common anabolic processes are those that synthesize proteins from amino acids, glycogen from glucose, and triglycerides from sources of excess calories (such as glucose and amino acids). Cell division and growth are also anabolic processes.

Catabolism, on the other hand, is the breakdown of large molecules into smaller ones, and is generally accompanied by the release of energy. Catabolic processes supply the fuels that are needed to drive anabolism, and they can also provide the substrates needed for a number of anabolic processes. The balance between all anabolic and catabolic processes over the course of several days will determine if an individual's weight will remain stable, or whether he or she will experience a change in body weight. For example, if the total number of catabolic processes exceeds that of anabolic processes, an individual's body weight would decrease, as adipose tissue and muscle mass are lost.

Energy metabolism is the chemical reactions that are involved in storing fuels, or breaking them down to provide the energy necessary to drive a variety of chemical reactions and other cellular processes (such as active transport and muscle contractions). This energy comes from one of two main fuel sources: glucose and fatty acids. Both of these fuels are rich in chemical energy, stored in the chemical bonds that hold each molecule together. As fuels are slowly metabolized and broken down, energy is released and the product of each reaction contains less energy than the starting substrate. This released energy is not in a form the body cells can use; it must be converted into a molecule called **adenosine triphosphate** (**ATP**).

Commonly referred to as the cell's energy currency, ATP stores chemical energy in the bonds of its three phosphate groups. When

Adenosine Triphosphate (ATP) *is produced during energy metabolism. ATP has a high energy content and is often referred to as the energy currency of cells.*



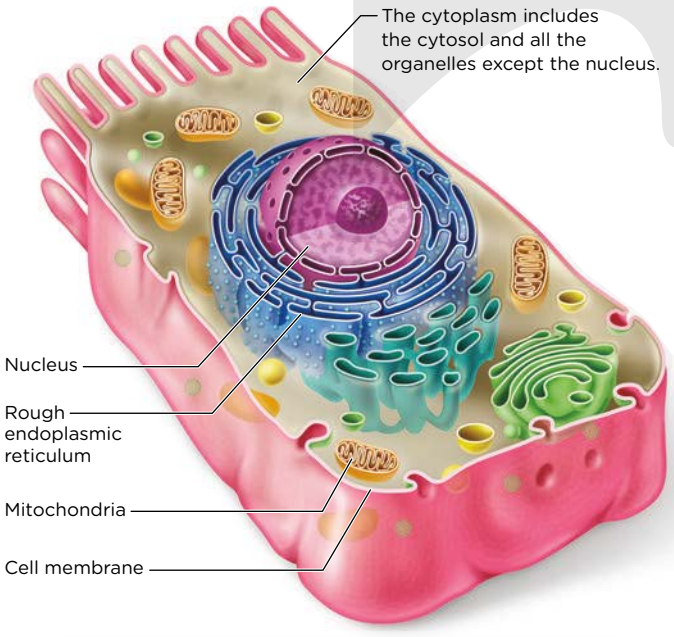
Energy is released when the bond between the second and third phosphate of ATP is broken. A portion of the released energy can be captured to do work, such as fueling muscle contractions. ADP is then used to reform ATP.

our cells need energy, they typically break the bond between the last two phosphates, releasing the stored energy and forming **adenosine diphosphate (ADP)**. (The "di" in diphosphate means "two," as in two phosphates; the "tri" in "triphosphate" refers to its three phosphates.)

You can think of the energy in glucose and fat as the value of a gold brick: It's worth a lot of money, but you can't buy a cup of coffee with it. ATP, however, is like bills and coins—it's energy your cells can actually spend. The primary metabolic pathways involved in producing ATP are glycolysis, the citric acid cycle, and the electron transport chain (ETC).

The reactions of energy metabolism primarily occur in two cellular compartments, the **cytosol** and the **mitochondria**. Recall that cells are surrounded by a cell membrane. Within the cell membrane is an aqueous fluid called the cytosol, as well as a number of cellular organelles and other structures. The membrane-enclosed organelles (such as mitochondria, endoplasmic reticulum, and the nucleus) carry out a variety of specialized functions. The **cytoplasm** includes the cytosol and all the organelles except the nucleus. Glucose oxidation (glycolysis) is the only ATP-producing pathway that occurs in the cytosol.

All other pathways involved in the production of ATP occur in mitochondria, which produce the majority of ATP in most cells. Mitochondria are organelles surrounded by a double-membrane system composed of an inner and outer membrane. The space that is enclosed by the inner membrane is called the **matrix**. See the Cellular Respiration illustration on page 7. The majority of the functions carried out by mitochondria occur in the matrix, and in this location the oxygen we breathe is used to generate ATP.



Cells are the smallest functional unit of living organisms. This is an example of the most common type of cell (an Enterocyte) found in the lining of the small intestine. A few of the cellular organelles are labeled.

Oxidation-reduction reactions involve the transfer of electrons between compounds and play a vital role in energy metabolism. **Oxidation** is the loss of electrons and **reduction** is the gain of electrons. Because electrons do not float around free in solution they are always transferred from one substance to another, so that as one substance loses an electron another substance simultaneously gains that electron. The substance that loses an electron is oxidized and the substance that gains an electron is reduced.

OVERVIEW OF ENERGY METABOLISM

As fuels provided by our diet are broken down into smaller and smaller molecules they undergo a series of oxidation reactions. Energy to produce ATP is extracted from the fuels as they are oxidized in what is essentially a controlled burn. This gradual breakdown and oxidation of fuels allows us to capture some of the chemical energy in those fuels to do work, such as physical movement, anabolic reactions, and active transport.

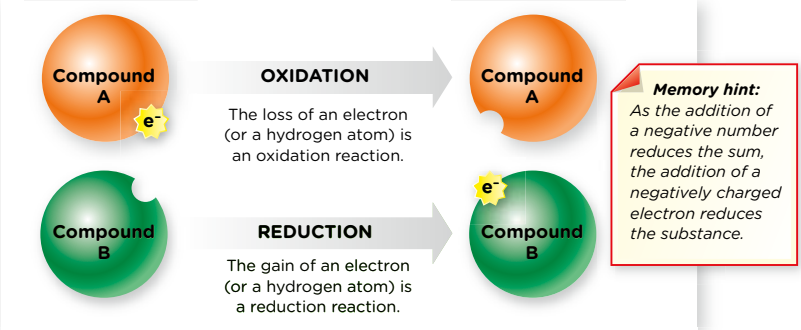
Coenzymes synthesized from the vitamins niacin and riboflavin function as electron carriers and are involved in transferring electrons (and/or hydrogen atoms) from one substance to another in energy metabolism. As fuels are oxidized, high-energy electrons are transferred to these coenzymes. It is the reduction of coenzymes that conserves much of the chemical bond energy that is released during the oxidation of our metabolic fuels. The reduced coenzymes shuttle their high-energy electron cargo to the **electron transport chain (ETC)** in mitochondria where a series of electron-carrier molecules are embedded in the inner mitochondrial membrane. As electrons are passed from one molecule to another, energy is released. This energy can be used to synthesize ATP. See the Overview of Energy Metabolism illustration on page 4.

