CHAPTER 7

Metabolism

THINK About It

1 You are driving on "the energy highway." You stop at the tollbooth. What kind of currency do you need to pay the toll?

2 When you think of "cell power," what comes to mind?

3 What do you think is meant by the saying "Fat burns in a flame of carbohydrate"?

4 When it comes to fasting, what's your body's first priority?

Visit nutrition.jbpub.com

EXTRACTION OF ENERGY

| Proteins (amino acids) | Carbohydrates (sugars) | Fats (fatty acids) |

Molecular building blocks

Energy

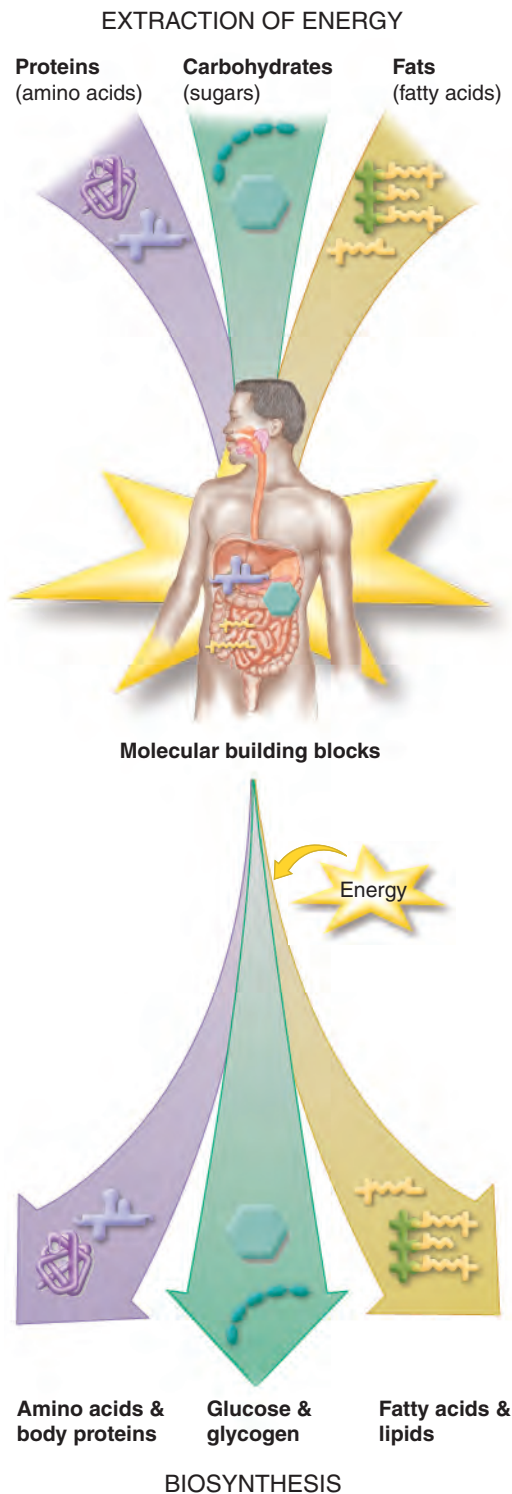| Amino acids & body proteins | Glucose & glycogen | Fatty acids & lipids |

BIOSYNTHESIS

Figure 7. **Metabolism.** Cells use metabolic reactions to extract energy from food and to form building blocks for biosynthesis.

Your body is a wonderfully efficient factory. It accepts raw materials (food), burns some to generate power, uses some to produce finished goods, routes the rest to storage, and discards waste and by-products. Constant turnover of your stored inventory keeps it fresh. Your body draws on these stored raw materials to produce compounds, and nutrient intake replenishes the supply.

Do you ever wonder how your biological factory responds to changing supply and demand? Under normal circumstances, it hums along nicely with all processes in balance. When supply exceeds demand, your body stores the excess raw materials in inventory. When supply fails to meet demand, your body draws on these stored materials to meet its needs. Your biological factory never stops; even though a storage or energy-production process may dominate, all your factory operations are active at all times.

Collectively, these processes are known as **metabolism**. (See **Figure 7.1**.) Whereas some metabolic reactions break down molecules to extract energy, others synthesize building blocks to produce new molecules. To carry out metabolic processes, thousands of chemical reactions occur every moment in cells throughout your body. The most active metabolic sites include your liver, muscle, and brain cells.

Energy: Fuel for Work

To operate, machines need energy. Cars use gasoline for fuel, factory machinery uses electricity, and windmills rely on wind power. So what about you? All cells require energy to sustain life. Even during sleep, your body uses energy for breathing, pumping blood, maintaining body temperature, delivering oxygen to tissues, removing waste products, synthesizing new tissue for growth, and repairing damaged or worn-out tissues. When awake, you need additional energy for physical movement (such as standing, walking, and talking) and for the digestion and absorption of foods.

Where does the energy come from to power your body's "machinery"? Biological systems use heat, mechanical, electrical, and chemical forms of energy. Our cells get their energy from **chemical energy** held in the molecular bonds of carbohydrates, fats, and protein—the energy macronutrients—as well as alcohol. The chemical energy in foods and beverages originates as light energy from the sun. Green plants use light energy to make carbohydrate in a process called **photosynthesis**. In photosynthesis, carbon dioxide (CO_2) from the air combines with water (H_2O) from the earth to form a carbohydrate, usually glucose ($C_6H_{12}O_6$), and oxygen (O_2). Plants store glucose as starch and release oxygen into the atmosphere. Plants such as corn, peas, squash, turnips, potatoes, and rice store especially high amounts of starch in their edible parts. In the glucose molecule, the chemical bonds between the carbon (C) and hydrogen (H) atoms hold energy from the sun.[1] When our bodies extract energy from food and convert it to a form that our cells can use, we lose more than half of the total food energy as heat.[2]

Within any system (including the universe), the total amount of energy is constant. Although energy can change from one form to another and can move from one location to another, the system never gains or loses energy. This principle, called the first law of thermodynamics, is known as conservation of energy.

Transferring Food Energy to Cellular Energy

Although burning food releases energy as heat, we cannot use heat to power the many cellular functions that maintain life. Rather than using combustion,

we transfer energy from food to a form that our cells can use. (See **Figure 7.2**.) This transfer is not completely efficient; we lose roughly half of the total food energy as heat as our bodies extract energy from food in three stages:[3]

> *Stage 1: Digestion, absorption, and transportation.* Digestion breaks food down into small subunits—simple sugars, fatty acids, monoglycerides, glycerol, and amino acids—that the small intestine can absorb. The circulatory system then transports these nutrients to tissues throughout the body.
>
> *Stage 2: Breakdown of many small molecules to a few key metabolites.* Inside individual cells, chemical reactions convert simple sugars, fatty acids, glycerol, and amino acids into a few key **metabolites** (products of metabolic reactions). This process liberates a small amount of usable energy.

metabolism All chemical reactions within organisms that enable them to maintain life. The two main categories of metabolism are catabolism and anabolism.

chemical energy Energy contained in the bonds between atoms of a molecule.

photosynthesis The process by which green plants use radiant energy from the sun to produce carbohydrates (hexoses) from carbon dioxide and water.

metabolites Any substances produced during metabolism.

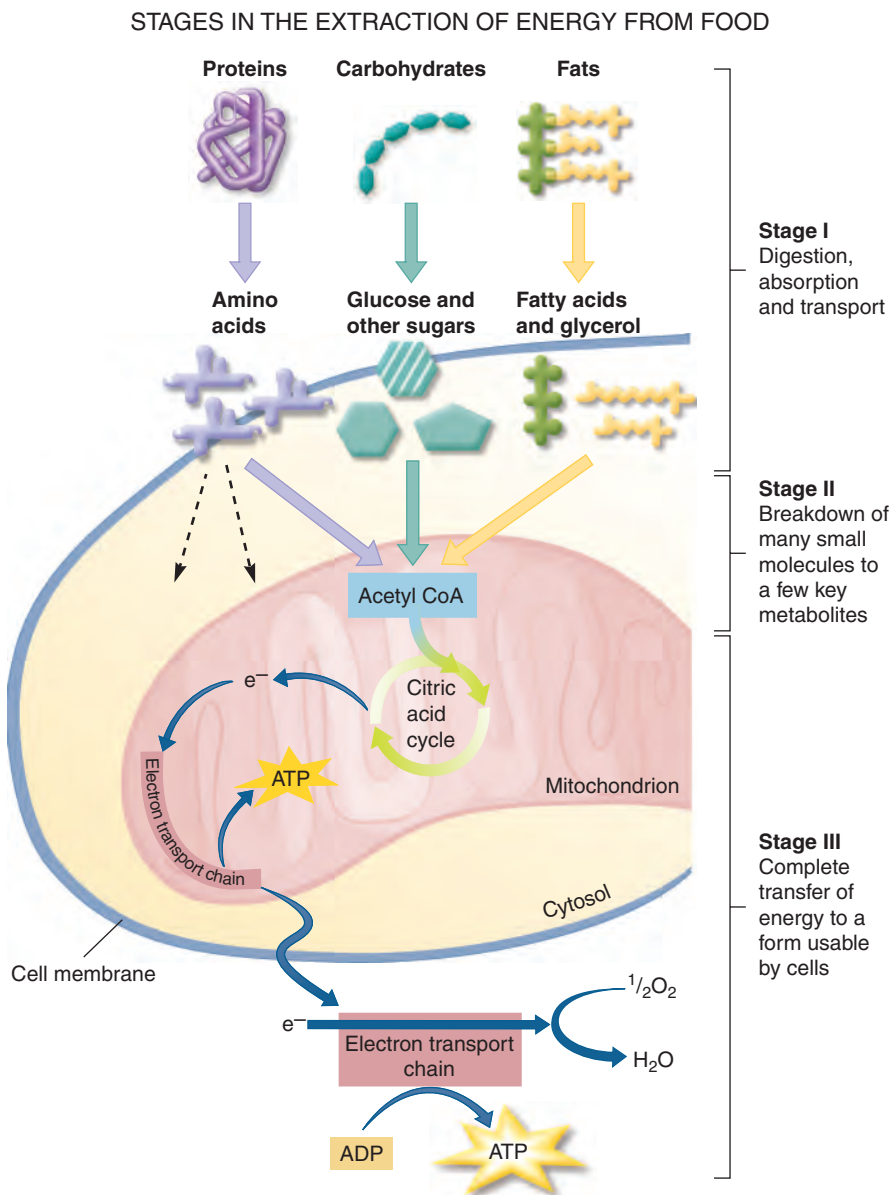STAGES IN THE EXTRACTION OF ENERGY FROM FOOD

Figure 7.2   **Energy extraction from food.** In the first stage, the body breaks down food into amino acids, monosaccharides, and fatty acids. In the second stage, cells degrade these molecules to a few simple units, such as acetyl CoA, that are pervasive in metabolism. In the third stage, the oxygen-dependent reactions of the citric acid cycle and electron transport chain liberate large amounts of energy in the form of ATP.

metabolic pathway A series of chemical reactions that either break down a large compound into smaller units (catabolism) or synthesize more complex molecules from smaller ones (anabolism).

catabolism [ca-TA-bol-iz-um] Any metabolic process whereby cells break down complex substances into simpler, smaller ones.

anabolism [an-A-bol-iz-um] Any metabolic process whereby cells convert simple substances into more complex ones.

cells The basic structural units of all living tissues, which have two major parts: the nucleus and the cytoplasm.

nucleus The primary site of genetic information in the cell, enclosed in a double-layered membrane. The nucleus contains the chromosomes and is the site of messenger RNA (mRNA) and ribosomal RNA (rRNA) synthesis, the "machinery" for protein synthesis in the cytosol.

cytoplasm The material of the cell, excluding the cell nucleus and cell membranes. The cytoplasm includes the semifluid cytosol, the organelles, and other particles.

cytosol The semifluid inside the cell membrane, excluding organelles. The cytosol is the site of glycolysis and fatty acid synthesis.

organelles Various membrane-bound structures that form part of the cytoplasm. Organelles, including mitochondria and lysosomes, perform specialized metabolic functions.

mitochondria (mitochondrion) The sites of aerobic production of ATP, where most of the energy from carbohydrate, protein, and fat is captured. Called the "power plants" of the cell, the mitochondria contain two highly specialized membranes, an outer membrane and a highly folded inner membrane, that separate two compartments, the internal matrix space and the narrow intermembrane space. A human cell contains about 2,000 mitochondria.

Stage 3: Transfer of energy to a form that cells can use. The complete breakdown of metabolites to carbon dioxide and water liberates large amounts of energy. The reactions during this stage are responsible for converting more than 90 percent of the available food energy to a form that our bodies can use.

What Is Metabolism?

Metabolism is a general term that encompasses all chemical changes occurring in living organisms. The term **metabolic pathway** describes a series of chemical reactions that either break down a large compound into smaller units (**catabolism**) or build more complex molecules from smaller ones (**anabolism**).[4] For example, when you eat bread or rice, the GI tract breaks down the starch into glucose units. Cells can further catabolize these glucose units to release energy for activities such as muscle contractions. Conversely, anabolic reactions take available glucose molecules and assemble them into glycogen for storage. **Figure 7.3** illustrates catabolism and anabolism.

Metabolic pathways are never completely inactive. Their activity continually ebbs and flows in response to internal and external events. Imagine, for example, that your instructor keeps you late and you have only five minutes to get to your next class. As you hustle across campus, your body ramps up energy production to fuel the demand created by your rapidly contracting muscles. As you sit in your next class, your body continues to break down and extract glucose from the banana you recently ate. Your body assembles the glucose into branched chains to replenish the glycogen stores you depleted while running across campus.

The Cell Is the Metabolic Processing Center

Cells are the "work centers" of metabolism. (See **Figure 7.4**.) Although our bodies are made up of different types of cells (e.g., liver cells, brain cells, kid-
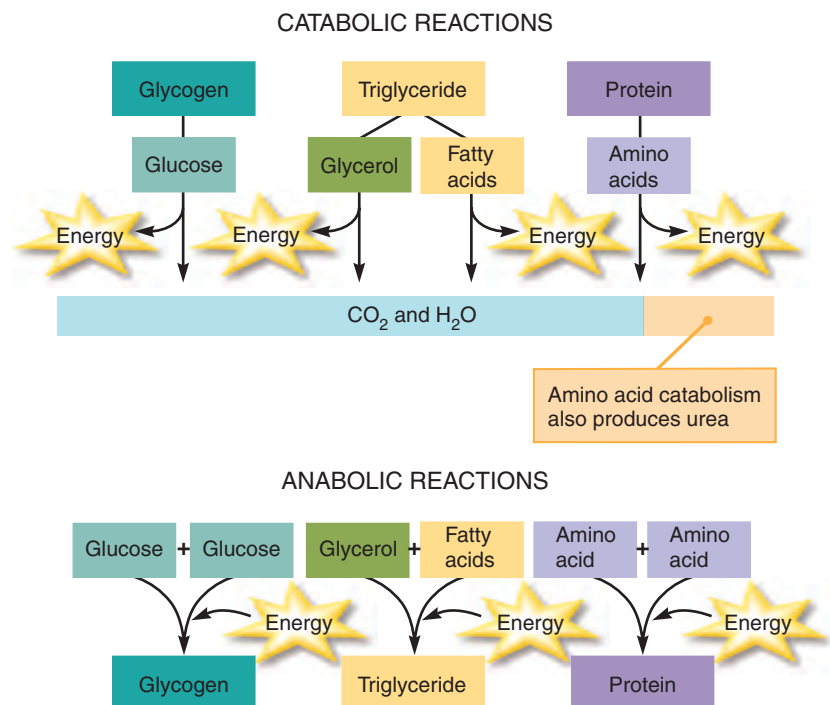

Figure 7.3 **Catabolism and anabolism.** Catabolic reactions break down molecules and release energy and other products. Anabolic reactions consume energy as they assemble complex molecules.

ney cells, muscle cells), most have a similar structure. The basic animal cell has two major parts: the cell **nucleus** and a membrane-enclosed space called the **cytoplasm**. As we zoom in for a closer look, we see that the semifluid **cytosol** fills the cytoplasm. Floating in the cytosol are many organelles, small units that perform specialized metabolic functions. A large number of these **organelles**—the capsule-like **mitochondria**—are power generators that contain many important energy-producing pathways.

Figure 7.4	**Cell structure.** Liver cells, brain cells, kidney cells, muscle cells, and so forth all have a similar structure.

Organelles
Endoplasmic reticulum (ER)
- An extensive membrane system extending from the nuclear membrane.
- Rough ER: The outer membrane surface contains ribosomes, the site of protein synthesis.
- Smooth ER: Devoid of ribosomes, the site of lipid synthesis.

Golgi apparatus
- A system of stacked membrane-encased discs.
- The site of extensive modification, sorting and packaging of compounds for transport.

Lysosome
- Vesicle containing enzymes that digest intracellular materials and recycle the components.

Mitochondrion
- Contains two highly specialized membranes, an outer membrane and a highly folded inner membrane. Membranes separated by narrow intermembrane space. Inner membrane encloses space called mitochondrial matrix.
- Often called the power plant of the cell. Site where most of the energy from carbohydrate, protein, and fat is captured in ATP (adenosine triphosphate).
- About 2,000 mitochondria in a cell.

Ribosome
- Site of protein synthesis.

Nucleus
- Contains genetic information in the base sequences of the DNA strands of the chromosomes.
- Site of RNA synthesis – RNA needed for protein synthesis.
- Enclosed in a double-layered membrane.