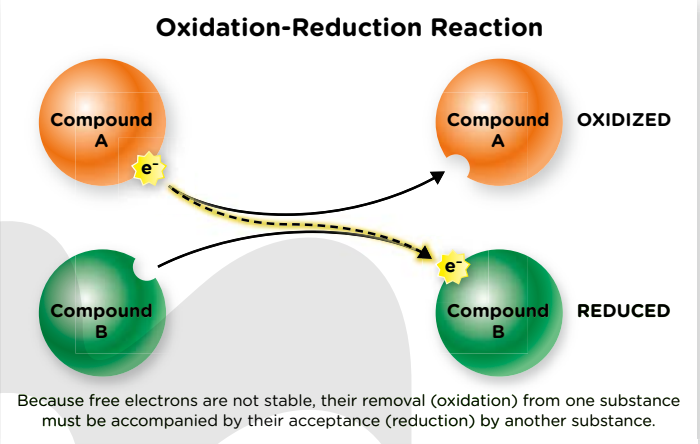
THE BREAKDOWN OF GLUCOSE

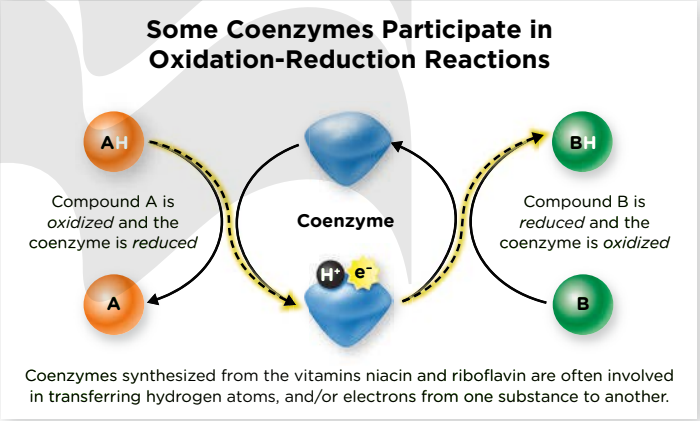
Glucose Metabolism Begins in the Cytosol and Is Completed in Mitochondria

All cells in the body are able to use glucose as fuel to produce ATP. The first step in glucose oxidation occurs in the cytosol with the process of **glycolysis** (or the glycolytic pathway), which does not require oxygen.

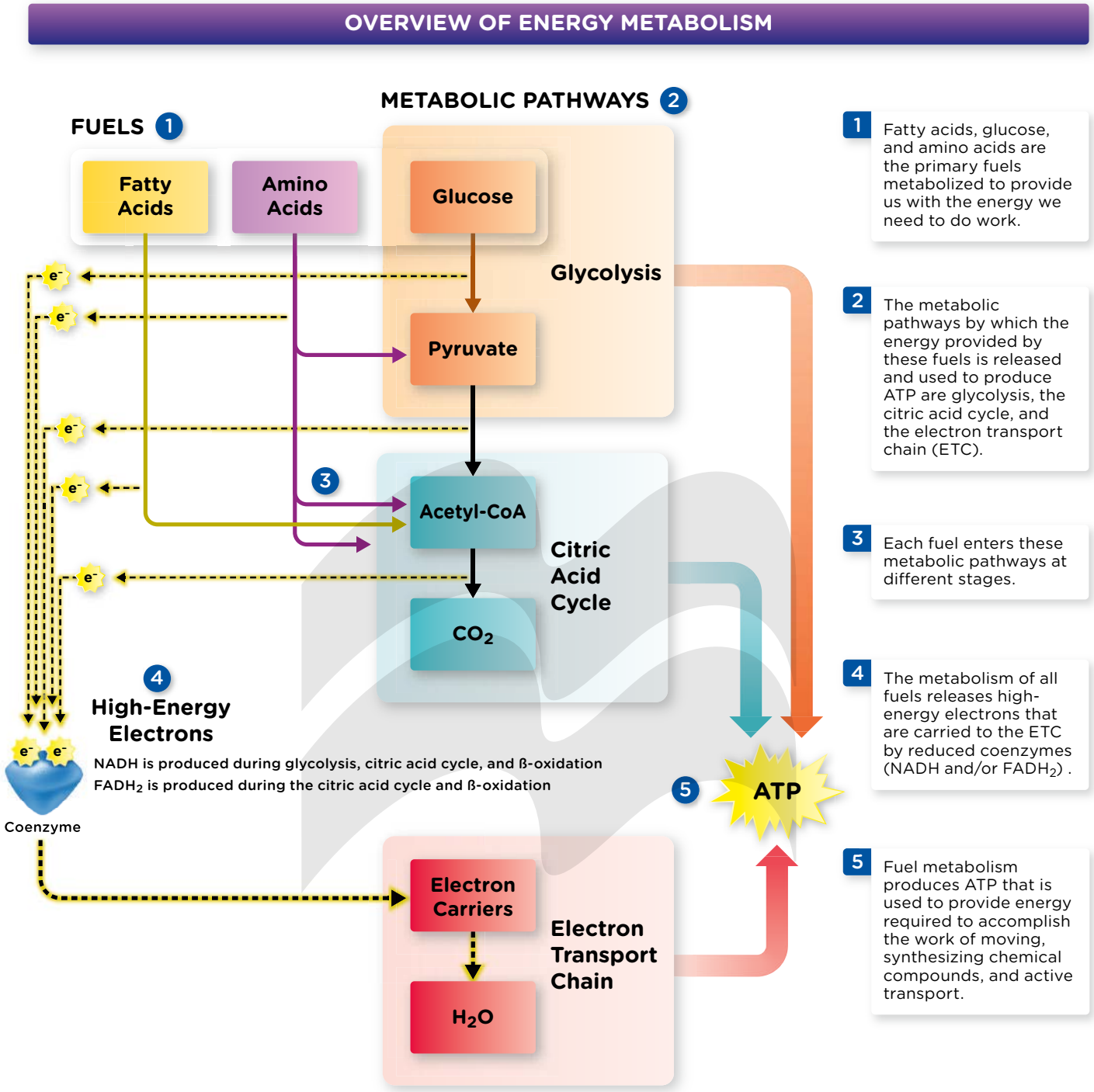
Glycolysis means *to break apart glucose*, and it splits the six-carbon glucose molecule into two 3-carbon molecules of pyruvate, with a net gain of two ATP and the production of two reduced coenzymes. The final steps in glucose oxidation occur in mitochondria. When there is adequate oxygen, pyruvate is transported







What Are Oxidation-Reduction Reactions? *Biological oxidation-reduction reactions are critical to life and are essential for energy metabolism. Oxidation-reduction reactions involve the transfer of electrons (or hydrogen atoms) between compounds, and are vital for the extraction and use of the energy that is supplied by the fuels that are provided in the foods we eat.*



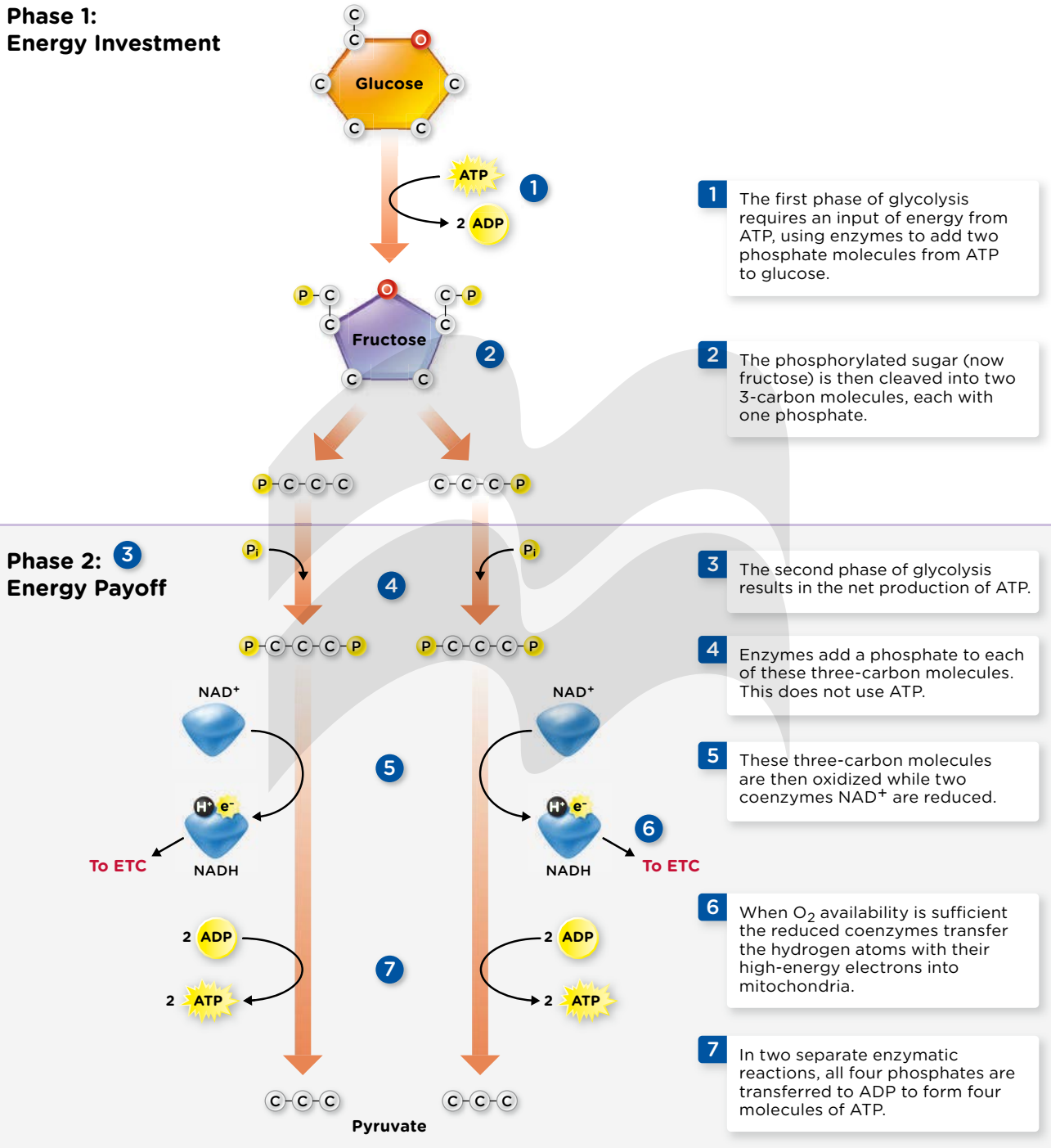
into mitochondria, where the **aerobic** (oxygen-dependent) oxidation of pyruvate to carbon dioxide (CO_2) and water completes the oxidation of glucose.

Glycolysis—the First Step in Glucose Oxidation
Glycolysis is a universal process that allows every cell in the body to extract energy from carbohydrates.

Glycolysis occurs in two phases, an **energy investment phase** and an **energy payoff phase**. During the first phase, glucose is rearranged into fructose, and energy is invested as phosphates from two ATP molecules are transferred to the sugar molecule to make it more reactive. The doubly phosphorylated fructose can then be split into two 3-carbon phosphate-containing molecules.

Glycolysis *is the metabolic pathway by which all cells can produce ATP by breaking down glucose to pyruvate. Glycolysis occurs in the cytosol of the cell and does not require oxygen.*

GLYCOLYSIS



Summary: Each molecule of glucose produces two molecules of pyruvate, two reduced coenzymes, and four ATP. Since two ATP were used during the energy investment phase, glycolysis results in the net production of two ATP.

In the energy payoff phase of glycolysis, energy is harvested as these phosphorylated three-carbon molecules are oxidized to form two molecules of pyruvate. During this phase of glycolysis four ATP are produced. Since two ATP were used during the energy investment phase there is a net yield of two ATP.

In addition, two coenzymes (NAD^+) are reduced (to NADH) as they acquire high-energy electrons (along with a positively charged hydrogen ion). When sufficient oxygen is present these high-energy electrons will be transferred to the ETC in mitochondria.

The Bridge Reaction Prepares Pyruvate for Complete Oxidation

Sufficient oxygen availability also allows pyruvate to enter mitochondria where its oxidation can be completed. The aerobic oxidation of pyruvate is responsible for generating the majority of ATP that is derived from glucose metabolism. However, for pyruvate to enter the next major pathway of energy metabolism (the citric acid cycle), it must first be transformed into a two-carbon molecule in a reaction catalyzed by the enzyme pyruvate dehydrogenase. This is step 3 in the Cellular Respiration illustration following.