Cytoplasm
- Enclosed in the cell membrane and separated from the nucleus by the nuclear membrane.
- Filled with particles and organelles, which are dispersed in a clear semifluid called cytosol.
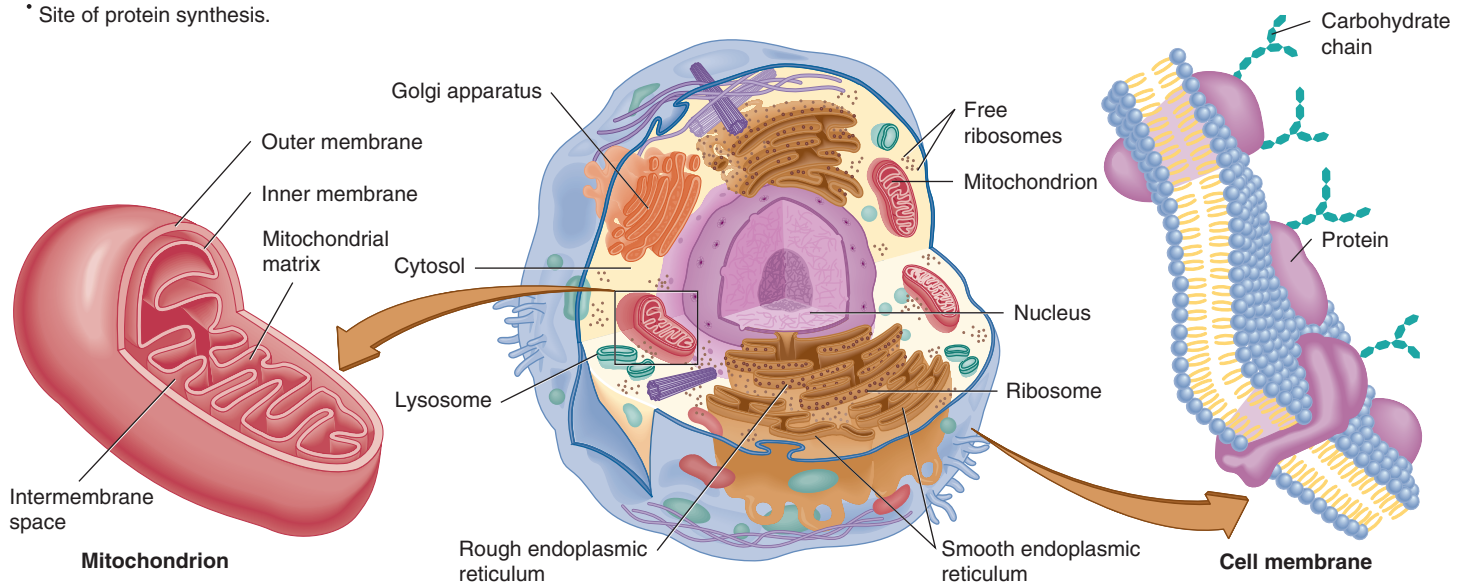
Cytosol
- The semifluid inside the cell membrane.
- Site of glycolysis and fatty acid synthesis.

Cell membrane
- A double-layered sheet, made up of lipid and protein, that encases the cell.
- Controls the passage of substances in and out of the cell.
- Contains receptors for hormones and other regulatory compounds.

Golgi apparatus · Outer membrane · Inner membrane · Mitochondrial matrix · Cytosol · Lysosome · Intermembrane space · **Mitochondrion** · Rough endoplasmic reticulum · Free ribosomes · Mitochondrion · Nucleus · Ribosome · Smooth endoplasmic reticulum · Carbohydrate chain · Protein · **Cell membrane**

Quick Bite

Key Players in the Energy Game

Each of the "key players" in the energy game has a common acronym by which it is usually called:

ATP: adenosine triphosphate
NAD$^+$: nicotinamide adenine dinucleotide (oxidized)
NADH: nicotinamide adenine dinucleotide (reduced)
NADP$^+$: nicotinamide adenine dinucleotide phosphate (oxidized)
NADPH: nicotinamide adenine dinucleotide phosphate (reduced)
FAD$^+$: flavin adenine dinucleotide (oxidized)
FADH$_2$: flavin adenine dinucleotide (reduced)

cofactors Compounds required for an enzyme to be active. Cofactors include coenzymes and metal ions such as iron (Fe^{2+}), copper (Cu^{2+}), and magnesium (Mg^{2+}).

coenzymes Organic compounds, often B vitamin derivatives, that combine with an inactive enzyme to form an active enzyme. Coenzymes associate closely with these enzymes, allowing them to catalyze certain metabolic reactions in a cell.

adenosine triphosphate (ATP) [ah-DEN-oh-seen try-FOS-fate] A high-energy compound that is the main direct fuel that cells use to synthesize molecules, contract muscles, transport substances, and perform other tasks.

NADH The reduced form of nicotinamide adenine dinucleotide (NAD$^+$). This coenzyme, derived from the B vitamin niacin, acts as an electron carrier in cells, and undergoes reversible oxidation and reduction.

FADH2 The reduced form of flavin adenine dinucleotide (FAD). This coenzyme, which is derived from the B vitamin riboflavin, acts as an electron carrier in cells and undergoes reversible oxidation and reduction.

NADPH The reduced form of nicotinamide adenine dinucleotide phosphate. This coenzyme, which is derived from the B vitamin niacin, acts as an electron carrier in cells, undergoing reversible oxidation and reduction. The oxidized form is NADP$^+$.

To remember the major parts of a cell, think about a bowl of thick vegetable soup with a single meatball floating in it. For our example, think of the broth as having a runny, jellylike consistency and the bowl as a thin flexible structure with the consistency of a wet paper bag. The bowl surrounds and holds the mixture, similar to the way a cell membrane encloses a cell. The meatball represents the cell nucleus, and the remaining mixture is the cytoplasm. This cytoplasmic soup is made up of a thick, semiliquid fluid (cytosol) and vegetables (organelles). Among the vegetables, think of those kidney beans as mitochondria.

Enzymes, which are catalytic proteins, speed up chemical reactions in metabolic pathways. Many enzymes are inactive unless they are combined with certain smaller molecules called **cofactors**, which usually are derived from a vitamin or mineral. Vitamin-derived cofactors are also called **coenzymes**. All the B vitamins form coenzymes used in metabolic reactions. (For more on coenzymes, see Chapter 11, "Water-Soluble Vitamins.")

Key Concepts *Metabolism encompasses the many reactions that take place in cells to build tissue, produce energy, break down compounds, and do other cellular work. Anabolism refers to reactions that build compounds, such as protein or glycogen. Catabolism is the breakdown of compounds to yield energy. Mitochondria, the power plants within cells, contain many of the breakdown pathways that produce energy.*

Who Are the Key Energy Players?

Certain compounds have recurring roles in metabolic activities. **Adenosine triphosphate (ATP)** is the fundamental energy molecule used to power cellular functions, so it is known as the universal energy currency. Two other molecules, **NADH** and **FADH$_2$**, are important couriers that carry energy for the synthesis of ATP. A similar energy carrier, **NADPH**, delivers energy for **biosynthesis**.

THINK
About It
1

ATP: The Body's Energy Currency

To power its needs, your body must convert the energy in food to a readily usable form—ATP. This universal energy currency kick-starts many energy-releasing processes, such as the breakdown of glucose and fatty acids, and powers energy-consuming processes, such as building glucose from other compounds. Remember that making large molecules from smaller ones, like constructing a building from bricks, requires energy.

Production of ATP is the fundamental goal of metabolism's energy-producing pathways. Just as the ancient Romans could claim that all roads lead to Rome, you can say that, with a few exceptions, your body's energy-producing pathways lead to ATP production.

The ATP molecule has three phosphate groups attached to adenosine, which is an organic compound. Because breaking the bonds between the phosphate groups releases a tremendous amount of energy, ATP is an energy-rich molecule. (See **Figure 7.5**.) Cells can use this energy to power biological work. When a metabolic reaction breaks the first phosphate bond, it breaks down ATP to **adenosine diphosphate (ADP)** and **pyrophosphate (P$_i$)**. Breaking the remaining phosphate bond releases an equal amount of energy and breaks down ADP to **adenosine monophosphate (AMP)** and P$_i$.

Because the reaction can proceed in either direction, ATP and ADP are interconvertible, as **Figure 7.6** shows. When extracting energy from carbohy-
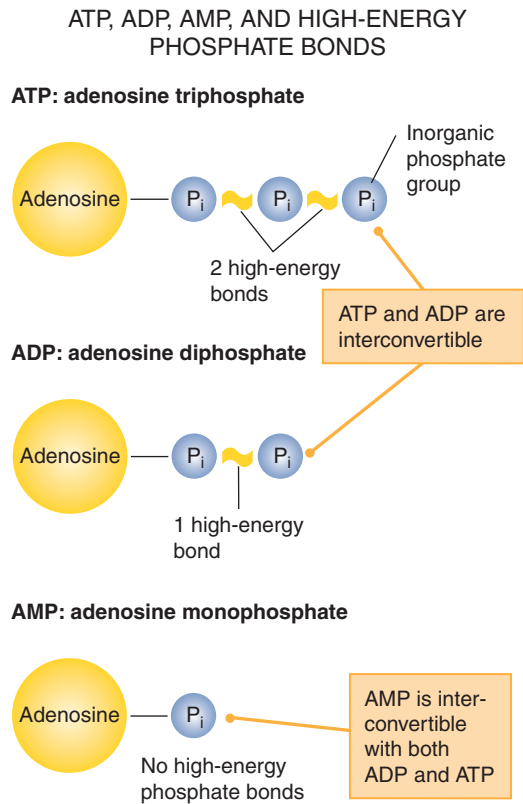
ATP, ADP, AMP, AND HIGH-ENERGY PHOSPHATE BONDS

ATP: adenosine triphosphate

ADP: adenosine diphosphate

AMP: adenosine monophosphate

Figure 7.5 **ATP, ADP, and AMP.** Your body can readily use the energy in high-energy phosphate bonds. During metabolic reactions, phosphate bonds form or break to capture or release energy.

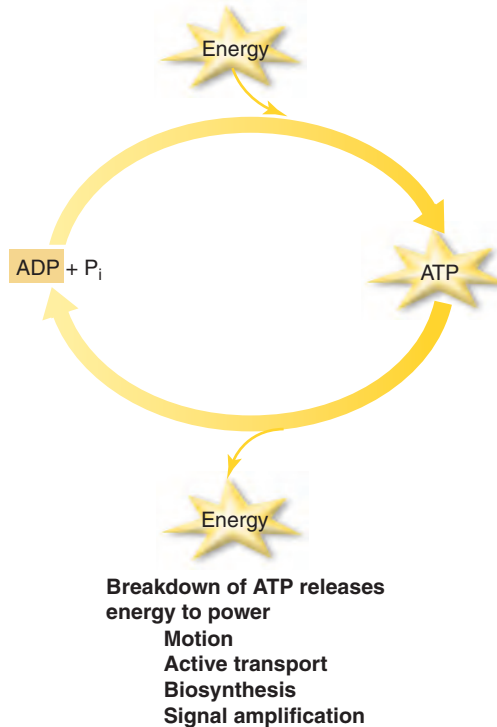**Formation of ATP captures energy from the oxidation of energy nutrients**

Breakdown of ATP releases energy to power
Motion
Active transport
Biosynthesis
Signal amplification

Figure 7.6 **The ADP–ATP cycle.** When extracting energy from nutrients, the formation of ATP from ADP + P$_i$ captures energy. Breaking a phosphate bond in ATP to form ADP + P$_i$ releases energy for biosynthesis and work.

ATP   Adenosine–P~P~P

GTP   Guanosine–P~P~P

drate, protein, and fat, ADP binds P$_i$, forming a phosphate bond and capturing energy in a new ATP molecule. When the reaction flows in the opposite direction, ATP releases P$_i$, breaking a phosphate bond and liberating energy while re-forming ADP. This liberated energy can power biological activities such as motion, active transport across cell membranes, biosynthesis, and signal amplification.

The body's pool of ATP is a small, immediately accessible energy reservoir rather than a long-term energy reserve. The typical lifetime of an ATP molecule is less than one minute, and ATP production increases or decreases in direct relation to energy needs. At rest, you use about 40 kilograms of ATP in 24 hours (an average rate of about 28 grams per minute). In contrast, if you are exercising strenuously, you can use as much as 500 grams per minute! On average, you turn over your body weight in ATP every day.[5]

The molecule **guanosine triphosphate (GTP)** is similar to ATP and holds the same amount of available energy. Like ATP, GTP has high-energy phosphate bonds and three phosphate groups, but they are linked to guanosine rather than to adenosine. Energy-rich GTP molecules are crucial for vision and supply part of the power needed to synthesize protein and glucose. GTP readily converts to ATP.

biosynthesis Chemical reactions that form simple molecules into complex biomolecules, especially carbohydrate, lipids, protein, nucleotides, and nucleic acids.

adenosine diphosphate (ADP) The compound produced upon hydrolysis of ATP, and used to synthesize ATP. Composed of adenosine and two phosphate groups.

pyrophosphate (Pi) Inorganic phosphate. This high-energy phosphate group is an important component of ATP, ADP, and AMP.

adenosine monophosphate (AMP) Hydrolysis product of ADP and of nucleic acids. Composed of adenosine and one phosphate group.

guanosine triphosphate (GTP) A high-energy compound, similar to ATP, but with three phosphate groups linked to guanosine.

$$NAD^+ + 2H^+ \leftrightarrow NADH + H^+$$
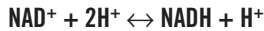
NADH carries two high-energy electrons

$$FAD + 2H^+ \leftrightarrow FADH_2$$
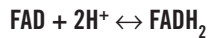
FADH$_2$ carries two high-energy electrons

$$NADPH + H^+ \leftrightarrow NADP^+ + 2H^+$$

NADPH releases energy for biosynthesis when converted to NADP$^+$

nicotinamide adenine dinucleotide (NAD+) The oxidized form of nicotinamide adenine dinucleotide. This coenzyme, which is derived from the B vitamin niacin, acts as an electron carrier in cells, undergoing reversible oxidation and reduction. The reduced form is NADH.

hydrogen ions Also called a proton. This lone hydrogen has a positive charge (H$^+$). It does not have its own electron, but it can share one with another atom.

flavin adenine dinucleotide (FAD) A coenzyme synthesized in the body from riboflavin. It undergoes reversible oxidation and reduction and thus acts as an electron carrier in cells. FAD is the oxidized form; FADH$_2$ is the reduced form.

glycolysis [gligh-COLL-ih-sis] The anaerobic metabolic pathway that breaks a glucose molecule into two molecules of pyruvate and yields two molecules of ATP and two molecules of NADH. Glycolysis occurs in the cytosol of a cell.

NADH and FADH$_2$: The Body's Energy Shuttles

When breaking down nutrients, metabolic reactions release high-energy electrons. Further reactions transfer energy from these electrons to ATP. (See **Figure 7.7**.) To reach the site of ATP production, high-energy electrons hitch a ride on special molecular carriers. One major electron acceptor is **nicotinamide adenine dinucleotide (NAD$^+$)**, a derivative of the B vitamin niacin. The metabolic pathways have several energy-transfer points where an NAD$^+$ accepts two high-energy electrons and two **hydrogen ions** (two protons [2H$^+$]) to form NADH + H$^+$. For simplicity, the "+ H$^+$" is often dropped when talking about NADH.

The other major electron acceptor is **flavin adenine dinucleotide (FAD)**, a derivative of the B vitamin riboflavin. When FAD accepts two high-energy electrons, it picks up two protons (2H$^+$) and forms FADH$_2$.

NADPH: An Energy Shuttle for Biosynthesis

Energy powers the assembly of building blocks into complex molecules of carbohydrate, fat, and protein. NADPH, an energy-carrying molecule similar to NADH, delivers much of the energy these biosynthetic reactions require. The only structural difference between NADPH and NADH is the presence or absence of a phosphate group. Although both molecules are energy carriers, their metabolic roles are vastly different. Whereas the energy carried by NADH primarily produces ATP, nearly all the energy carried by NADPH drives biosynthesis. When a reaction transforms NADPH into NADP$^+$ (nicotinamide adenine dinucleotide phosphate), NADPH releases its cargo of two energetic electrons.

Key Concepts *ATP is the energy currency of the body. Your body extracts energy from food to produce ATP. NADH and FADH$_2$ are hydrogen and electron carriers that shuttle energy to ATP production sites. NADPH is also a hydrogen and electron carrier, but it shuttles energy for anabolic processes.*
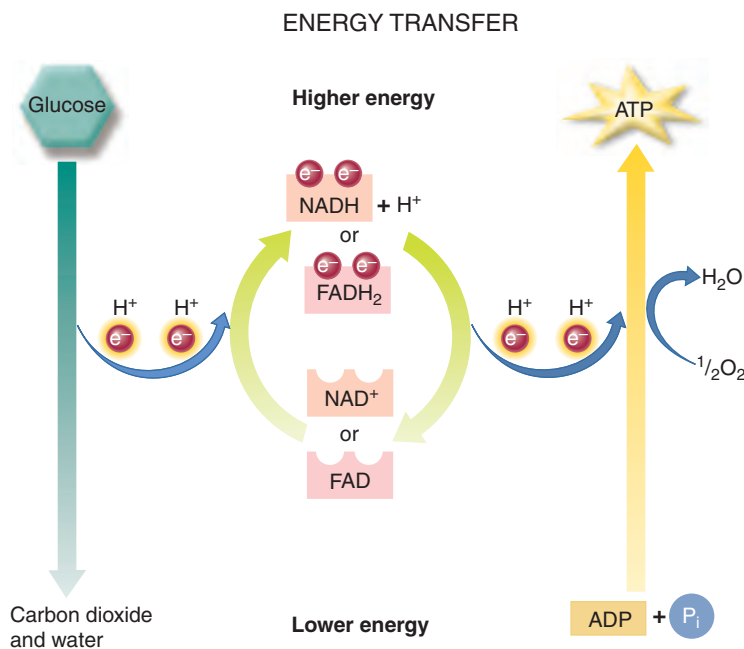
ENERGY TRANSFER

Figure 7.7 **Energy transfer**. As energy moves from glucose to ATP, molecules become high-energy or low-energy as they collect and transfer high-energy electrons and hydrogen ions (protons).