Coenzyme A attaches to pyruvate, which allows a CO_2 to be released. This produces the two-carbon **acetyl-coenzyme A** molecule (acetyl-CoA) and a reduced coenzyme (NADH). (The release of CO_2 at this step is directly dependent on a coenzyme synthesized from thiamin. A similar thiamin-dependent CO_2-producing reaction also occurs approximately midway through the citric acid cycle.)

The Citric Acid Cycle is the Final Step in Glucose Oxidation

The final step in the oxidation of glucose involves entry of acetyl-CoA into the mitochondrial pathway called the **citric acid cycle** (step 4 in the Cellular Respiration illustration following). This pathway is also commonly referred to by two other names: the tricarboxylic acid (TCA) cycle and the Krebs cycle (after the scientist who first described it).

In the citric acid cycle, acetyl-CoA is oxidized to produce two molecules of CO_2, four reduced coenzymes (three NADH and one $FADH_2$), and a GTP, which is an ATP-like molecule that is energetically equivalent to producing ATP (step 5 in the Cellular Respiration illustration).

The citric acid cycle not only completes the oxidation of glucose, it is also the final oxidative pathway for fatty acids and amino acids. Fatty acids also enter the citric acid cycle as acetyl-CoA, while amino acids enter at several different points along the pathway.

Reduced Coenzymes Transfer High-Energy Electrons to the Electron Transport Chain

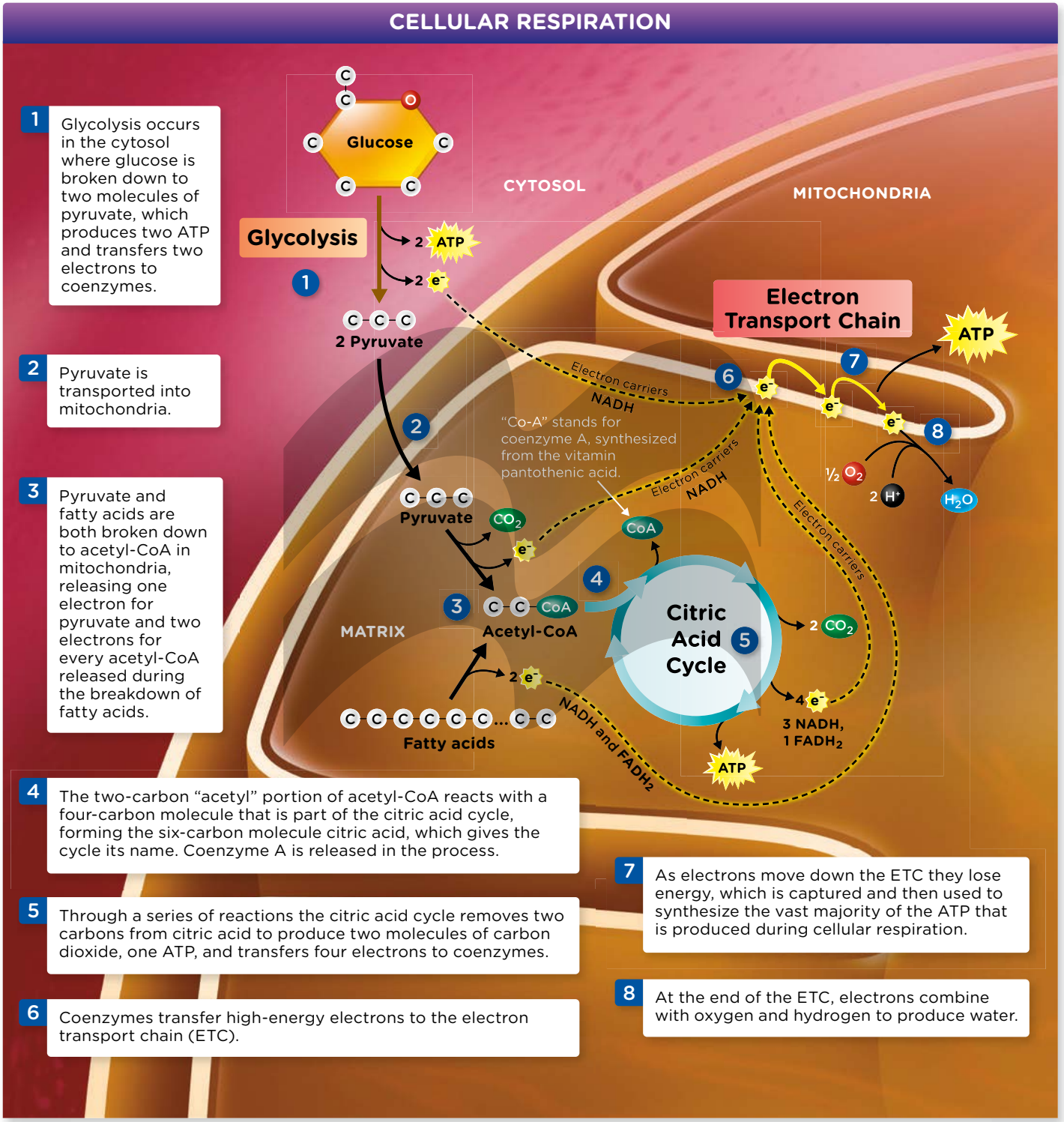
At the completion of the citric acid cycle the oxidation of glucose has yielded 12 reduced coenzymes: two from glycolysis, two from the oxidation of two molecules of pyruvate to acetyl-CoA, and eight from the oxidation of two molecules of acetyl-CoA to CO_2 in the citric acid cycle. With the completion of glucose oxidation in the citric acid cycle the majority of the chemical bond energy originally present is now conserved in the high-energy electrons carried by these reduced coenzymes.

To use the energy conserved in reduced coenzymes, they transfer their high-energy electrons to the ETC embedded in the inner-mitochondrial membrane. As electrons move down the ETC they gradually lose energy, which is captured, and can then be used to synthesize the majority of ATP that is produced by the metabolism of glucose (steps 6 and 7 in the Cellular Respiration illustration following).

The transfer of electrons from reduced coenzymes to the ETC is also critically important because it returns the coenzymes to their oxidized form, which allows them to continue participating in the oxidation of metabolic fuels. If the electron transfer did not occur reduced coenzymes would accumulate, and oxidized coenzymes would become depleted. With an inadequate number of coenzymes available to accept electrons from fuels as they are oxidized, oxidation would slow dramatically and eventually stop.

At the end of the ETC, electrons combine with oxygen and positively charged hydrogen ions to form water (step 8 in the Cellular Respiration illustration following).