Breakdown and Release of Energy

The complete catabolism of carbohydrate, protein, and fat for energy occurs via several pathways. Although different pathways initiate the breakdown of these nutrients, complete breakdown eventually proceeds along two shared catabolic pathways—the citric acid cycle and the electron transport chain. This section first describes the pathways that catabolize glucose. It then discusses the steps that start the breakdown of fat and protein.

Extracting Energy from Carbohydrate

Cells extract usable energy from carbohydrate via four main pathways: glycolysis, conversion of pyruvate to acetyl CoA, the citric acid cycle, and the electron transport chain. (See **Figure 7.8**.) Although glycolysis and the citric acid cycle produce small amounts of energy, the electron transport chain is the major ATP production site.

Glycolysis

Glycolysis ("glucose splitting") is an **anaerobic** process; that is, it does not require oxygen. In the cytosol, this sequence of reactions splits each 6-carbon glucose molecule into two 3-carbon **pyruvate** molecules while producing a relatively small amount of energy.

Just as a pump requires priming, glycolysis requires the input of two ATP molecules to get started. In the later stages, various reactions produce energy-rich molecules of NADH and release four ATP molecules. Although glycolysis both consumes and releases energy, it produces more than it uses. Glycolysis is rapid, but it produces a comparatively small amount of ATP. The glycolysis of one glucose molecule yields a net of two NADH and two ATP, along with the two pyruvates. (See **Figure 7.9**.)

Although most glycolytic reactions can flow in either direction, some are irreversible, one-way reactions. These one-way reactions prevent glycolysis from running backward.

What about the other simple sugars, fructose and galactose? In liver cells, glycolysis usually breaks them down, and normally they are not available to other tissues.[6] Although fructose and galactose enter glycolysis at intermediate points, the end result is the same as for glucose. One molecule of glucose, fructose, or galactose produces two NADH, a net of two ATP, and two pyruvates. Once glycolysis is complete, the pyruvate molecules easily pass from the cytosol to the interior of mitochondria, the cell's power generators, for further processing.

Conversion of Pyruvate to Acetyl CoA

When a cell requires energy, and oxygen is readily available, **aerobic** reactions in the mitochondria convert each pyruvate molecule to an **acetyl CoA** molecule. These reactions produce CO_2 and transfer a pair of high-energy electrons to form NADH. (See **Figure 7.10**.) The NADH shuttle carries the electrons to the electron transport chain.

Although many metabolic pathways can proceed either forward or backward, the formation of acetyl CoA is a one-way (irreversible) process. To form

anaerobic [AN-ah-ROW-bic] Referring to the absence of oxygen or the ability of a process to occur in the absence of oxygen.

pyruvate The three-carbon compound that results from glycolytic breakdown of glucose. Pyruvate, the salt form of pyruvic acid, also can be derived from glycerol and some amino acids.

aerobic [air-ROW-bic] Referring to the presence of or need for oxygen. The complete breakdown of glucose, fatty acids, and amino acids to carbon dioxide and water occurs only via aerobic metabolism. The citric acid cycle and electron transport chain are aerobic pathways.

acetyl CoA A key intermediate in the metabolic breakdown of carbohydrates, fatty acids, and amino acids. It consists of a two-carbon acetate group linked to coenzyme A, which is derived from pantothenic acid.
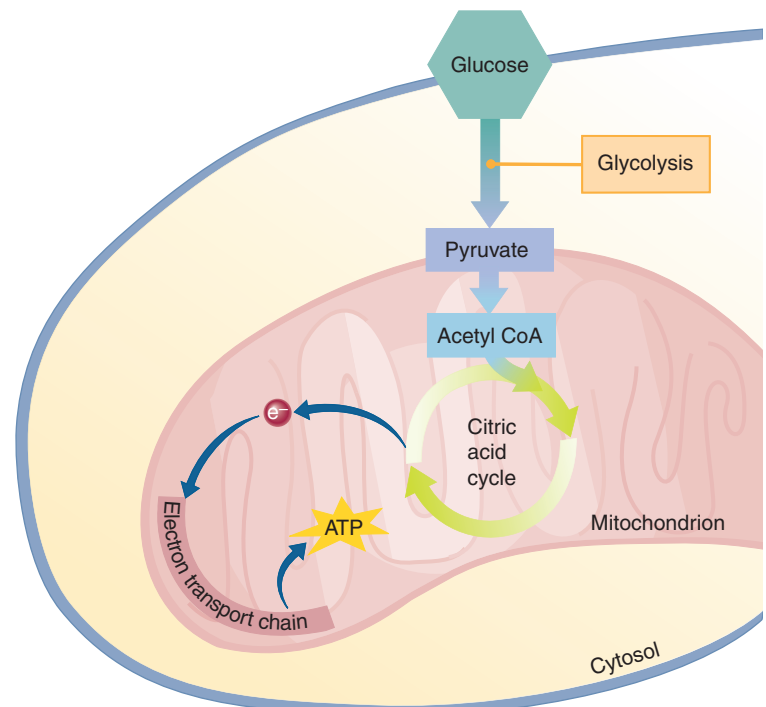

Figure 7.8 **Obtaining energy from carbohydrate.** The complete oxidation of glucose uses four major metabolic pathways: glycolysis, conversion of pyruvate to acetyl CoA, the citric acid cycle, and the electron transport chain. Glycolysis takes place in the cytosol. The remaining reactions take place in the mitochondria.

coenzyme A Coenzyme A is a cofactor derived from the vitamin pantothenic acid.

lactate The ionized form of lactic acid, a three-carbon acid. It is produced when insufficient oxygen is present in cells to oxidize pyruvate.

acetyl CoA, reactions remove one carbon from the three-carbon pyruvate and add **coenzyme A**, a molecule derived from the B vitamin pantothenic acid. After combining with oxygen, the carbon is released as part of carbon dioxide. Recall that glycolysis splits glucose into two pyruvate molecules, so we now have two NADH and two acetyl CoA molecules.

In rapidly contracting muscle, oxygen is in short supply, and pyruvate cannot form acetyl CoA. Instead, pyruvate is rerouted to form **lactate**, another three-carbon compound. Lactate is an alternative fuel that muscle cells can

Quick Bite

When Glycolysis Goes Awry

Red blood cells do not have mitochondria, so they rely on glycolysis as their only source of ATP. They use ATP to maintain the integrity and shape of their cell membranes. A defect in red blood cell glycolysis can cause a shortage of ATP, which leads to deformed red blood cells. Destruction of these cells by the spleen leads to a type of anemia called hemolytic anemia.
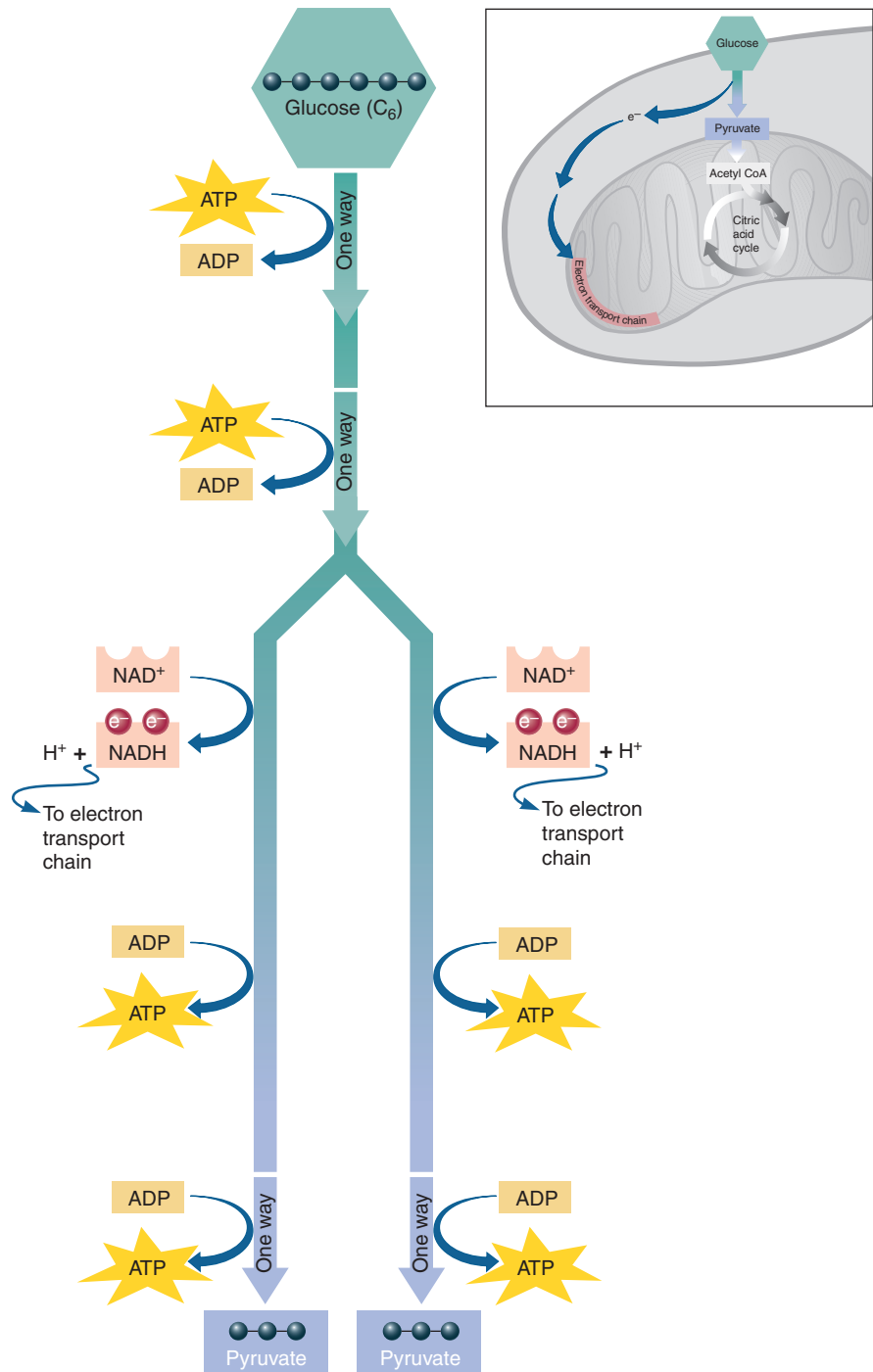

Figure 7.9 **Glycolysis.** The breakdown of one glucose molecule yields two pyruvate molecules, a net of two ATP and two NADH molecules. The two NADH molecules shuttle pairs of high-energy electrons to the electron transport chain for ATP production. Glycolytic reactions do not require oxygen, and some steps are irreversible.

Figure 7.10 **Conversion of pyruvate to acetyl CoA.** When oxygen is readily available, each pyruvate formed from glucose yields one acetyl CoA, one CO_2, and one NADH. The NADH shuttles high-energy electrons to the electron transport chain for ATP production.
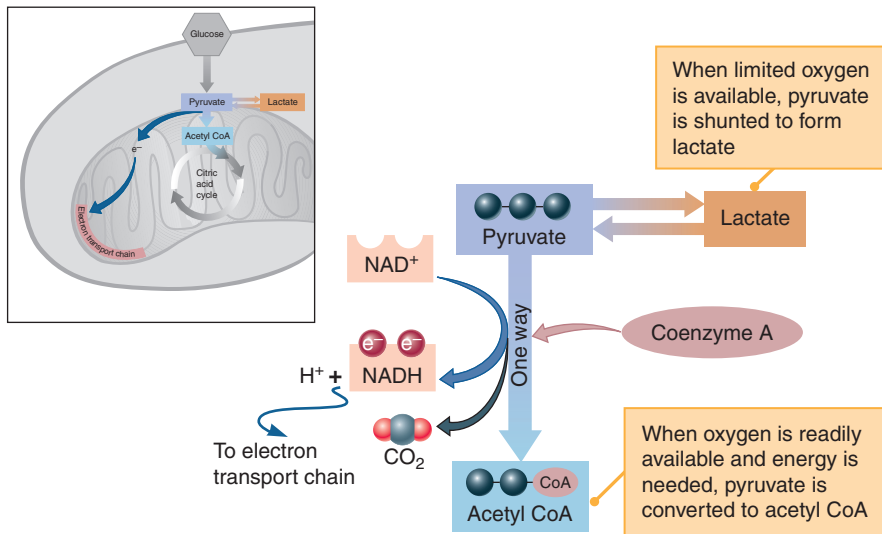
use or that liver cells can convert to glucose. When oxygen again becomes readily available, lactate is converted back to pyruvate, which irreversibly forms acetyl CoA. You will learn more about lactate production, cycling, and use in Chapter 14, "Sports Nutrition."

Although pyruvate passes easily between the cytosol and the mitochondria, the mitochondrial membrane is impervious to acetyl CoA. The acetyl CoA produced from pyruvate is trapped inside the mitochondria, ready to enter the citric acid cycle.

Citric Acid Cycle

The **citric acid cycle** is an elegant set of reactions that proceed along a circular pathway in the mitochondria. To begin the cycle, acetyl CoA combines with **oxaloacetate**, freeing coenzyme A and yielding a six-carbon compound called citrate (citric acid). The coenzyme A leaves the cycle, becoming available to react with another pyruvate and form a new acetyl CoA. Subsequent reactions in the citric acid cycle transform citrate into a sequence of intermediate compounds as they remove two carbons and release them in two molecules of CO_2. Because acetyl CoA adds two carbons to the cycle and the cycle releases two carbons as CO_2, there is no net gain or loss of carbon atoms. The final step in the citric acid cycle regenerates oxaloacetate.

The citric acid cycle extracts most of the energy that ultimately powers the generation of ATP. For each acetyl CoA entering the cycle, one complete "turn" produces one GTP and transfers pairs of high-energy electrons to three NADH and one $FADH_2$. Because the breakdown of one glucose molecule yields two molecules of acetyl CoA, the citric acid cycle "turns" twice for each glucose molecule and produces twice these amounts (i.e., six NADH, two $FADH_2$, and two GTP).

The citric acid cycle goes by many names. It often is called the **Krebs cycle** after Sir Hans Krebs, the first scientist to explain its operation, who was awarded the Nobel Prize in 1953 for his work. It also is called the **tricarboxylic acid (TCA) cycle** because a tricarboxylic acid (citrate)

citric acid cycle The metabolic pathway occurring in mitochondria in which the acetyl portion ($CH_3COO–$) of acetyl CoA is oxidized to yield two molecules of carbon dioxide and one molecule each of NADH, $FADH_2$, and GTP. Also known as the Krebs cycle and the tricarboxylic acid cycle.

oxaloacetate A four-carbon intermediate compound in the citric acid cycle. Acetyl CoA combines with free oxaloacetate in the mitochondria, forming citrate and beginning the cycle.

Krebs cycle See *citric acid cycle.*

tricarboxylic acid (TCA) cycle See *citric acid cycle.*

Figure 7.11   **The citric acid cycle.** This circular pathway accepts one acetyl CoA and yields two CO_2, three NADH, one $FADH_2$ and one GTP (readily converted to ATP). The electron shuttles NADH and $FADH_2$ carry high-energy electrons to the electron transport chain for ATP production.
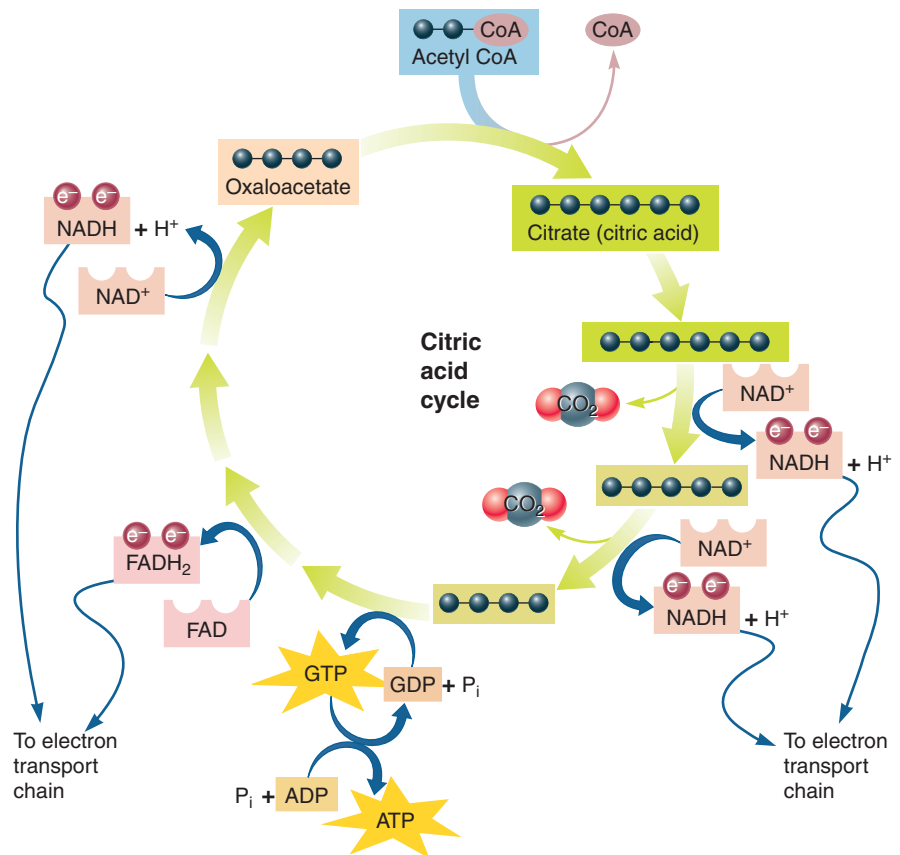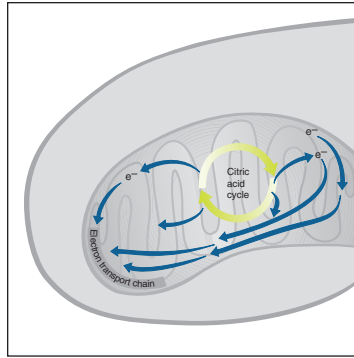
is formed in the first step. Most nutritionists use the term *citric acid cycle*. **Figure 7.11** shows an overview of the citric acid cycle.