Cellular Respiration *is the process by which the energy stored in fuels is transferred to ATP through a series of enzyme-catalyzed reactions. Aerobic respiration requires oxygen and occurs in mitochondria, where fatty acids and pyruvate are broken down to carbon dioxide and water.*



What carries electrons produced during glycolysis, the citric acid cycle, and fatty acid oxidation to the electron transport chain?

Total Net Yield of ATP from Glucose Oxidation

The complete aerobic oxidation of one molecule of glucose produces a total of 32 molecules of ATP from three different sources. Glycolysis produces a net yield of two ATP. Two ATP (GTP) are produced by the citric acid cycle, and 28 ATP are produced from the energy captured by the transport of electrons down the ETC. Since both the citric acid cycle and the ETC are aerobic pathways, 30 of the maximum 32 ATP produced by glucose oxidation are produced in an oxygen-dependent manner.

Under some circumstances glycolysis produces pyruvate and reduced coenzymes faster than the aerobic pathways in mitochondria can process them. This may occur when glycolysis metabolizes glucose at very rapid rates to meet high energy demands, or if the activity of the ETC is slowed because of limited oxygen availability. See the Aerobic Versus Anaerobic Glycolysis illustration on page 9.

In these circumstances an alternative means to return reduced coenzymes (NADH) in the cytosol to their oxidized form (NAD^+) must be used so that glycolysis can continue to provide ATP. This is accomplished by pyruvate functioning as an alternative hydrogen atom acceptor (both the electron and the positively charged hydrogen ion). Reduced coenzymes can transfer their hydrogen atom to pyruvate, transforming it to lactate. This quickly regenerates oxidized coenzymes that can then participate in another round of glycolysis.

FATTY ACID OXIDATION OCCURS IN THE MITOCHONDRIAL MATRIX

Unlike glucose, the oxidation of fatty acids for energy occurs completely in mitochondria and only in aerobic conditions. Before fatty acids can be transported into the matrix they must be activated by the enzymatic attachment of coenzyme A, a reaction that requires energy input equivalent to that of converting two molecules of ATP to ADP.

Once fatty acids have been transported into the mitochondrial matrix they are oxidized by a process called **beta-oxidation**. Similar to what occurred with the mitochondrial oxidation of pyruvate, beta-oxidation involves the attachment of coenzyme A and the cutting-off of two carbons at a time (as acetyl-CoA) from the fatty acid. However, with the release of each acetyl-CoA molecule from the fatty acid, two coenzymes (one NAD and one FAD) are reduced, instead of just one as occurred with pyruvate. Refer to the Cellular Respiration illustration on page 7.

For an 18-carbon fatty acid this produces nine acetyl-CoA molecules that will be oxidized by the citric acid cycle. Since one coenzyme A was attached to the fatty acid when it was activated, and the last reaction of beta-oxidation yields two acetyl-CoA molecules, this requires only eight rounds of beta-oxidation, producing 16 reduced coenzymes.

Tallying Total ATP Production by Fatty Acid Oxidation

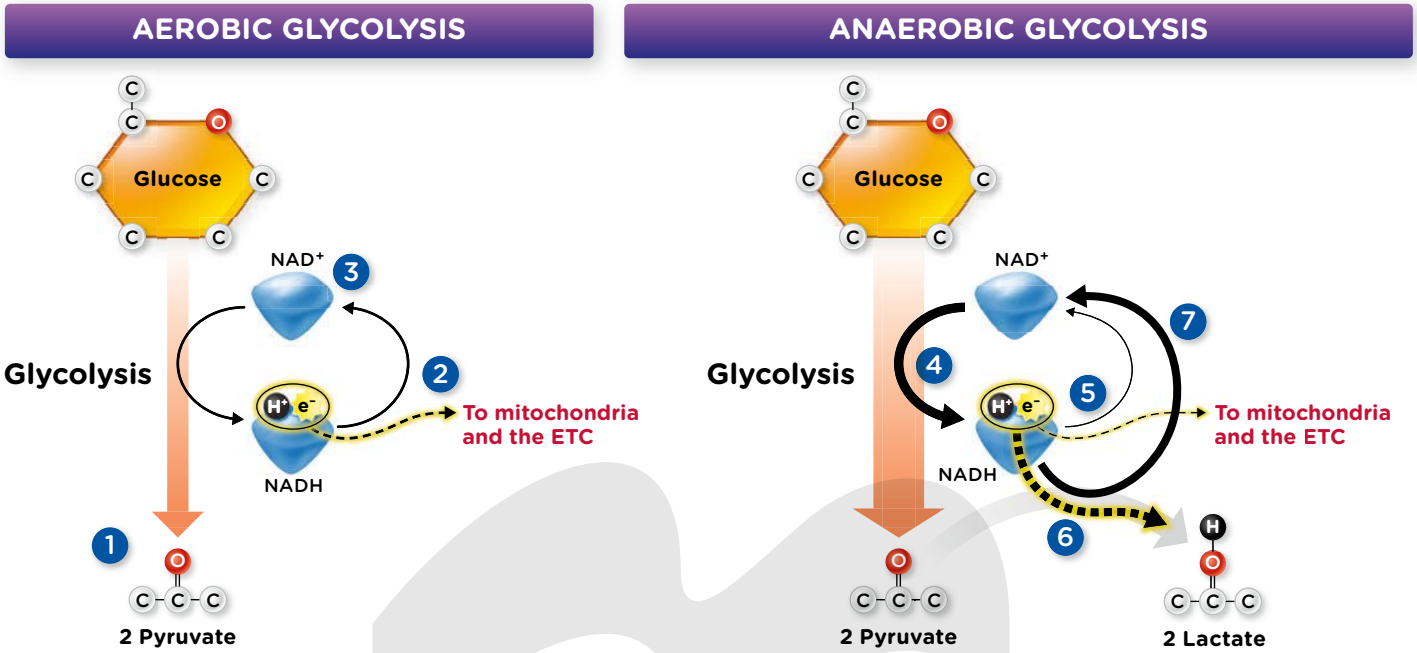
Recall that each turn of the citric acid cycle produces four reduced coenzymes and the equivalent of one ATP, so the oxidation of these nine acetyl-CoA molecules produced from an 18-carbon fatty acid will yield nine ATP and 36 reduced coenzymes. In addition, 16 coenzymes were reduced during beta-oxidation, so there is a total production of 52 reduced coenzymes. With the transfer of their high-energy electrons to the ETC the reduced coenzymes yield 113 ATP, for a total of 122 ATP produced. After subtracting the 2 ATP required for the initial activation of the fatty acid the final net yield of ATP produced from an 18-carbon fatty acid is 120 ATP.