The citric acid cycle is also an important source of building blocks for the biosynthesis of amino acids and fatty acids. Rather than using the cycle's intermediate molecules to complete the cycle, the cell may siphon them off for biosynthesis. Cells may use oxaloacetate, for example, to make glucose or certain amino acids. If alternate uses deplete the supply of oxaloacetate, the citric acid cycle can slow or even stop. Fortunately, cells can make oxaloacetate directly from pyruvate, easily replenishing the citric acid cycle's supply.

Electron Transport Chain

The final step in glucose breakdown is a sequence of linked reactions that take place in the **electron transport chain**, which is located in the inner

electron transport chain An organized series of carrier molecules—including flavin mononucleotide (FMN), coenzyme Q, and several cytochromes—that are located in mitochondrial membranes and shuttle electrons from NADH and $FADH_2$ to oxygen, yielding water and ATP.

THINK About It 2

mitochondrial membrane. Most ATP is produced here, and as long as oxygen is available, it can dispense ATP and maintain exercise for hours. Because the mitochondrion is the site of both the citric acid cycle and the electron transport chain, it truly is the energy power plant of the cell.

NADH and FADH$_2$ now deliver their cargo of high-energy electrons. NADH produced in the mitochondria by the citric acid cycle delivers its pair of high-energy electrons to the beginning of the chain. In the inner mitochondrial membrane, these electrons are passed along a chain of linked reactions, giving up energy along the way to power the final production of ATP. At the end of the electron transport chain, oxygen accepts the energy-depleted electrons and reacts with hydrogen to form water. This formation of ATP coupled to the flow of electrons along the electron transport chain is called **oxidative phosphorylation** because it requires oxygen and it phosphorylates ADP (joins it to P$_i$) to form ATP. (See **Figure 7.12**.)

mitochondrial membrane The mitochondria are enclosed by a double shell separated by an intermembrane space. The outer membrane acts as a barrier and gatekeeper, selectively allowing some molecules to pass through while blocking others. The inner membrane is where the electron transport chains are located.

oxidative phosphorylation Formation of ATP from ADP and P$_i$ coupled to the flow of electrons along the electron transport chain.

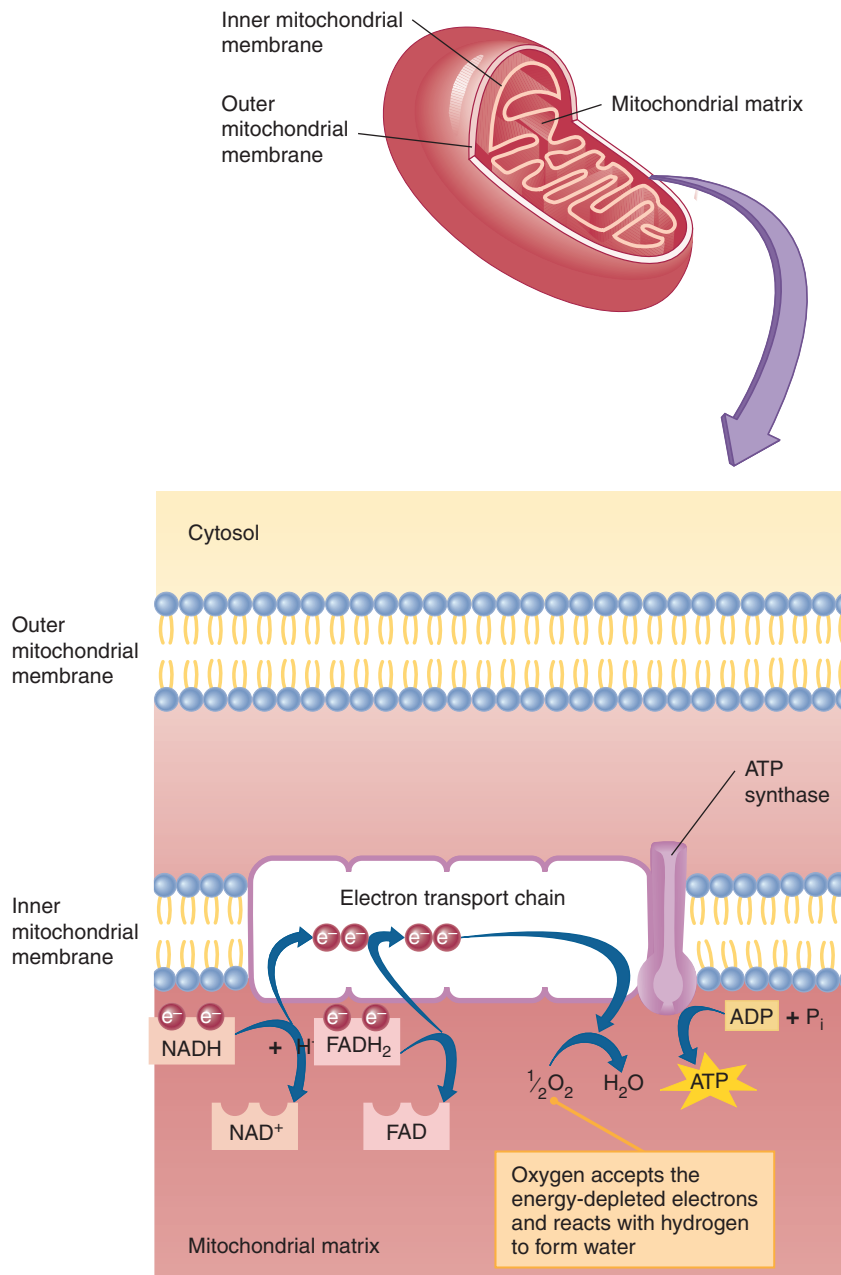**Figure 7.12 Electron transport chain.** This pathway produces most of the ATP available from glucose. NADH molecules deliver pairs of high-energy electrons to the beginning of the chain. The pairs of high-energy electrons carried by FADH$_2$ enter this pathway farther along and produce fewer ATP than electron pairs carried by NADH. Water is the final product of the electron transport chain.

Quick Bite

The Latest ATP Count

The number of ATP (or GTP) molecules formed directly in glycolysis and the citric acid cycle is unequivocally known, but the number of ATP molecules formed from NADH and $FADH_2$ in the electron transport chain is less certain. Old estimates credited NADH from the citric acid cycle with 3 ATP, and $FADH_2$ with 2 ATP. The best current estimates are 2.5 and 1.5, respectively. "Hence, about 30 ATP are formed when glucose is completely oxidized to CO_2; this value supersedes the traditional estimate of 36 ATP." —*Lubert Stryer, Professor of Biochemistry, Stanford University*
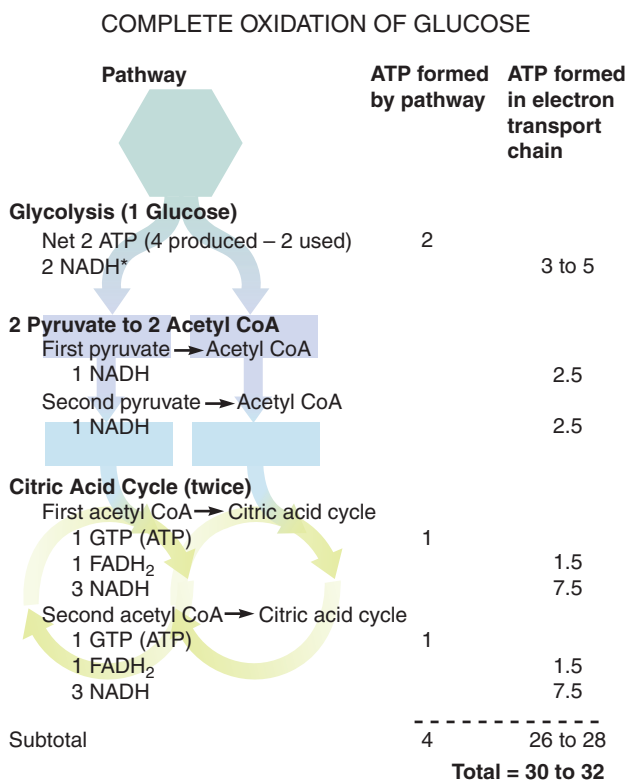
Without an oxygen "basket" at the end to accept the energy-depleted electrons, the transport of electrons down the chain would halt, stopping ATP production. Without ATP, there would be no power for our body's essential functions. If our oxygen supply was not rapidly restored, we would die.

What about $FADH_2$? The high-energy electrons from $FADH_2$ enter the electron transport chain at a later point than the electrons from NADH. Because they travel through fewer reactions, the electrons from $FADH_2$ generate fewer ATP molecules.

Biochemists have revised their estimates of the amount of ATP produced by the electron transport chain. Scientists had estimated that electron pairs from NADH produced 3 ATP and those from $FADH_2$ produced 2 ATP. Experiments have shown, however, that the actual amounts are slightly smaller—2.5 ATP from NADH and 1.5 ATP from $FADH_2$. Because each pair of electrons that traverses the electron transport chain produces slightly fewer ATP molecules than once thought, biochemists have revised their estimates for the total amount of ATP produced from one glucose molecule. Historically, they believed that the complete breakdown of glucose produced 36 to 38 ATP, but the current estimate is 30 to 32 ATP.[7]

What about the electron pairs carried by NADH from glycolysis? Recall that glycolysis takes place in the cytosol, whereas the citric acid cycle and electron transport chain are located in the mitochondria. NADH in the cytosol cannot penetrate the outer mitochondrial membrane. Instead, cytosolic NADH transfers its high-energy electrons to special molecules that shuttle them across the outer mitochondrial membrane. Once inside the mitochondrion, the electron pair may be picked up by the formation of either NADH or $FADH_2$. Depending on which shuttle is formed, an electron pair from glycolytic NADH generates either 2.5 or 1.5 ATP. Because of this difference, the complete oxidation of a glucose molecule does not always produce the same amount of ATP. (See **Figure 7.13**.)

End Products of Glucose Catabolism

Now you've seen all the steps in glucose breakdown. What has the cell produced from glucose? The end products of complete catabolism are carbon dioxide (CO_2), water (H_2O), and ATP. Both the conversion of pyruvate to acetyl CoA and the citric acid cycle produce CO_2. The electron transport chain produces water. While glycolysis makes small amounts of ATP and the citric acid cycle makes a little ATP as GTP, the electron transport chain generates the vast majority of this universal energy currency. **Table 7.1** summarizes the pathways of glucose metabolism.

Key Concepts *The metabolism of glucose to yield energy occurs in several steps. Glycolysis breaks the six-carbon glucose molecule into two pyruvate molecules. Each pyruvate loses a carbon and combines with coenzyme A to form acetyl CoA, which then enters the citric acid cycle. Two carbons enter the cycle as part of acetyl CoA, and two carbons leave as part of two carbon dioxide molecules. Because two acetyl CoA molecules are formed from a single glucose molecule, the citric acid cycle operates twice. Finally, the NADH and $FADH_2$ formed in these pathways carry pairs of high-energy electrons to the electron transport chain, where ATP and water are produced. When completely oxidized, each glucose molecule yields carbon dioxide, water, and ATP.*

Figure 7.13 **Complete oxidation of glucose.** These metabolic pathways and molecules move energy from glucose to ATP. Complete oxidation of one glucose molecule yields 30 to 32 ATP.

COMPLETE OXIDATION OF GLUCOSE

Pathway	ATP formed by pathway	ATP formed in electron transport chain
Glycolysis (1 Glucose)		
Net 2 ATP (4 produced – 2 used)	2	
2 NADH*		3 to 5
2 Pyruvate to 2 Acetyl CoA		
First pyruvate → Acetyl CoA		
1 NADH		2.5
Second pyruvate → Acetyl CoA		
1 NADH		2.5
Citric Acid Cycle (twice)		
First acetyl CoA → Citric acid cycle		
1 GTP (ATP)	1	
1 $FADH_2$		1.5
3 NADH		7.5
Second acetyl CoA → Citric acid cycle		
1 GTP (ATP)	1	
1 $FADH_2$		1.5
3 NADH		7.5
Subtotal	4	26 to 28
Total = 30 to 32		

*Each NADH formed in the cytosol by glycolysis will produce either 2.5 or 1.5 ATP in the electron transport chain.

Table 7.1   **Summary of the Major Metabolic Pathways in Glucose Metabolism**

Pathways	Location	Type	Summary	Starting Materials	End Products
Glycolysis	Cytosol	Anaerobic	A series of reactions that convert one glucose molecule to two pyruvate molecules.	Glucose, ATP	Pyruvate, ATP, NADH
Pyruvate to acetyl CoA	Mitochondria	Aerobic	Pyruvate from glycolysis combines with coenzyme A to form acetyl CoA while releasing carbon dioxide.	Pyruvate, coenzyme A	Acetyl CoA, carbon dioxide, NADH
Citric acid cycle	Mitochondria	Aerobic	This cycle of reactions degrades the acetyl portion of acetyl CoA and releases the coenzyme A portion. This cycle releases carbon dioxide and produces most of the energy-rich molecules, NADH and $FADH_2$, generated by the breakdown of glucose.	Acetyl CoA	Carbon dioxide, NADH, $FADH_2$, GTP
Electron transport chain	Mitochondria (membrane)	Aerobic	As the electrons from NADH and $FADH_2$ pass along this chain of transport proteins, they release energy to power the generation of ATP. Oxygen is the final electron acceptor and combines with hydrogen to form water.	NADH, $FADH_2$	ATP, water

Extracting Energy from Fat

To extract energy from fat, the body first breaks down triglycerides into their component parts, glycerol and fatty acids. Glycerol, a small three-carbon molecule, carries a relatively small amount of energy and can be converted by the liver to pyruvate or glucose. Fatty acids store nearly all the energy found in triglycerides.

The breakdown of fatty acids takes place inside the mitochondria. Before a fatty acid can cross into a mitochondrion, it must be linked to coenzyme A, which activates the fatty acid. Just as the input of ATP launched glycolysis, the input of ATP powers fatty acid activation. The breakdown of one ATP molecule to one AMP and two P_i provides the energy to drive this reaction. Although this activation reaction requires only one molecule of ATP, it breaks both of ATP's high-energy phosphate bonds and consumes the energetic equivalent of two ATP molecules (double the amount of energy released from the reaction ATP $\rightarrow$ ADP + P_i).
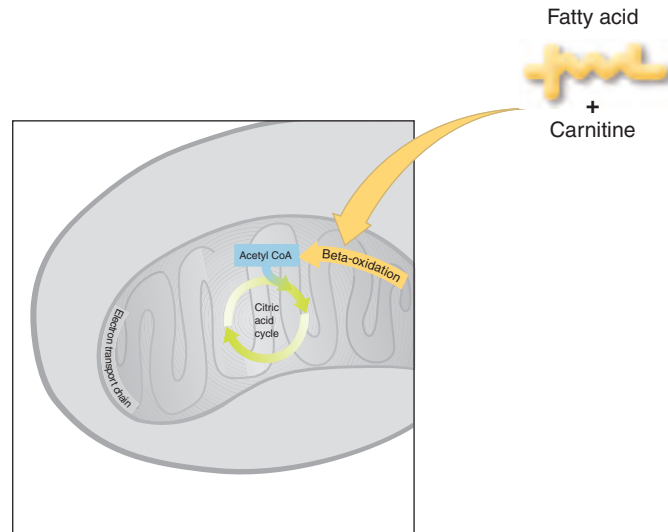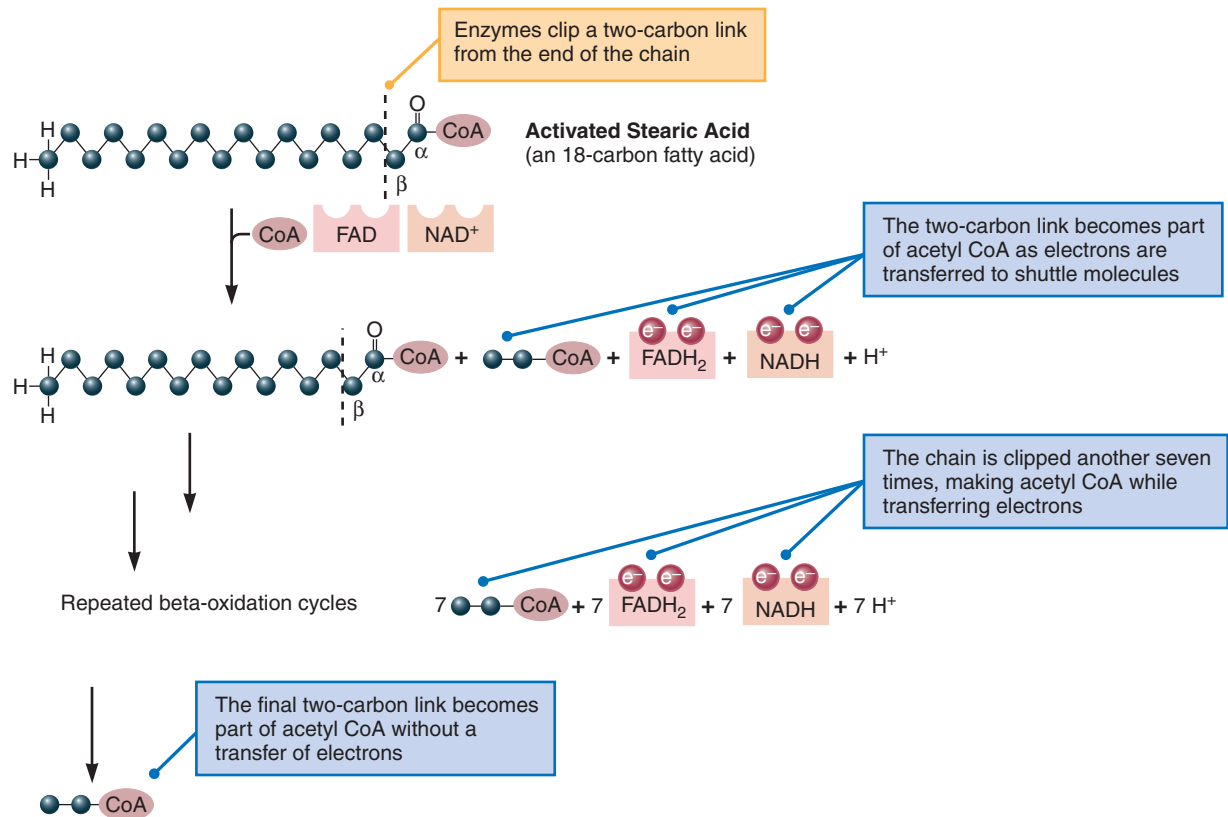
Carnitine Shuttle

Without assistance, the activated fatty acid cannot get inside the mitochondria where fatty acid oxidation and the citric acid cycle operate. This entry problem is solved by **carnitine**, a compound formed from the amino acid lysine. Carnitine has the unique task of ferrying activated fatty acids across the mitochondrial membrane, from the cytosol to the interior of the mitochondrion. When carnitine is in short supply, the production of ATP slows. Moderate carnitine deficiency in heart or skeletal muscle reduces muscle endurance; more extreme deficiency causes muscular strength to fail more quickly.[8] Based on its role in fatty acid oxidation, some people claim that carnitine supplements act as "fat burners." Research data show that carnitine supplementation in healthy people has little or no effect on fatty acid oxidation rates or athletic performance.[9]

carnitine [CAR-nih-teen] A compound that transports fatty acids from the cytosol into the mitochondria, where they undergo beta-oxidation.