Fat versus Glucose—ATP Production and Oxygen Consumption

The oxidation of fatty acids yields more ATP per carbon atom than is produced from glucose oxidation. Oxidation of an 18-carbon fatty acid produces a total of 120 ATP, while the oxidation of three molecules of glucose (with a total of 18 carbons) produces a total of 96 ATP ($3 \times 32 = 96$).

Although the oxidation of fats produces more ATP per carbon than is obtained from carbohydrates, it also requires a greater amount of oxygen consumption. The complete oxidation of an 18-carbon fatty acid or three molecules of glucose both produce

Aerobic Versus Anaerobic Glycolysis: *In aerobic glycolysis reduced coenzymes are oxidized by the electron transport chain, while in anaerobic glycolysis reduced coenzymes are oxidized by converting pyruvate to lactate.*



1. During glycolysis, two NAD^+'s are reduced when they each pick up a hydrogen atom (a hydrogen ion and an electron) as glucose is metabolized to pyruvate.
2. Typically, the reduced coenzymes would be oxidized in the mitochondria as they deliver the hydrogen atom into mitochondria, with the electron entering the electron transport chain (ETC).
3. This regenerates the oxidized form of the coenzyme that is needed for glycolysis to continue.
4. Under some conditions, such as during intense exercise, or when oxygen availability is limiting, glycolysis produces NADH faster than they can be oxidized back to NAD^+ by the ETC in mitochondria.
5. The limited capacity of the ETC to oxidize a sufficient number of reduced coenzymes (carrying a hydrogen atom) would cause glycolysis to slow dramatically as the availability of NAD^+ (oxidized coenzymes without a hydrogen atom) decreases.
6. To prevent this from occurring, the reduced coenzymes can donate their hydrogen atom to pyruvate to form lactate.
7. The reduction of pyruvate to lactate quickly regenerates NAD^+, allowing glycolysis to continue at a rapid rate. This is referred to as "anaerobic" glycolysis, even though it often occurs in situations where oxygen is abundant.

What are two ways that the coenzymes reduced during glycolysis can be returned to their oxidized form?

When rates of glycolysis are very high, how are the vast majority of coenzymes returned to their oxidized form?

How would the elimination of mitochondria from skeletal muscle affect both the availability of oxygen in muscle, and its reliance on anaerobic glycolysis for ATP production?

18 CO_2 molecules and 18 H_2O molecules, containing a total of 54 oxygen atoms. Because the fatty acid initially contains only two oxygen atoms this requires an input of 52 oxygen atoms, or 26 molecules of O_2, from the air we breathe. In contrast, the three molecules of glucose (with a total of 18 carbons) initially contain 18 oxygen atoms, so only 36 oxygen atoms, or 18 molecules of O_2, from the air we breathe are needed.

	Carbons	ATP produced	O_2 consumed	ATP/O_2
Three glucose molecules	18	96	18	5.3
One 18-carbon fatty acid	18	120	26	4.6

An examination of the ratio of ATP produced to oxygen consumed during carbohydrate and fat oxidation reveals that carbohydrate oxidation produces more ATP per molecule of oxygen consumed.

KETOGENESIS

When individuals undergo fasting, follow a very-low-carbohydrate diet, or have untreated type 1 diabetes, a class of compounds called *ketone bodies* are synthesized from acetyl-CoA produced by beta-oxidation in liver mitochondria. These compounds are beta-hydroxybutyrate, acetoacetate, and acetone. Ketone bodies are produced when insulin concentrations are very low and the rate of fatty acid oxidation produces acetyl-CoA faster than it can enter the citric acid cycle.

The resulting increase in acetyl-CoA concentrations in liver mitochondria causes two molecules of acetyl-CoA to be joined together, which begins the process of ketone body synthesis (also known as **ketogenesis**). As will be discussed later, the production of ketone bodies during a fast is an important metabolic adaptation, as it provides an alternative energy source for the brain that slows the catabolism and loss of body proteins.

AMINO ACID METABOLISM

Amino acids are supplied by our diet as well as by the continual breakdown of body proteins. Although most amino acids in the body are used to synthesize proteins, they are also used to synthesize a variety of other compounds. In many cases amino acid metabolism requires that they first be stripped of their amino group, and the remaining carbon skeleton has several possible fates.

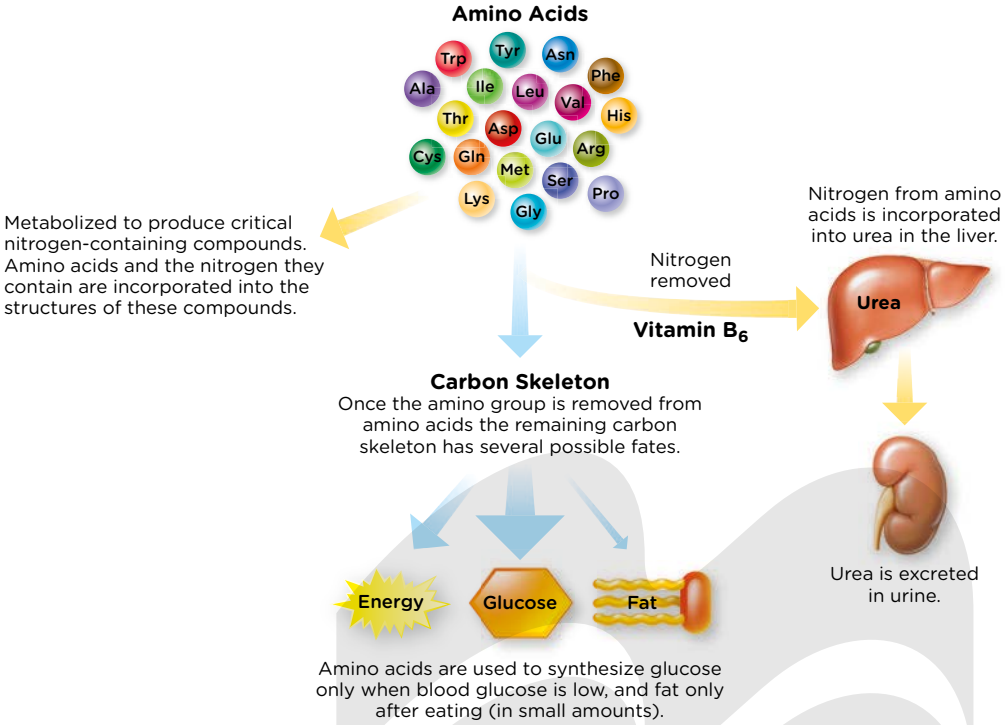
The liver is the major site of amino acid metabolism in the body. In many cases, the amino group is removed from amino acids and then transferred to other compounds in reactions that require a coenzyme (pyridoxal phosphate) synthesized from vitamin B_6. The transfer of the amino group allows nonessential amino acids to be synthesized. It also prevents the release of large quantities of the amino group, which would accumulate in the body as ammonia and is potentially toxic. Instead, the transfer of the amino group allows the liver to carefully control the release of the amino group so that the ammonia can be effectively converted into the less-toxic waste product urea. Urea is then transported in blood to the kidneys where it is filtered and then excreted in urine.