Figure 7.14 **Beta-oxidation.** Beta-oxidation reactions repeatedly clip the two-carbon end off a fatty acid until it is degraded entirely. Beta-oxidation of 18-carbon stearic acid produces nine acetyl CoA, eight $FADH_2$, and eight NADH.

Fatty acid

+
Carnitine

BETA-OXIDATION

Enzymes clip a two-carbon link from the end of the chain

Activated Stearic Acid (an 18-carbon fatty acid)

CoA   FAD   NAD$^+$

The two-carbon link becomes part of acetyl CoA as electrons are transferred to shuttle molecules

CoA + CoA + $FADH_2$ + NADH + H$^+$

The chain is clipped another seven times, making acetyl CoA while transferring electrons

Repeated beta-oxidation cycles

7 CoA + 7 $FADH_2$ + 7 NADH + 7 H$^+$

The final two-carbon link becomes part of acetyl CoA without a transfer of electrons

CoA

Beta-Oxidation

beta-oxidation The breakdown of a fatty acid into numerous molecules of the two-carbon compound acetyl coenzyme A (acetyl CoA).

Once in the mitochondria, a process called **beta-oxidation** disassembles the fatty acid and converts it into several molecules of acetyl CoA. (See **Figure 7.14**.) Starting at the beta carbon of the fatty acid (the second carbon from the acid end), enzymes clip a two-carbon "link" off the end of the chain. Reactions convert this two-carbon link to one acetyl CoA, while also transferring one pair of electrons to $FADH_2$ and another pair to NADH. This process repeats

in stepwise fashion, shortening the chain by two carbons at a time until only one two-carbon segment remains. This final two-carbon link simply becomes one acetyl CoA without producing $FADH_2$ and NADH.

In nature, almost all fatty acids have an even number of carbons. Although they can vary in length from 4 to 26 carbons, they often are 16 or 18 carbons long. If your body encounters an odd-numbered fatty acid, it breaks down this chain in the same way until it reaches a final three-carbon link. Rather than try to clip this link into smaller segments, a reaction joins it with coenzyme A. This three-carbon compound enters the citric acid cycle at a point farther along than acetyl CoA's entry point. Because it skips some of the early citric acid cycle reactions, it has a shorter journey than acetyl CoA and produces two fewer NADH molecules.

The Citric Acid Cycle and Electron Transport Chain Complete Fatty Acid Breakdown

Beta-oxidation of a fatty acid produces a flood of acetyl CoA that can enter the citric acid cycle. The citric acid cycle and electron transport chain complete the extraction of energy from fatty acids. Just as they processed acetyl CoA, NADH, and $FADH_2$ from glucose, these same pathways use acetyl CoA, NADH, and $FADH_2$ from fatty acids to produce ATP.
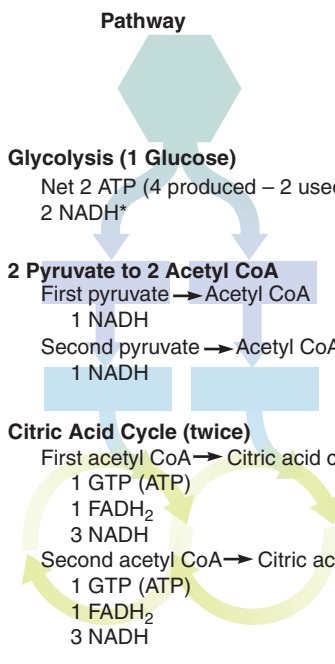
The end products of fatty acid breakdown are the same as those of glucose breakdown: carbon dioxide, water, and ATP. The exact amount of ATP depends on the length of the fatty acid chain. Because longer chains have more carbon bonds, beta-oxidation of longer chains produces more acetyl CoA and thus more ATP. The complete breakdown of an 18-carbon fatty acid, for example, produces 120 ATP (see **Figure 7.15**), whereas a 10-carbon fatty acid produces only 66 ATP. Because a fatty acid chain typically contains many more carbon atoms than a molecule of glucose, a single fatty acid produces substantially more ATP. For a single triglyceride with three 18-carbon fatty acids, complete breakdown of the fatty acids produces 360 ATP, more than 10 times the 30 to 32 ATP produced from the complete oxidation of glucose.

Fat Burns in a Flame of Carbohydrate

Acetyl CoA from beta-oxidation can enter the citric acid cycle only when fat and carbohydrate breakdown are synchronized. Without available oxaloacetate, acetyl CoA cannot start the citric acid cycle. Conditions such as starvation and consumption of high-fat, low-carbohydrate diets can deplete oxaloacetate, blocking acetyl CoA from entry. This reroutes the acetyl CoA to form a family of compounds called ketone bodies. (See the section "Making Ketone Bodies" later in this chapter.) Production of ketone bodies can occur with popular high-protein diets that are low in carbohydrate but also high in fat.

For fatty acid oxidation to continue efficiently and unchecked, reactions in the mitochondria must ensure a reliable supply of oxaloacetate. These reactions convert some pyruvate directly to oxaloacetate rather than to acetyl CoA. Since carbohydrate (glucose) is the original source of the pyruvate, and hence this oxaloacetate, scientists coined the adage "Fat burns in a flame of carbohydrate."

THINK
About It
3

Figure 7.15 **The complete breakdown of stearic acid.** The complete oxidation of one 18-carbon fatty acid yields about four times as much ATP as the complete oxidation of one glucose molecule.

COMPLETE OXIDATION OF GLUCOSE

Pathway	ATP formed by pathway	ATP formed in electron transport chain
Glycolysis (1 Glucose)		
Net 2 ATP (4 produced – 2 used)	2	
2 NADH*		3 to 5
2 Pyruvate to 2 Acetyl CoA		
First pyruvate → Acetyl CoA		
1 NADH		2.5
Second pyruvate → Acetyl CoA		
1 NADH		2.5
Citric Acid Cycle (twice)		
First acetyl CoA → Citric acid cycle		
1 GTP (ATP)	1	
1 $FADH_2$		1.5
3 NADH		7.5
Second acetyl CoA → Citric acid cycle		
1 GTP (ATP)	1	
1 $FADH_2$		1.5
3 NADH		7.5
Subtotal	4	26 to 28
Total = 30 to 32		

*Each NADH formed in the cytosol by glycolysis will produce either 2.5 or 1.5 ATP in the electron transport chain.

Key Concepts *Extracting energy from fat involves several steps. First, triglycerides are separated into glycerol and three fatty acids. Glycerol forms pyruvate and can be broken down to yield a small amount of energy. Beta-oxidation breaks down fatty acid chains to two-carbon links that form acetyl CoA, which enters the citric acid cycle. Beta-oxidation and the citric acid cycle form NADH and $FADH_2$, which carry pairs of high-energy electrons to the electron transport chain, where ATP and water are made. The complete breakdown of one triglyceride molecule yields water, carbon dioxide, and substantially more ATP than the complete breakdown of one glucose molecule.*

Going Green

Biofuel Versus Fossil Fuel

Just as calories provide energy for our bodies, machine fuel supplies the energy for our lifestyles. We obtain calories from varied sources, and we obtain fuel from different sources. The two main fuel sources for machines are biofuel and fossil fuel. Both types of fuels present unique challenges in their impact on the environment, as well as on our carbon footprints.

Fossil fuels come from organisms that died millions of years ago. Coal is an example of a fossil fuel created from dead plant material that settled in swamps and underwent changes over millions of years. Fossil fuels are a nonrenewable resource because their replenishment rate is extremely low relative to their consumption rate. How do fossil fuels affect the environment? The prospecting and extracting, transporting, refining, and distribution of fossil fuel all contribute to greenhouse gas emissions and thus to climate change.

Biofuels can be produced from a number of different food crops that are derived directly or indirectly from photosynthesis. Although considered a renewable resource, this process raises environmental concerns and issues as well. The United States is the world's biggest producer of biofuels, derived mostly from corn. The environmental impacts of corn ethanol are significant. Soil erosion in addition to the heavy use of nitrogen fertilizer and pesticides leads to water and soil pollution. These factors in turn contribute to climate change. In addition, producing each gallon of ethanol requires 1,700 gallons of water (mostly to grow the corn) and generates 6 to 12 gallons of noxious organic effluent.[1]

Are biofuels a better alternative to fossil fuels? Some scientific research has established that some kinds of biofuel generate as much carbon dioxide as the fossil fuels they replace. Additionally, many people are focusing on how best to proceed globally with biofuel production in light of its potential impact on the world's food supply and hunger.[2]

One issue of increasing concern regards the quantity of arable land needed to produce biofuel rather than to produce food crops. Supporters of biofuel contend that biofuels are the only renewable alternative to fossil fuels and do generally result in greenhouse gas emission savings. Although there is great concern about the ultimate impact of biofuel production on hunger among the world's poorest people, the major increase in biofuels does have the potential to benefit the world's population living in poverty.[3]

So, what type of fuel is best for the environment? We do not have a definitive answer yet. Alternatives that have proven to be efficient for biofuel production are cellulose-containing materials, such as trees; grasses; woodchips; and field crop residues from wheat, rice straw, and cornstalks.[4] Until we have more definitive answers, we need to use every technique and strategy available. These will involve, in addition to experimenting with fuel sources, conservation of electricity and other resources. Small steps in energy conservation today can have a significant impact on your carbon footprint of tomorrow!

1   Bournay E. *Atlas Environment du Monde Diplomatique 2007*, as cited in UNEP/GRID-Arendal. Biofuel versus fossil fuel. http://maps. Grida.no/go/graphic/biofuel-versus-fossil-fuel1. Accessed 7/15/09.

2   Stein K. Food vs biofuel. *J Am Diet Assoc.* 2007;107(11):1870.

3   Ibid.

4   Runge CF, Senauer B. How biofuels could starve the poor. *Foreign Affairs* May/June 2007. http://www.foreignaffairs. org/20070501faessay86305/c-ford-runge-benjamin-senauer/how-biofuels-could-starve-the-poor.html. Accessed 8/15/09.

Extracting Energy from Protein

Because protein has vital structural and functional roles, proteins and amino acids are not considered primary sources of energy. The primary and unique role of amino acids is to serve as building blocks for the synthesis of body protein and nitrogen-containing compounds. However, if energy production falters due to a lack of available carbohydrate and fat, protein comes to the rescue. During starvation, for example, energy needs take priority, so the body breaks down protein and extracts energy from the amino acid building blocks.

To use amino acids as an energy source, a process called deamination first strips off the amino group (–NH2), leaving a "carbon skeleton." (See **Figure 7.16**.) The liver quickly converts the amino group first to ammonia and then to urea, which the kidneys excrete in urine. When you eat more protein than you need, your kidneys excrete the excess nitrogen and your liver uses the carbon skeletons to produce energy, glucose, or fat. Much to the dismay of bodybuilders, when they attempt to build muscle by drinking pricey protein drinks, they can end up gaining fat instead!

Carbon Skeletons Enter Pathways at Different Points

Like a crowd of people streaming into a concert through five different doors rather than one main entrance, carbon skeletons—unlike glucose—can enter the breakdown pathways at several different points. The carbon skeleton from each type of amino acid has a unique structure and number of carbon atoms. These characteristics determine the carbon skeleton's fate, be it pyruvate, acetyl CoA, ketone bodies, or one of the intermediates of the citric acid cycle.

End Products of Amino Acid Catabolism

The complete breakdown of an amino acid yields urea, carbon dioxide, water, and ATP. The carbon skeleton's point of entry into the breakdown pathways determines the amount of ATP it produces. Whereas the complete breakdown of alanine, for example, produces 12.5 ATP, methionine produces only 5 ATP. Compared with glucose and fatty acids, no amino acid produces much ATP. (See **Figure 7.17**.)

Key Concepts *To extract energy from amino acids, first deamination removes the amino groups, leaving behind carbon skeletons. The liver quickly converts these amino groups to urea and sends them to the kidneys for excretion. The carbon skeleton structure determines where it enters the catabolic pathways. Some carbon skeletons become pyruvate, others become acetyl CoA, and still others become intermediate compounds of the citric acid cycle. Complete breakdown of amino acids yields water, carbon dioxide, urea, and ATP.*

Biosynthesis and Storage

Uh oh! Surveying the results of those holiday dinners and treats, you cringe with regret. Your clothes no longer fit, and you hate the idea of stepping on the scale. Your biosynthetic pathways have been hard at work, building fat stores from your excess intake of energy.

You head for the gym. After sweating through many workouts, your body begins to firm. You drop fat and add muscle. Now any problem with clothes fitting is due to muscle gain, not fat gain. To build muscle protein, different biosynthetic pathways have been busy making amino acids and assembling proteins.
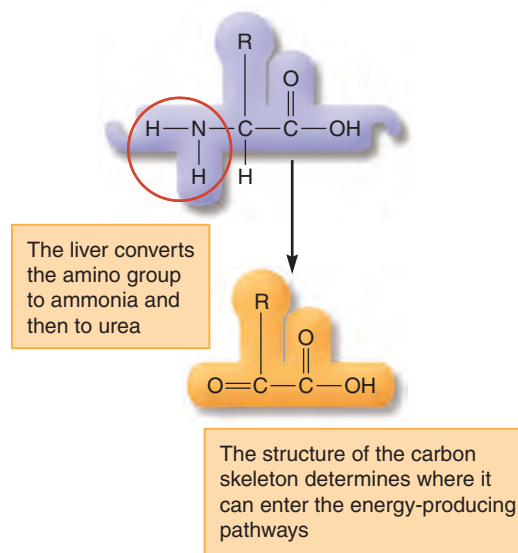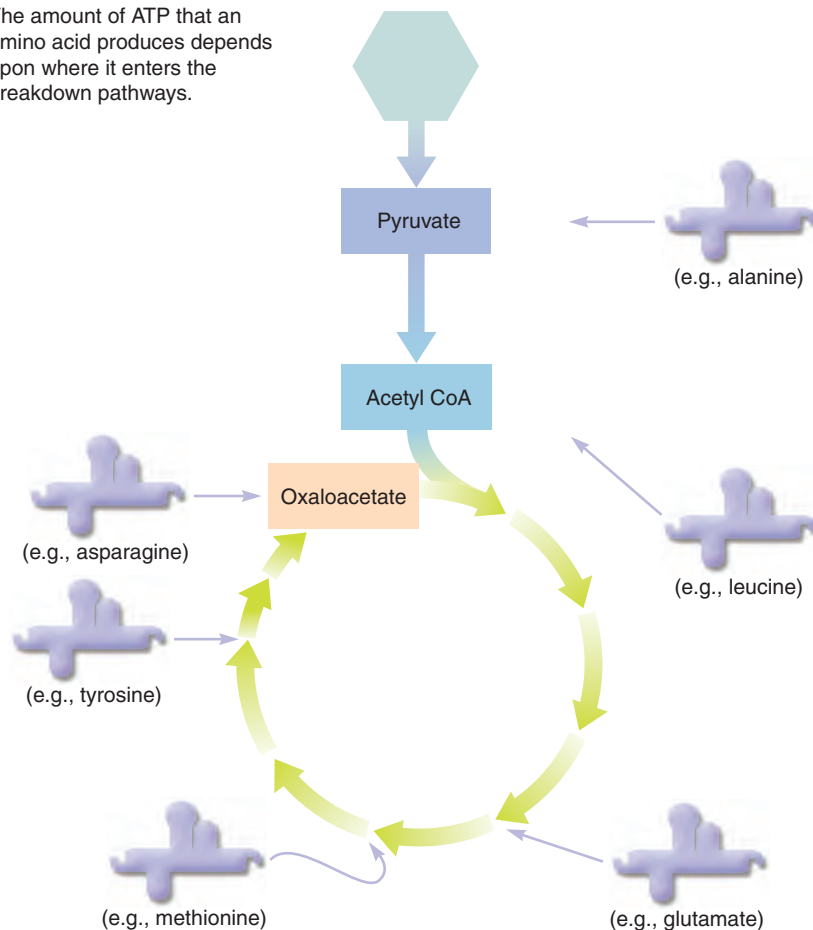

The liver converts the amino group to ammonia and then to urea

The structure of the carbon skeleton determines where it can enter the energy-producing pathways

Figure 7.16 **Deamination.** A deamination reaction strips the amino group from an amino acid.

Figure 7.17   Extracting energy from amino acids. The carbon skeletons of amino acids have several different entrances to the breakdown pathways. Compared with glucose and fatty acids, amino acids yield much smaller amounts of energy (ATP).

Amino acid oxidation
The amount of ATP that an amino acid produces depends upon where it enters the breakdown pathways.

Pyruvate

(e.g., alanine)

Acetyl CoA

Oxaloacetate

(e.g., asparagine)

(e.g., leucine)

(e.g., tyrosine)

(e.g., methionine)

(e.g., glutamate)

Perhaps you've heard of "carb loading." (See Chapter 14, "Sports Nutrition.") This strategy uses high-carbohydrate meals to pack carbohydrate into your muscle glycogen stores before a race. Biosynthetic pathways assemble glucose into glycogen chains for storage. When needed, your body also can make glucose from certain amino acids and other precursors.

Both the breakdown and biosynthetic pathways are active at all times. While some cells are breaking down carbohydrate, fat, and protein to extract energy, other cells are busy building glucose, fatty acids, and amino acids. When your body needs energy, the breakdown pathways prevail. When it has an excess of nutrients, the biosynthetic pathways dominate. The activities in these pathways ebb and flow so that they proceed at just the right rate, not too rapidly and not too slowly. **Figure 7.18** illustrates the interconnections among the metabolic pathways.

Making Carbohydrate (Glucose)

Your body sets a high priority on maintaining an adequate amount of glucose circulating in the bloodstream. **Table 7.2** shows the amount of energy, in kilocalories, that a typical 70-kilogram man has available. Blood glucose is the primary source of energy for your brain, central nervous system, and
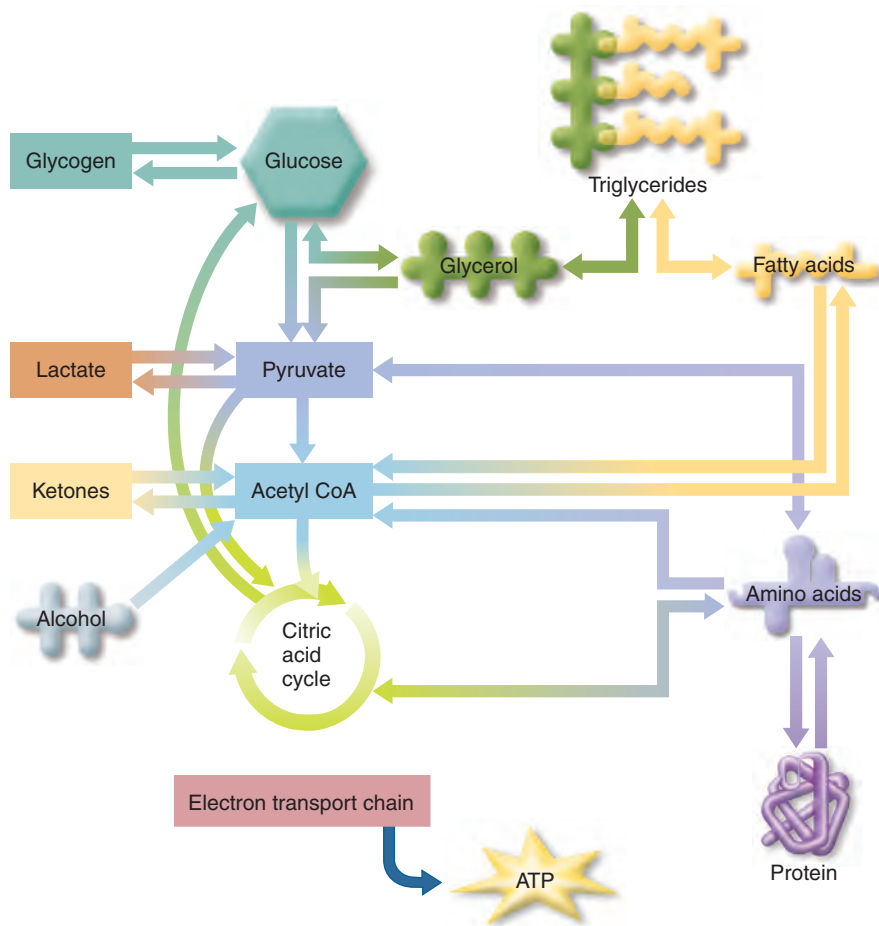
Figure 7.18 **Overview of metabolic pathways.** As if they were traveling through a maze of city streets, molecules move through a network of breakdown and biosynthetic pathways. Not all pathways are available to a molecule. Just as traffic lights and one-way streets regulate traffic flow, cellular mechanisms control the flow of molecules in metabolic pathways. These mechanisms include hormones, irreversible reactions, and the location of the reactions in the cell.

red blood cells. In fact, while you're at rest, your brain consumes about 60 percent of the energy consumed by your entire body.

The brain stores little glucose—only about 8 kilocalories. About 140 kilocalories of glucose circulate in the blood or are stored in adipose tissue. Your primary carbohydrate stores are in the form of glycogen. Muscle tissue holds about 1,200 kilocalories of glycogen, and the liver stores another 400 kilocalories.

Table 7.2 **Available Energy (kcal) in a Typical 70-Kilogram Man**

Organ	Glucose or Glycogen	Triglycerides	Mobilizable Proteins
Blood	60	45	0
Liver	400	450	400
Brain	8	0	0
Muscle	1,200	450	24,000
Adipose tissue	80	135,000	40

Source: Adapted from Berg JM, Tymoczko JL, Stryer L. *Biochemistry.* 5th ed. New York: WH Freeman, 2002.

Quick Bite

gluconeogenesis [gloo-ko-nee-oh-JEN-uh-sis] Synthesis of glucose within the body from noncarbohydrate precursors such as amino acids, lactate, and glycerol. Fatty acids cannot be converted to glucose.

Cori cycle The circular path that regenerates NAD^+ and glucose when oxygen is low and lactate and NADH build up in excess in muscle tissue.

glucogenic In the metabolism of amino acids, a term describing an amino acid broken down into pyruvate or an intermediate of the citric acid cycle; that is, any compound that can be used in gluconeogenesis to form glucose.

ketogenic In the metabolism of amino acids, a term describing an amino acid broken down into acetyl CoA (which can be converted into ketone bodies).

glycogenesis The formation of glycogen from glucose.

glycogenolysis The breakdown of glycogen to glucose.

Gluconeogenesis: Pathways to Glucose

When you are exercising intensely or when you aren't taking in enough carbohydrate, your body can remake glucose from pyruvate by using a clever strategy called **gluconeogenesis**. (See **Figure 7.19**.) Your liver is the major site of gluconeogenesis, accounting for about 90 percent of glucose production. Your kidneys make the rest.

Gluconeogenesis and glycolysis share many—but not all—reactions. During gluconeogenesis, reactions flow in the opposite direction as they do during glycolysis. Because some reactions of glycolysis flow only one way, however, gluconeogenesis must use energy-consuming detours to bypass them. Thus gluconeogenesis is *not* simply a reversal of glycolysis.

Your body can make glucose from pyruvate, lactate, and some noncarbohydrate sources—glycerol and most amino acids. Although gluconeogenesis can use the glycerol portion of fat, it cannot make glucose from fatty acids.

Although some lactate is continually formed and degraded, lactate production increases substantially in exercising muscle. Low oxygen levels in actively contracting muscle cells inhibit the conversion of pyruvate to acetyl CoA. In the liver, gluconeogenesis converts some of the lactate back to glucose via the **Cori cycle**. For more on the Cori cycle, see Chapter 14, "Sports Nutrition."

If the carbon skeleton of an amino acid can be made into glucose, the amino acid is called **glucogenic**. Glucogenic amino acids provide carbon skeletons that become pyruvate or directly enter the citric acid cycle at intermediate points without forming acetyl CoA. If the carbon skeleton of an amino acid directly forms acetyl CoA (which your body can convert to ketone bodies but not glucose), the amino acid is called **ketogenic** (see the section "Ketogenesis: Pathways to Ketone Bodies" later in this chapter).

Key Concepts *Your body can make glucose from pyruvate, lactate, glucogenic amino acids, and glycerol, but not from fatty acids. Although most gluconeogenesis takes place in the liver, the kidneys are responsible for about 10 percent of glucose synthesis.*

Storage: Glucose to Glycogen

Our main storage form of glucose is glycogen, a branched-chain polysaccharide made of glucose units (see Chapter 4, "Carbohydrates"). Both the liver and muscle store glycogen. Liver glycogen serves as a glucose reserve for the blood, and muscle glycogen supplies glucose to exercising muscle tissue. Glycogen stores are limited; fasting or strenuous exercise can deplete them rapidly.

A pathway called **glycogenesis** assembles glucose molecules into branched chains for storage as glycogen. When the body needs glucose, a different series of reactions known as **glycogenolysis** breaks down the glycogen chains into individual glucose molecules. In muscle, these glucose molecules enter glycolysis and continue along the metabolic pathways to produce ATP. In the liver, glycogenolysis yields glucose that moves into the bloodstream to maintain blood glucose levels.

Making Fat (Fatty Acids)

Acetyl CoA is the most important ingredient in fatty acid synthesis. Compounds that can be metabolized to form acetyl CoA can feed fatty acid synthesis. Such precursors include ketogenic amino acids, alcohol, and fatty acids themselves.

Key
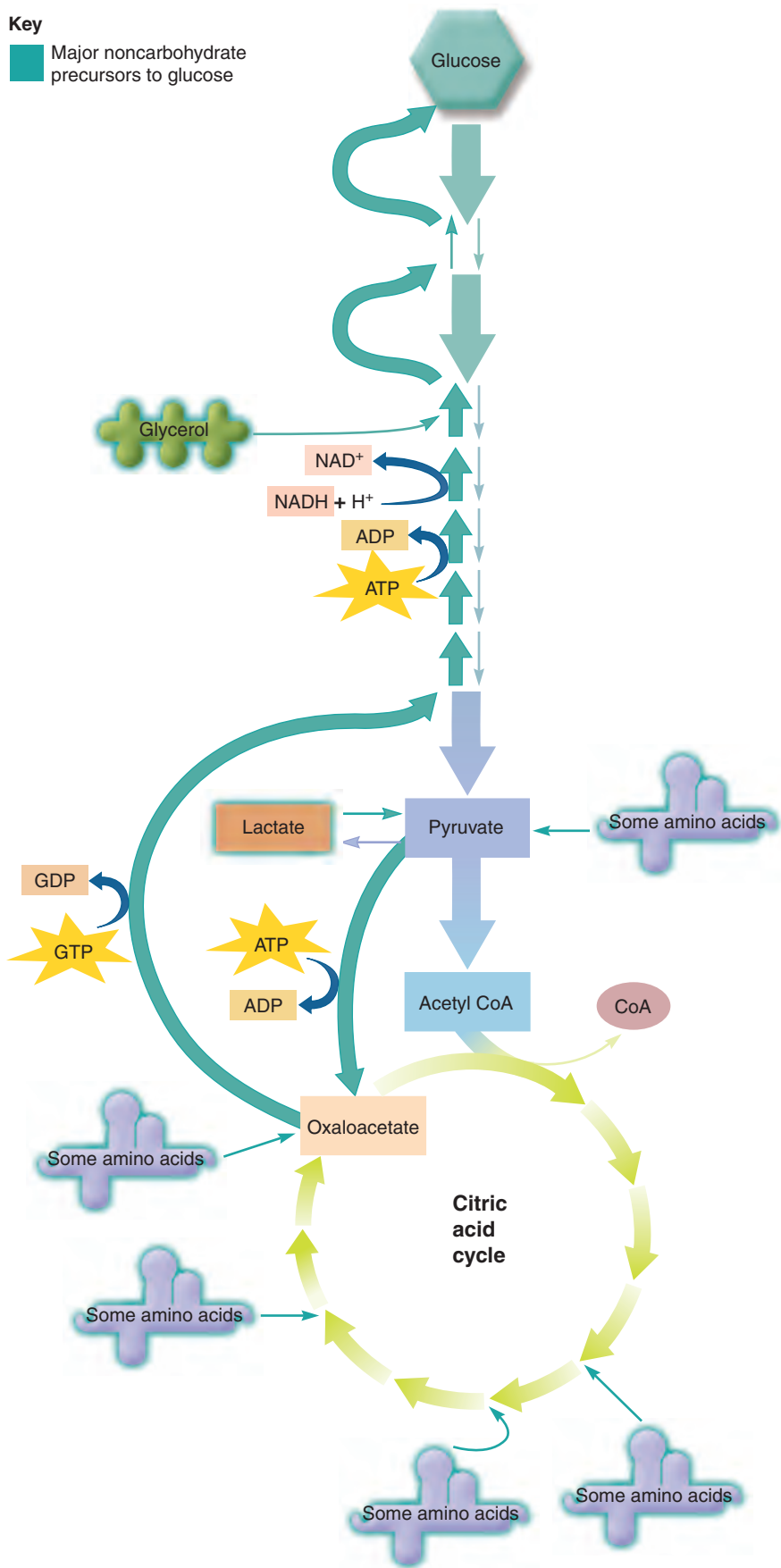■ Major noncarbohydrate precursors to glucose

Figure 7.19 **Gluconeogenesis.** Liver and kidney cells make glucose from pyruvate by way of oxaloacetate. Gluconeogenesis is *not* the reverse of glycolysis. Although these pathways share many reactions, albeit in the reverse direction, gluconeogenesis must detour around the irreversible steps in glycolysis.

lipogenesis [lye-poh-JEN-eh-sis]
Synthesis of fatty acids, primarily in liver cells, from acetyl CoA derived from the metabolism of alcohol and some amino acids.

Lipogenesis: Pathways to Fatty Acids

When your body has a plentiful supply of energy (ATP) and abundant building blocks, it can make long-chain fatty acids using a process called **lipogenesis**. To do this, your body assembles two-carbon acetyl CoA "links" into fatty acid chains. Where do these acetyl CoA building blocks come from? Ketogenic amino acids, alcohol, and fatty acids themselves supply acetyl CoA for lipogenesis.

Although you can think of fatty acid synthesis as reassembling the links broken apart by beta-oxidation, lipogenesis is *not* the reversal of beta-oxidation. These pathways use different reactions and take place in different locations: fatty acid synthesis occurs in the cytosol, whereas beta-oxidation operates inside the mitochondria. Another important distinction is that beta-oxidation releases energy, whereas fatty acid synthesis requires energy. In beta-oxidation, reactions deliver high-energy electrons to NADH for ultimate ATP synthesis. In lipogenesis, NADPH supplies energy to power the synthesis of fatty acids. Your endoplasmic reticulum, a type of organelle in cells, assembles surplus fatty acids and glycerol into triglycerides for storage as body fat.

Storage: Dietary Energy to Stored Triglyceride

When you overeat, your body uses body fat as a long-term energy storage depot. When you eat an excess of fat, most extra dietary fatty acids head straight to your fat stores. If you eat more protein than your tissues can use, your body converts most of the excess protein to body fat. Interestingly, excess carbohydrate does not readily become fat. In research studies, massive overfeeding of carbohydrate in normal men caused only minimal amounts of fat synthesis. (See the FYI feature "Do Carbohydrates Turn into Fat?") So are carbohydrate calories "free"? Unfortunately, no. The first law of thermodynamics—the law of conservation of energy—still holds. Although excess carbohydrate does not dramatically increase fat synthesis, it shifts your body's fuel preferences toward burning more carbohydrate and fewer fatty acids.[10] Thus, eating excess carbohydrates still can make you fat by allowing your fat intake to go directly to storage rather than to make ATP. (See **Table 7.3**.)

Table 7.3   **Summary of Energy Yield and Interconversions**

Dietary Nutrient	Yields Energy?	Convertible to Glucose?	Convertible to Amino Acids and Body Proteins?	Convertible to Fat?
Carbohydrate (glucose, fructose, galactose)	Yes	Yes	Yes, can yield certain amino acids when amino groups are available	Insignificant
Fat (triglycerides)				
Fatty acids	Yes, large amounts	No	No	Yes
Glycerol	Yes, small amounts	Yes, small amounts	Yes (see carbohydrate)	Insignificant
Protein (amino acids)	Yes, generally not much (see starvation in text)	Yes, if insufficient carbohydrate is available	Yes	Yes, from some amino acids
Alcohol (ethanol)	Yes	No	No	Yes

Key Concepts *When ATP is plentiful and the diet supplies an excess of energy, your cells make fatty acids and triglycerides. Energy carried by NADPH powers the synthesis of fatty acids from acetyl CoA building blocks. Glycerol and fatty acids are assembled into triglycerides on the endoplasmic reticulum. Although excess dietary carbohydrate is not readily converted to fat, it does shift the body's selection of fuel and encourages the accumulation of dietary fat in body fat stores.*

ketones [KEE-tones] Organic compounds that contain a chemical group consisting of C=O (a carbon–oxygen double bond) bound to two hydrocarbons. Pyruvate and fructose are examples of ketones. Acetone and acetoacetate are both ketones and ketone bodies. Although beta-hydroxybutyrate is not a ketone, it is a ketone body.

Making Ketone Bodies

Ketone bodies (sometimes incorrectly called **ketones**) include three compounds: acetoacetate, beta-hydroxybutyrate, and acetone. Acetoacetate and

FYI
For Your Information

Do Carbohydrates Turn into Fat?
Marc Hellerstein, M.D., Ph.D.