Once the amino group has been removed the remaining carbon skeleton can be used to synthesize glucose when blood glucose is low, or fatty acids when excess energy is consumed. To a lesser degree it can also be metabolized directly as a source of energy. When used as a direct energy source the carbon skeletons from various amino acids enter the citric acid cycle at several different points in the cycle where they are oxidized to produce reduced coenzymes. As we have seen with the oxidation of pyruvate and fatty acids, the majority of ATP is then produced once the high-energy electrons carried by the reduced coenzymes are transferred to the ETC. See the Amino Acid Metabolism illustration on page 11.

ALCOHOL METABOLISM

Alcohol is readily absorbed into the bloodstream through diffusion and then is transported to the body's cells and tissues and dispersed throughout the water-containing portions of the body. Approximately one-fifth of all alcohol consumed is absorbed through the stomach; the rest is absorbed in the small intestine. When consumed in moderate amounts, alcohol is metabolized primarily in the liver by a two-step process to form **acetate**. In the first step, the enzyme **alcohol dehydrogenase (ADH)** converts alcohol to

Amino Acid Metabolism *Amino acids are metabolized to produce many important compounds. When used as a source of energy or to synthesize glucose or fat, the first step in their metabolism is to remove the amino group and transfer it to another chemical compound in a reaction requiring a coenzyme synthesized from vitamin B_6.*



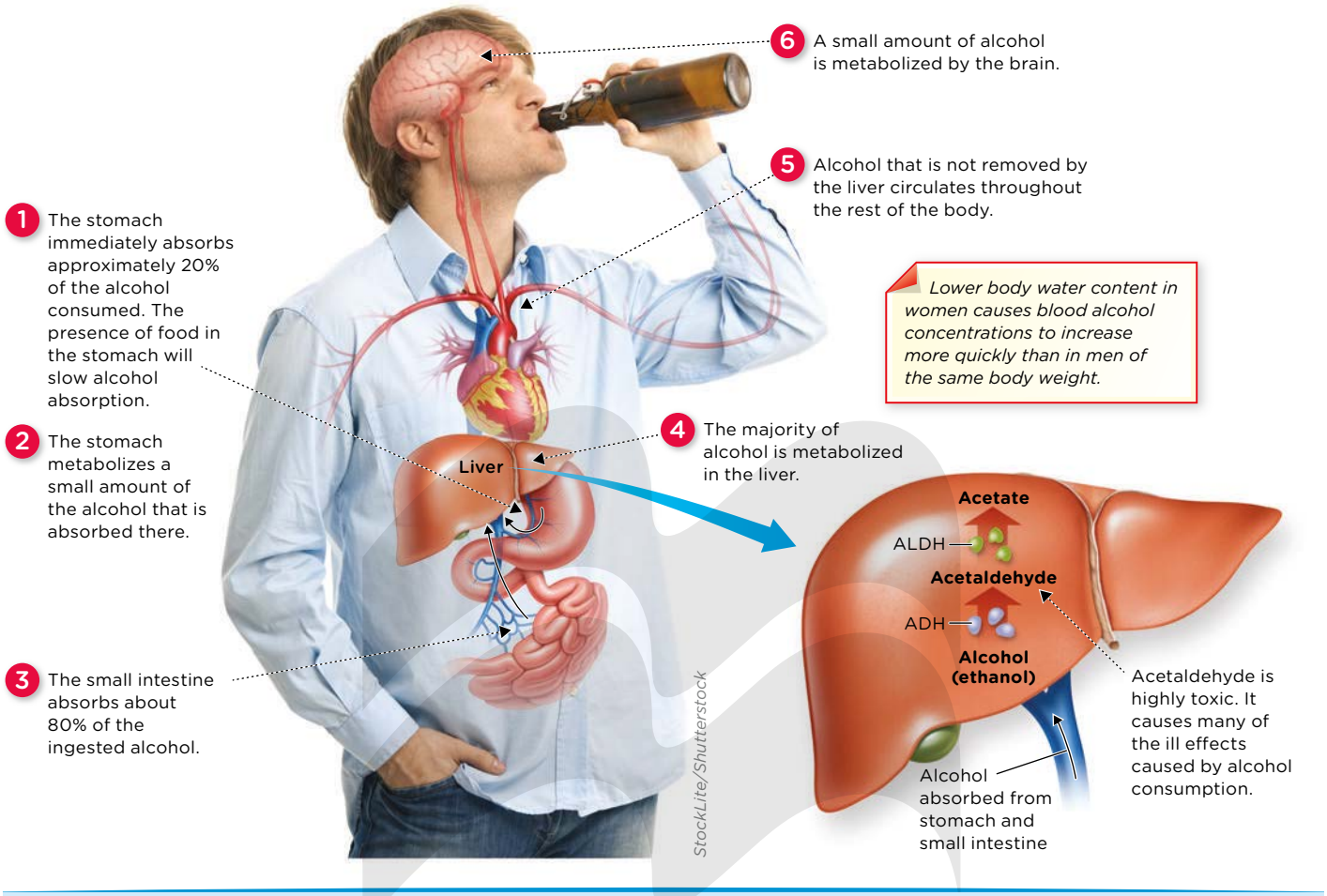
acetaldehyde, which is a highly reactive and toxic compound that can damage cellular components, including DNA. Acetaldehyde is then converted to acetate by the enzyme **acetaldehyde dehydrogenase (ALDH)**, and acetate then disperses to tissues throughout the body where it is converted to acetyl-coenzyme A, which can be used as a source of energy in the liver and elsewhere in the body. With higher levels of alcohol intake, the excessive amount of acetyl-coenzyme A that is produced in the liver results in high levels of fat synthesis that can cause a fatty liver and, eventually, liver damage. Most alcohol is metabolized to acetate in the liver, but a small amount can also be metabolized in the stomach by the same two-step process. See the Alcohol Absorption and Metabolism illustration on page 12.