Thirty years ago, Jules Hirsch and his colleagues addressed this question indirectly. They found that the composition of fatty acids in adipose tissue closely resembled the subjects' dietary fat intake. Moreover, when they put these subjects on controlled diets of different fatty acid composition for six months, adipose fatty acids slowly changed to reflect the new dietary fatty acid composition. These studies concluded that "we are what we eat" with regard to body fat and that fatty acid synthesis is minimal at best.

The body's ability to make fat from carbohydrate is called *de novo lipogenesis* (DNL). Numerous studies using a technique called indirect calorimetry have shown that net DNL is absent or very low in humans under most dietary conditions, even after a large carbohydrate meal. But could there be concurrent synthesis and use of fat that results in no net change?

Concurrent DNL and burning of fatty acids is called *futile cycling*. About 25 to 28 percent of the carbohydrate energy is lost during the inefficient conversion to fatty acids. Does this costly conversion really happen? New stable isotopic methods have helped answer this question.

Direct Evidence

Direct evidence from stable isotopic methods shows that DNL is minimal in normal (non-obese, nondiabetic, nonoverfed) men. DNL represents less than 1 gram of saturated fat per day, whether the subjects are given large meals, intravenous glucose, or a liquid diet.

Do any circumstances stimulate DNL? Jean-Marc Schwarz gave fructose and glucose orally to lean and obese subjects. The

dietary fructose increased DNL up to twentyfold compared with equal calorie loads of glucose. Nevertheless, fat synthesis still represented only a small percentage of the fructose load given (<5 percent). Scott Siler has shown that drinking alcohol stimulates DNL. Again, however, only a small percentage (<5 percent) of the alcohol was converted to fat; the great majority was released from the liver as acetate.

My laboratory studied the effect of five to seven days of carbohydrate overfeeding or underfeeding in normal men. Fat synthesis by the liver was highly sensitive to the degree of dietary carbohydrate excess. In fact, we could determine exactly which diet a person was eating by measuring DNL. Even so, the absolute amount of fat synthesis remained low, even on massively excessive carbohydrate intakes. DNL may be a sensitive *signal* of excess carbohydrate in the diet, but it is not a quantitatively important route for excess carbohydrate disposal.

Other conditions yield similar findings. Very low-fat diets (10 percent of energy as fat; 70 percent as carbohydrate) stimulate lipogenesis, but, again, not a large amount.
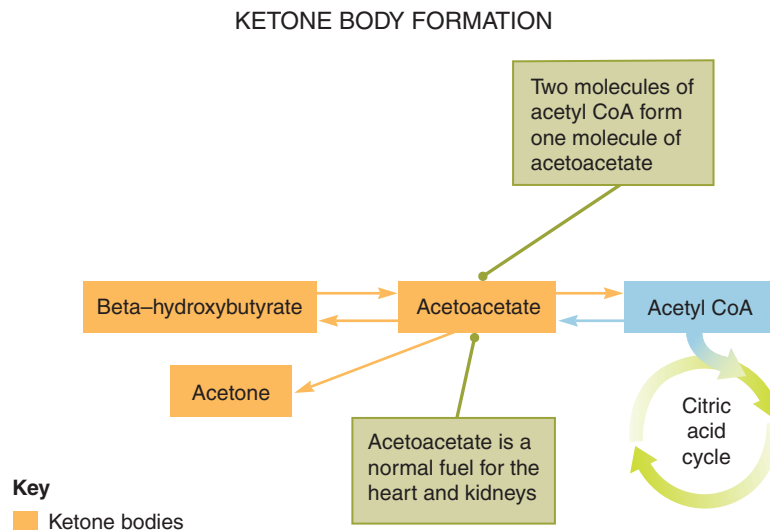
In young women, lipogenesis increases during the follicular phase of the menstrual cycle, but the amount is small, representing only one to two pounds of extra fat per year. A high rate of DNL has been documented in humans only under conditions of massive carbohydrate overfeeding—for example, 5,000 to 6,000 carbohydrate calories per day for more than a week.

Are Carbohydrate Calories "Free"?

Alas, we still become fatter if we overeat carbohydrate. At rest, our bodies normally burn fat as our primary fuel source. An excess of dietary carbohydrate energy causes a fat-sparing shift in fuel selection as it markedly reduces the use of fat to fuel the body. Dietary fat makes a beeline for body fat storage rather than being burned to release energy. Thus, excess dietary carbohydrate is not "free" when the diet also contains fat, because the carbohydrate spares fat use.

Dr. Hellerstein is Professor of Medicine at the University of California, San Francisco, and Professor of Nutritional Sciences at the University of California at Berkeley.

Figure 7.20 **Ketogenesis.** For acetyl CoA from fatty acid oxidation to enter the citric acid cycle, fat and carbohydrate metabolism must be synchronized. When acetyl CoA cannot enter the citric acid cycle, it is shunted to form ketone bodies, a process called ketogenesis.

KETONE BODY FORMATION

Two molecules of acetyl CoA form one molecule of acetoacetate

Beta–hydroxybutyrate → Acetoacetate → Acetyl CoA

Acetone

Acetoacetate is a normal fuel for the heart and kidneys

Citric acid cycle

Key
Ketone bodies

ketogenesis The process in which excess acetyl CoA from fatty acid oxidation is converted into the ketone bodies acetoacetate, beta-hydroxybutyrate, and acetone.

ketoacidosis Acidification of the blood caused by a buildup of ketone bodies. It is primarily a consequence of uncontrolled type 1 diabetes mellitus and can be life threatening.

Quick Bite

Why Didn't My Cholesterol Levels Drop?
Your body can make cholesterol from acetyl CoA by way of ketone bodies In fact, all 27 carbons in synthesized cholesterol come from acetyl CoA. The rate of cholesterol formation is highly responsive to cholesterol levels in cells. If levels are low, the liver makes more. If levels are high, synthesis decreases. This is why dietary cholesterol in the absence of dietary fat often has little effect on blood cholesterol levels.

beta-hydroxybutyrate are acids, so they are sometimes referred to as keto acids. You may recognize the term *acetone*, since this chemical is a common solvent. In fact, you can smell the strong odor of acetone on the breath of people with high levels of ketone bodies in their blood: their breath smells like some nail polish removers!

Your body makes and uses small amounts of ketone bodies at all times. Although long considered to be just an emergency energy source or the result of an abnormal condition such as starvation or uncontrolled diabetes, ketone bodies are normal, everyday fuels. In fact, your heart and kidneys prefer to use the ketone body acetoacetate rather than glucose as a fuel source.[11]

Ketogenesis: Pathways to Ketone Bodies

During the breakdown of fatty acids, not all acetyl CoA enters the citric acid cycle. Your liver converts some acetyl CoA to ketone bodies, a process called **ketogenesis**. (See **Figure 7.20**.)

Ketogenesis is highly active when fatty acid oxidation in the liver produces such an abundance of acetyl CoA that it overwhelms the available supply of oxaloacetate. Unable to enter the citric acid cycle, the excess acetyl CoA is shunted to ketone body production. When a person has uncontrolled diabetes or is actually starving, ketone bodies help provide emergency energy to all body tissues, especially the brain and the rest of the CNS. Other than glucose, ketone bodies are your central nervous system's only other effective fuel.[12] (See the section "Special States" for more details on starvation and diabetes mellitus.) After the liver makes ketone bodies from acetyl CoA molecules, the ketone bodies travel to other tissues via the bloodstream. Tissue cells can convert the ketone bodies back to acetyl CoA for ATP production via the citric acid cycle and electron transport chain.[13]

To dispose of excess ketone bodies, your kidneys excrete them in urine and your lungs exhale them. If this removal process cannot keep up with the production process, ketone bodies accumulate in the blood—a condition called ketosis. (See Chapter 4, "Carbohydrates.") During even a brief fast, the catabolism of fat and protein increases the production of ketone bodies and results in ketosis.[14] Ketosis is likely to occur in uncontrolled type 1 diabetes mellitus, and in this situation, blood acidity rises quickly. This **ketoacidosis**

can lead to a coma and eventually death if untreated.[15] During a short fast, ketoacidosis rarely occurs.

Because "fat burns in a flame of carbohydrate," a very high-fat, low-carbohydrate diet promotes ketosis. The lack of carbohydrate inhibits formation of oxaloacetate, slowing entry of acetyl CoA into the citric acid cycle and rerouting acetyl CoA to form ketone bodies. Given time, however, the body can adapt to a very high-fat, low-carbohydrate diet and avoid ketosis. Eskimos, for example, sometimes live almost entirely on fat but do not develop ketosis. Even brain cells can adapt to derive 50 to 75 percent of their fuel from ketone bodies (principally beta-hydroxybutyrate) after a few weeks of a low supply of glucose, their preferred fuel.[16]

Key Concepts *Although some ketone bodies are made and used for energy all the time, a lack of available carbohydrate accelerates ketone body production. Three types of ketone bodies—acetoacetate, beta-hydroxybutyrate, and acetone—can be made from any precursor of acetyl CoA: pyruvate, fatty acids, glycerol, and certain amino acids. Ketone bodies become an important fuel source during starvation, uncontrolled diabetes mellitus, and very high-fat, low-carbohydrate diets. In type 1 diabetes mellitus, an accumulation of ketone bodies can acidify the blood, a dangerous condition known as ketoacidosis.*
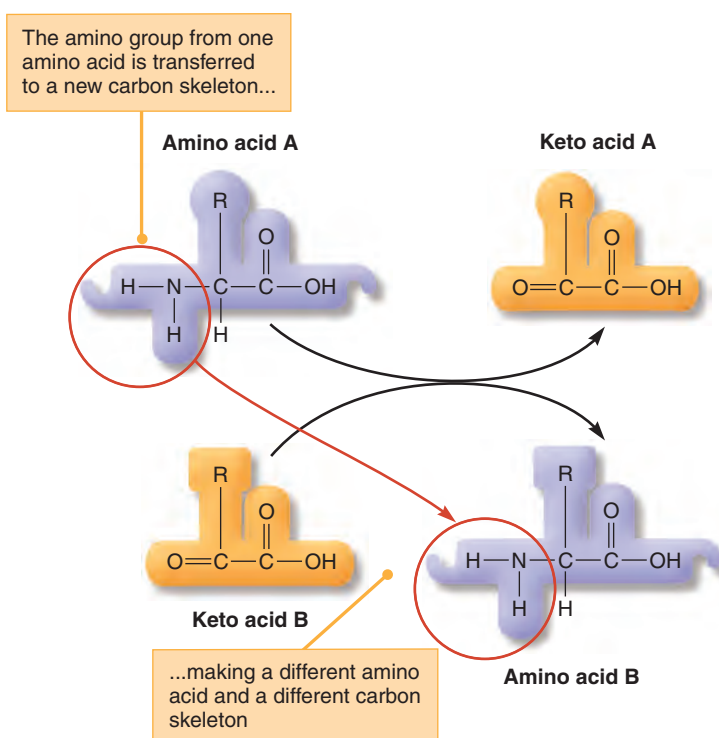

Figure 7.21 **Transamination.** A transamination reaction transfers the amino group from one amino acid to form a different amino acid.

Making Protein (Amino Acids)

Your body rebuilds proteins from a pool of amino acids in your cells. But how is that amino acid pool replenished? Your diet supplies some amino acids, the breakdown of body proteins supplies some, and cells make some. During protein synthesis, your cells can make dispensable amino acids and retrieve indispensable amino acids from the bloodstream. Your cells cannot make indispensable amino acids, however. If a cell lacks an indispensable amino acid and your diet doesn't supply it, protein synthesis stops. The cell breaks down this incomplete protein into its constituent amino acids, which are returned to the bloodstream. (See Chapter 6, "Proteins and Amino Acids," for more details of protein synthesis.)

Biosynthesis: Making Amino Acids

Your body uses many different pathways to synthesize dispensable amino acids. Each pathway is short, involving just a few steps, and builds amino acids from carbon skeletons. Pyruvate, along with intermediates of glycolysis and the citric acid cycle, supplies the carbon skeletons.

To make dispensable amino acids, the body transfers the amino group from one amino acid to a new carbon skeleton, a process called **transamination** (see **Figure 7.21**). To make the amino acid alanine, for example, pyruvate swipes an amino group from the amino acid glutamic acid to yield alanine and alpha-ketoglutaric acid. Transamination requires several enzymes. One group of enzymes, known as the aminotransferases, is derived from the B vitamin pyridoxine (B_6). Although vitamin B_6 deficiency is rare, a lack of B_6 will inhibit amino acid synthesis and impair protein formation.

transamination [TRANS-am-ih-NAY-shun] The transfer of an amino group from an amino acid to a carbon skeleton to form a different amino acid

Key Concepts *Proteins are made from combinations of indispensable and dispensable amino acids. The body synthesizes dispensable amino acids from pyruvate, other glycolytic intermediates, and compounds from the citric acid cycle. To form amino acids, transamination reactions transfer amino groups to carbon skeletons.*

Regulation of Metabolism

Just as the cruise control on your car regulates the vehicle's speed within a narrow range, your body tightly controls the reactions of your metabolic pathways. Whether highly or minimally active, each pathway proceeds at just the right speed, not too fast and not too slow. How does your body achieve this remarkable control? Although a number of strategies operate simultaneously, certain hormones are the master regulators.

FYI
For Your Information

Key Intersections Direct Metabolic Traffic

Pyruvate Is Pivotal

Pyruvate is a pivotal point in the metabolic pathways. How does it select a path? What determines its destination? When ATP levels are low, cellular energy is in short supply, so the metabolic pathways flow toward the production of ATP. Depending on oxygen availability, low ATP routes pyruvate to acetyl CoA or lactate. When ATP is abundant, cells have ample energy, so the biosynthetic pathways prevail as pyruvate is converted to oxaloacetate or the amino acid alanine; oxaloacetate is converted to glucose and stored as glycogen.

To Acetyl CoA

When cells need ATP and have readily available oxygen, they rapidly convert pyruvate to acetyl CoA. This irreversible reaction commits the carbons of carbohydrates to oxidation by the citric acid cycle or to the biosynthesis of lipids. Acetyl CoA cannot be converted to glucose.

To and from Lactate

When cells need ATP but lack readily available oxygen, they reroute most pyruvate to form lactate. Although this route is always at least minimally active, it prevails when oxygen levels are low. Reversible reactions convert pyruvate to lactate, so these substances are interconvertible. For more about lactate and its various fates, see the feature "Lactate Is Not a Metabolic Dead End" in Chapter 14. The reaction that converts pyruvate to lactate uses energy carried by NADH, so it also produces NAD^+. This regeneration of NAD^+

is critical to continued glycolysis. Anaerobic conditions cut off the supply of NAD^+ from other sources, so without the NAD^+ generated in the production of lactate, glycolysis would stop.

To Oxaloacetate

Cells also can convert pyruvate to oxaloacetate, another pivotal molecule. Oxaloacetate can react with acetyl CoA to start the citric acid cycle when ATP is needed, or it can provide the building blocks to make glucose.

Oxaloacetate is essential for acetyl CoA's entry into the citric acid cycle. A steady supply of oxaloacetate is critical to the citric acid cycle's efficient extraction of energy from fatty acids. Carbohydrate feeds the pool of oxaloacetate as reactions break down carbohydrate to pyruvate and irreversibly convert the pyruvate to oxaloacetate. Cells can also make glucose from this oxaloacetate and store energy in the branched glucose chains of glycogen.

When cells have abundant ATP, they restrict the activities of certain enzymes, thus slowing the entry of acetyl CoA into the citric acid cycle. This reroutes the acetyl CoA into energy-storage pathways to form fatty acids so as to store energy as fat.

To and from Alanine

Since a reversible process converts pyruvate to the amino acid alanine, pyruvate and alanine are interconvertible. Although alanine is the only amino acid made from pyruvate, many other amino acids can be converted to pyruvate. Thus, pyruvate is located at a major junction of amino acid and carbohydrate metabolism.
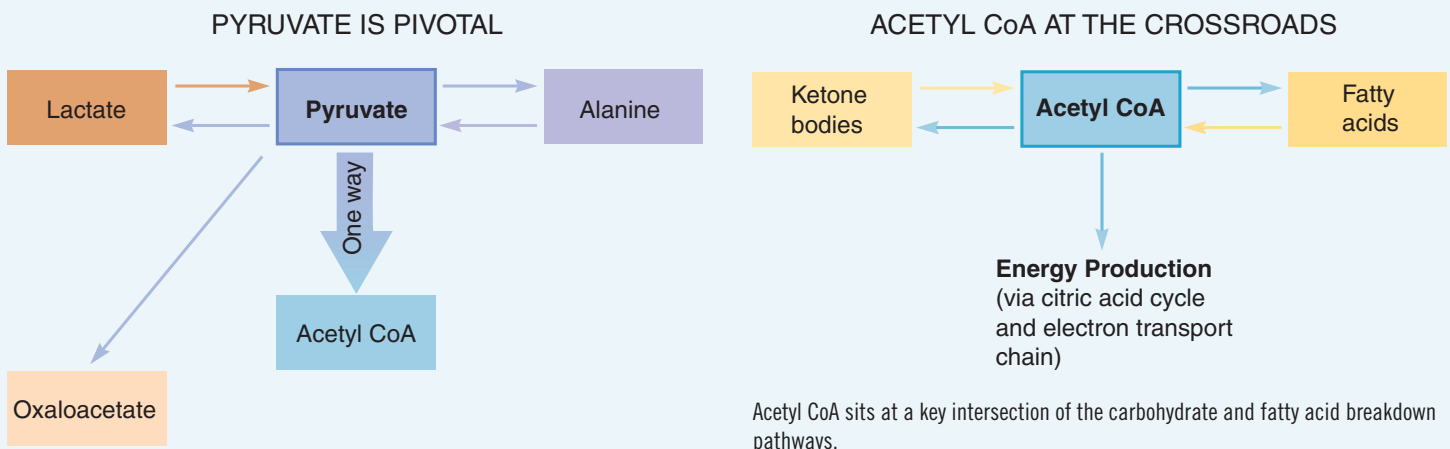
Acetyl CoA at the Crossroads

Acetyl CoA, like pyruvate, stands at a pivotal point in metabolism. The breakdown pathways for glucose, fatty acids, and some amino acids converge at acetyl CoA. Once formed,

Hormones of Metabolism

Hormones are chemical messengers that help determine whether metabolic processing favors catabolic (breakdown) or anabolic (building) pathways. The major regulatory hormones are insulin, glucagon, cortisol, and epinephrine.