The **microsomal ethanol-oxidizing system (MEOS)**, found in the endoplasmic reticulum of liver cells, is an alternative means of oxidizing alcohol (**ethanol**) to acetaldehyde. Normally this system contributes little to the metabolism of alcohol. However, the activity of this system increases with chronic consumption of high amounts of alcohol. As a result, alcohol is metabolized more quickly and alcohol concentrations in blood do not increase as much as they would under normal circumstances, which explains why tolerance of alcohol increases in those who drink frequently. The increased speed of alcohol metabolism has a downside; it also speeds production of the highly toxic acetaldehyde, which increases tissue damage and the risk of cancer.

FEASTING AND FASTING CYCLE—COORDINATING METABOLIC ADAPTATIONS IN PATHWAYS OF ENERGY METABOLISM

We all experience a daily cycle of feasting and fasting that occurs after we consume our last meal of the day, fast while we sleep, and then break our fast with our first meal the following day. This daily cycle of feasting and fasting requires pathways of energy metabolism to be carefully coordinated. Excess energy provided

Alcohol Absorption and Metabolism *Alcohol is metabolized primarily in the liver where the enzyme alcohol dehydrogenase (ADH) converts alcohol to acetaldehyde. Acetaldehyde is then converted to acetate by acetaldehyde dehydrogenase (ALDH). Acetate can either be metabolized as a source of energy-producing carbon dioxide and water, or it can be used to synthesize fat.*



Why are individuals with high rates of ADH activity and low rates of ALDH activity at low risk of alcohol use disorder?

by meals (feasting) beyond our immediate needs must be stored (anabolism) so that those stores can subsequently be mobilized (catabolism) to supply energy when fasting. Because pathways of energy storage and mobilization work in opposition to each other they must be regulated in opposite directions. This regulation is achieved largely by hormones that control the activities of key enzymes in metabolic pathways to coordinate the metabolic adaptions that accompany periods of feasting and fasting.

Insulin, **glucagon**, and **epinephrine** are the key hormones involved in the short-term regulation of the metabolic adaptations that occur with feasting and fasting. Insulin is released when meals containing carbohydrates and protein are consumed, and it is the key hormone that stimulates fuel storage. Glucagon and epinephrine are released as blood glucose concentrations drop during a fast, and they are the key hormones that stimulate fuel mobilization.

Primary Sites of Hormone Action

Insulin stimulates glycogen synthesis in the liver and muscle, and fat synthesis in the liver. It also inhibits the breakdown of glycogen, fat,

and proteins. The primary site of glucagon action is the liver, where it increases glucose production by stimulating glycogen breakdown and glucose synthesis from noncarbohydrate sources (**gluconeogenesis**). Although epinephrine is often associated with the fight-or-flight response, which requires the mobilization of fuels to supply energy to contracting muscles, it also has an important role in regulating energy metabolism during a fast. Like glucagon, epinephrine stimulates glucose production in the liver. It is also the primary hormone that stimulates the release of fatty acids from triglycerides stored in adipose tissue.

Feasting Metabolism—Fuel Storage Following a Meal

Insulin stimulates the storage of glucose as glycogen in the liver (and skeletal muscle if it has been depleted by exercise) after meals containing carbohydrates, proteins, and fats. Once glycogen stores are replenished the remaining glucose tends to be oxidized to meet the body's immediate energy needs. Insulin also stimulates the storage of fatty acids as triglycerides in adipose tissue. Generally, little glucose is used to synthesize fat, as it is more efficient to store ingested fat as triglycerides than it is to convert glucose into fatty acids. However, when carbohydrates are consumed in large excess, insulin stimulates both liver and adipose tissue to convert acetyl-CoA generated from glucose oxidation to be used to synthesize fatty acids and then store them in adipose tissue as triglycerides. The process of fatty acid synthesis is called **lipogenesis**.

Fasting Metabolism—Fuel Mobilization

Overnight Fast The principle goals of the metabolic adaptations that occur during an overnight fast are to mobilize fatty acids from triglycerides stored in adipose tissue and to maintain blood glucose concentrations. Although fatty acids can supply all the necessary energy for most tissues, the brain, red blood cells, and a few other tissues must have a steady supply of glucose to function.

As the time following the last evening meal lengthens blood glucose begins to decrease, causing insulin levels to fall and glucagon and epinephrine levels to rise. Glucagon and epinephrine stimulate the liver to breakdown glucagon to glucose and release it into blood. While these hormones also stimulate the liver to synthesize glucose (gluconeogenesis) from noncarbohydrate sources such as amino acids, this does not occur at high rates until liver glycogen has been significantly depleted.

Epinephrine also activates two lipases in adipose tissue that release fatty acids (**lipolysis**) from triglycerides stored there. Fatty acids supply the vast majority of energy for most tissues throughout the body while fasting.

Extended fast—starvation As the fast continues liver glycogen is depleted after approximately 24 hours and all glucose must be supplied by gluconeogenesis in the liver, which uses primarily the carbon skeletons from amino acids to synthesize glucose. This results in a rapid loss of skeletal muscle mass and high rates of urea production to dispose of the amino groups that have been stripped from these amino acids.

If a fast is extended and the individual moves into a state of starvation, additional adaptions occur to prolong the life. Key among these is the preservation of body proteins.

During a fast, the brain is by far the largest consumer of glucose in the body because it cannot obtain an appreciable amount of energy from fat; and the brain may account for as much as 20% of all energy used by the body. If an alternative source of energy for the brain were not available, survival time would be cut dramatically due to the rapid loss of body proteins to supply the amino acids from which to synthesize glucose.

Thankfully, the brain can also derive a significant portion of its energy needs from ketone bodies produced from fatty acids. Once the period of starvation reaches approximately 10 days, ketone bodies supply about two-thirds of the brain's total energy needs. This adaptation allows protein breakdown to slow as fewer amino acids are used for

gluconeogenesis, and this significantly prolongs survival time during starvation.

INBORN ERRORS OF METABOLISM

Inborn errors of metabolism are a group of disorders characterized by a block in a metabolic pathway. They are caused by mutations (or alterations) in the genes that direct the production of enzymes and the co-factors for metabolism. A mutation causes a gene to not function at all or function poorly. Most often these altered genes are inherited from one or more parent.

In general, the treatment of these metabolic disorders is to minimize or eliminate the buildup of toxic metabolites that result from the block in metabolism while maintaining growth and development. This may be accomplished by special modified diets, supplements, and medications. For example, in the disorder phenylketonuria (PKU) there is a defect in the gene that produces the enzyme that breaks down the amino acid phenylalanine. As a result, there is a buildup of that amino acid in the body. Individuals with PKU must limit phenylalanine in the diet for their lifetime.

Another example is maple syrup urine disease in which the body cannot break down the amino acids leucine, isoleucine, and valine. The urine of people with this condition can smell like maple syrup. Long-term treatment is a diet that is low in the problematic amino acids.