The pancreas secretes insulin, the leader of the storage (anabolic) team. Its mission is to decrease the amount of glucose in the blood, so it promotes carbohydrate use and storage (as glycogen). Because insulin stimulates the use of glucose over fat, its actions are said to be *fat-sparing*. In addition, insulin promotes fat storage in adipose tissue, cellular uptake of amino acids, and assembly of these amino acids into proteins. It also inhibits the breakdown of body proteins.

The pancreas also secretes glucagon, the leader of the breakdown (catabolic) team. Glucagon's mission is to increase the amount of glucose in

PYRUVATE IS PIVOTAL

The demand for ATP and the availability of oxygen determine pyruvate's destination.

ACETYL CoA AT THE CROSSROADS

Acetyl CoA sits at a key intersection of the carbohydrate and fatty acid breakdown pathways.

what are acetyl CoA's options? It cannot return to pyruvate or make glucose, but acetyl CoA can enter major energy-producing and biosynthetic pathways. The body's energy status determines the predominant route.

To Energy Production

When cells need ATP and have oxaloacetate available, acetyl CoA enters the citric acid cycle for the ultimate production of ATP by the electron transport chain.

To and from Ketone Bodies

When the production of oxaloacetate does not match acetyl CoA production, acetyl CoA cannot enter the citric acid cycle, so the metabolic pathways shunt acetyl CoA to form ketone bodies.

To and from Fatty Acids

When energy is abundant, acetyl CoA molecules become building blocks for fatty acid chains. The body assembles these fatty acid chains into triglycerides and stores them in adipose tissue.

circulation; it stimulates the breakdown of liver glycogen. The adrenal glands secrete two other members of the breakdown team—the hormones cortisol and epinephrine. Cortisol promotes the breakdown of amino acids for gluconeogenesis and helps increase the activity of the enzymes that drive gluconeogenic reactions.[17] Epinephrine stimulates the conversion of glycogen to glucose in muscle, increasing the amount of glucose available.

The actions of each team ebb and flow in response to the levels of available nutrients.[18] Although both the storage and the breakdown teams are always active, storage dominates in times of plenty, and breakdown dominates in times of need.

Key Concepts *Hormones and other factors regulate the balance of anabolic and catabolic pathways in energy metabolism. The hormone insulin stimulates glycogen, protein, and triglyceride synthesis. The hormones glucagon, cortisol, and epinephrine stimulate breakdown of glycogen and triglycerides.*

Special States

Now you can put your new knowledge of metabolism to work by evaluating case studies of special physiological states: feasting, fasting, stress, diabetes mellitus, and exercising. What happens to your metabolism under each situation? Read on to find out which states stimulate breakdown and which stimulate biosynthesis.

Feasting

You're stuffed. You just ate a huge holiday dinner: two servings of turkey with a big ladle of gravy and ample servings of dressing, mashed potatoes, caramelized sweet potatoes, green peas, and two bread rolls. To top it off, you ate a piece of pumpkin pie with whipped cream. You meant to stop there; you loudly proclaimed, "I'm so full, I can't eat another bite!" But eventually your grandmother convinced you to taste her special pecan pie. Gosh, that was good! But now you are lying prostrate on the couch, uncomfortable and bloated, with your belt loosened. Your feasting may be finished for now, but your body's work has just begun.

Your meal led to a huge influx of carbohydrate, fat, and protein—a plentiful supply for your tissues and far more energy than you need for life as a couch potato. The influx of food triggers the rapid secretion of the storage hormone insulin and inhibits the release of the breakdown hormones glucagon, cortisol, and epinephrine. Insulin is sometimes called the "hormone of plenty" because when energy is abundant, it promotes the replenishment of energy stores (glycogen and fat), the synthesis of protein, and the maintenance and repair of tissues. Its suppression of glucagon and cortisol reduces the rate of breakdown.

The storage hormone insulin signals your cells to "store, store, store!" Consequently, much of your holiday dinner will wind up stored as fat. The surplus carbohydrate first enters glycogen stores, filling their limited capacity. In the short term, excess carbohydrate primarily readjusts your body's fuel preferences.[19] In a fat-sparing shift, your body maximizes its use of carbohydrate and minimizes its use of fat, thus promoting fat storage.[20] Although your body does not directly make appreciable amounts of fat from carbohydrate, the shift in fuel use triggered by excess carbohydrate still leads to increased fat stores and weight gain.

What happens to the surplus fat and protein? Fat tissue is the perfect energy storage package for both. Although some ATP is produced from dietary fat, nearly all excess dietary fat becomes body fat. Excess protein, beyond what's needed to replenish the overall body pool of amino acids, also heads to fat storage. (See **Figure 7.22**.)

The Return to Normal

After this frenzied bout of storage, the amount of glucose and triglyceride circulating in the bloodstream drops to the fasting level. The level of amino acids in the blood also returns to baseline, and the secretion of insulin slows.

Hours later, after a nap and perhaps a game of touch football, a further decline in blood glucose levels signals the pancreas to secrete the breakdown hormone glucagon. Glucagon broadcasts the order "Release the glucose!" and your body swings into action to counteract falling blood glucose levels. The body breaks down liver glycogen to glucose, which is released into the bloodstream. Glucagon also stimulates the production of glucose from amino acids and slows the synthesis of glycogen and fatty acids. If blood glucose levels continue to fall, the adrenal glands secrete epinephrine, which signals the liver to further increase its release of glucose into the bloodstream. Epinephrine also stimulates the breakdown of muscle glycogen to form glucose that muscles can use. This glucose does not enter the bloodstream and is immediately available for muscle tissue to mount a fight-or-flight response to danger.

If low blood glucose levels persist for hours or days, the pituitary and adrenal glands join the battle by secreting growth hormone and cortisol, respectively. These hormones cause most cells to shift their fuel usage from glucose to fatty acids. Cortisol also promotes the breakdown of amino acids, and gluconeogenesis begins to ramp up and make glucose from circulating amino acids.[21] All breakdown hormones work in concert to maintain blood glucose levels and ensure a constant supply of glucose for the central nervous system and red blood cells[22]—until it is time to attack the leftovers!

Key Concepts *Feasting, or taking in too many calories, stimulates anabolic processes such as glycogen and triglyceride synthesis. Insulin is the key hormone that promotes synthesis and storage of glycogen and fat. Your body resists making fat from excess carbohydrate, but shifts its fuel preferences. This shift still leads to the accumulation of fat stores.*

Fasting

Feasting on a holiday dinner floods your body with excess energy that is stored for future use. In contrast, fasting and starvation deprive you of energy, so your body must employ an opposing strategy—the mobilization of fuel. (See **Figure 7.23**.) Whether starvation occurs in a child during a famine, a young woman with anorexia nervosa, a patient with AIDS wasting syndrome, or a person who is intentionally fasting, the body responds in the same way.

Some people deprive themselves of food for a particular purpose—to lose weight, to stage a political protest, to participate in a religious fast, or to "cleanse" their bodies. The cleansing motivation is ironic, because fasting actually unleashes potentially damaging toxins to circulate throughout the
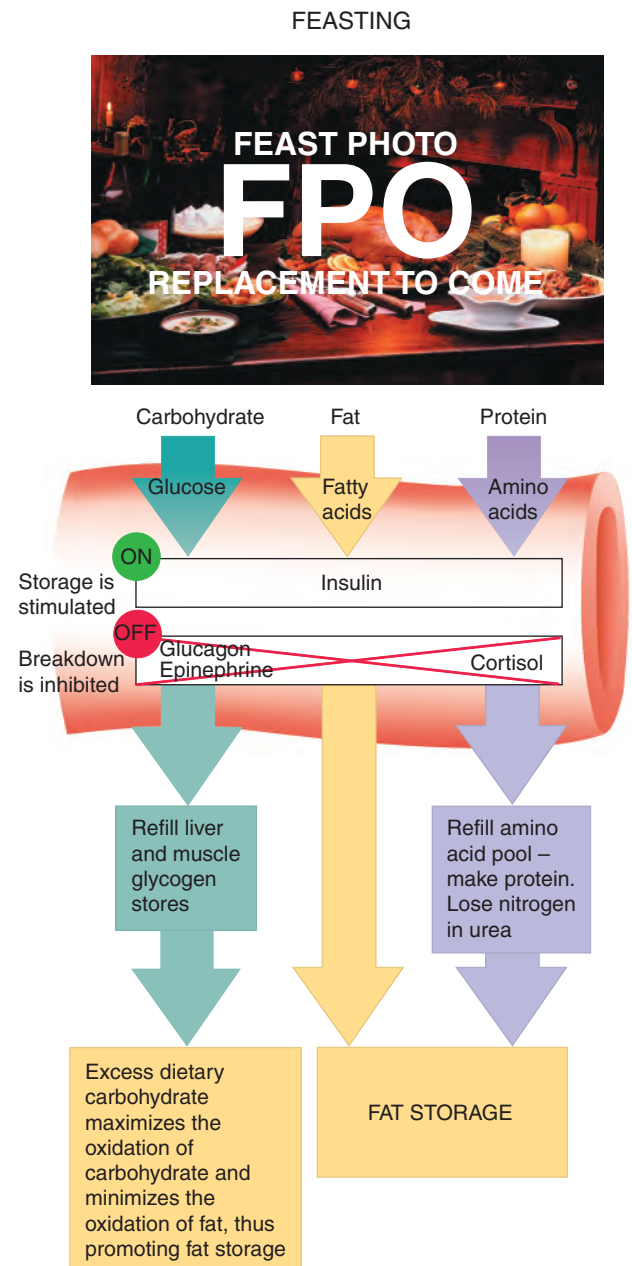
FEASTING

Figure 7.22 **Feasting.** Your body deals with a large influx of energy-yielding nutrients by increasing cellular uptake of glucose and promoting fat storage.

body. Over time, fat stores accumulate environmental toxins, such as DDT, PCBs, and benzene.[23] In the case of PCBs, despite the fact that Congress banned their use decades ago, more than 9 of 10 Americans still have traces of these compounds in their body fat.[24] When bound in adipose tissue, toxins are relatively harmless. Fasting, however, breaks down adipose tissue and releases these toxins, giving them a second chance to damage cells. Although the liver—the body's detoxification center—and the intestines remove a small

FYI
For Your Information

Metabolic Profiles of Important Sites

Brain

What powers your brain? Glucose! But brain cells cannot store glucose, so they need a constant supply. Your brain uses about 120 grams of glucose daily, which corresponds to a dietary energy intake of about 420 kilocalories. When your body's at rest, your brain accounts for about 60 percent of your glucose use.[1]
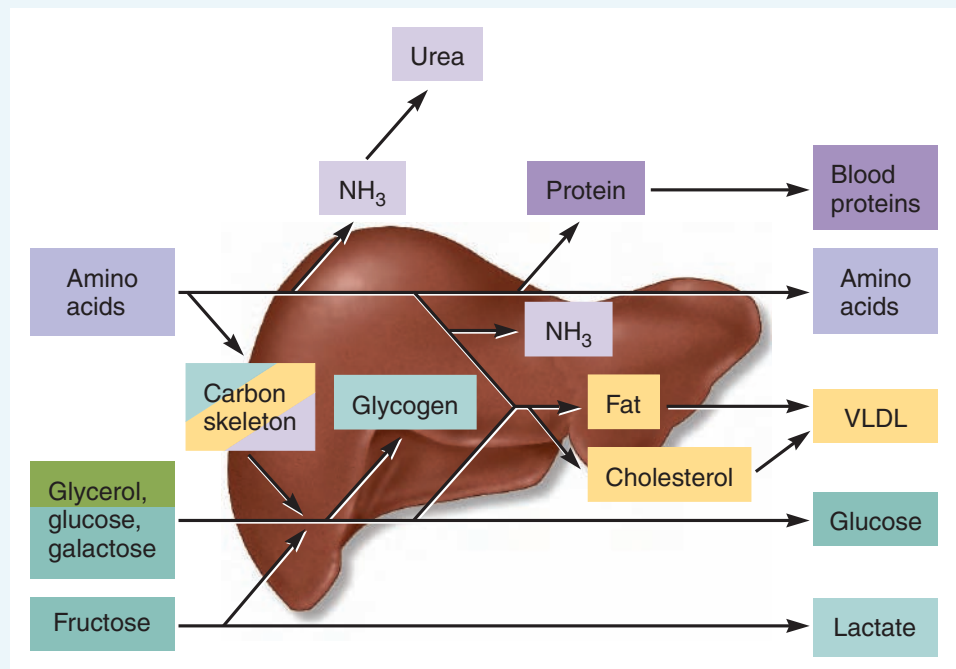
What happens during starvation? When glucose is in short supply, the liver comes to the rescue by converting fatty acids to ketone bodies. Ketone bodies are a critical source of replacement fuel that augments the supply of glucose to the brain.

Still, some brain cells can use only glucose. These cells survive by breaking down amino acids to make glucose via gluconeogenesis.[2]

Muscle

Muscle can use a variety of fuels: lactate, fatty acids, ketone bodies, glucose, and pyruvate. Unlike your brain, muscle stores large amounts of carbohydrate fuel—about 1,200 kilocalories—in the form of glycogen. This represents about three-fourths of the glycogen in your body. To fuel bursts of activity, muscle cells readily obtain glucose from glycogen.[3]

When your muscles actively contract, they rapidly deplete available oxygen, thus inhibiting the production of ATP via the aerobic breakdown pathways. ATP formed during glycolysis becomes the primary fuel. Muscle cells use the pyruvate from glycolysis to form lactate. The lactate travels to the liver, which converts it to glucose. The glucose returns to your muscle cells and undergoes anaerobic glycolysis. Known as the Cori cycle, this pathway rapidly produces ATP while shifting part of the metabolic burden from your muscles to your liver.

Whereas fatty acids are the primary fuel for muscles at rest, glycogen and glucose fuel short, intense activity, such as when you are sprinting to arrive at class on time. During prolonged exercise, such as running a marathon, fatty acid oxidation kicks in to help out. Fatty acids can directly supply energy or form ketone bodies to augment the fuel supply.

Your muscle cells are major sites for glycolysis, beta-oxidation, and the common aerobic breakdown pathways: the citric acid cycle and the electron transport chain.

portion of these liberated toxins, the balance remain in circulation, where they can wreak havoc.

Survival Priorities and Potential Energy Sources

Starvation confronts your body with several dilemmas. Where will it get energy to fuel survival needs? Which should it burn first—fat, protein, or

Adipose Tissue

Adipose tissue is your body's primary energy storage depot. A 55-kilogram (121-pound) woman with 25 percent body fat (a healthy body composition) stores about 105,000 kilocalories in adipose tissue, enough energy to run 40 marathons! Your liver assembles fatty acids into triglycerides and sends them to adipose tissue for storage. Eighty to 90 percent of the volume of an adipose cell is pure triglyceride.[4]

To supply fatty acids for energy production, adipose cells break down triglycerides to glycerol and free fatty acids.

Liver

Most substances absorbed by your intestines eventually pass through the liver, the body's main metabolic factory. This versatile organ performs glycolysis, gluconeogenesis, beta-oxidation, lipogenesis, ketogenesis, and cholesterol synthesis.

Your liver can store up to 400 kilocalories of glucose as glycogen. When blood glucose levels are low, the liver breaks down stored glycogen to glucose or makes glucose from noncarbohydrate precursors. Several sources pitch in to provide glucose building blocks: muscle supplies lactate and the amino acid alanine; adipose tissue supplies glycerol; and your diet supplies glucogenic amino acids.

The liver is the traffic cop for lipid metabolism. When energy is abundant, the liver directs fatty acids to storage. When energy is scarce, the liver breaks down fatty acids to form ATP. If an inadequate amount of carbo-hydrate blocks the entry of acetyl CoA into the citric acid cycle, the liver redirects fatty acids to ketone bodies.

Kidney

Your kidneys are important disposal systems of metabolic wastes. Without rapid elimination, these wastes can build up to toxic levels. When your liver deaminates amino acids (removes amino groups), a cooperative effort eliminates the released nitrogen. Your liver captures the nitrogen in urea, which it releases into the bloodstream. The kidneys filter out the urea and excrete it in urine.

The kidneys can make glucose (gluconeogenesis) from amino acids and other precursors. During prolonged starvation, the kidneys produce glucose in amounts that rival production by the liver![5]

Heart

Your heart relies on an interesting mix of fuels. Rather than glucose, which it uses in only small amounts, your heart relies on free fatty acids, lactate, and ketone bodies. During normal conditions, free fatty acids supply the bulk of its energy.[6] When glucose is in short supply, your heart makes a special effort to spare its use. It uses ketone bodies, then free fatty acids, and finally glucose as its fuel source.[7] During heavy exercise, your body releases large amounts of lactate into the bloodstream. Compared with other types of tissue, your heart is particularly capable of using lactate to supply the energy it needs.[8]

Red Blood Cells

Just like the brain, red blood cells rely primarily on glucose for fuel. In these cells, glycolysis and the pentose phosphate pathway (an alternative energy-producing pathway) extract energy from glucose. Since red blood cells have no mitochondria, they do not contain the pathways for beta-oxidation, the citric acid cycle, or the electron transport chain.

The pentose phosphate pathway generates the NADPH that is critical for a red blood cell's health. Energy carried by NADPH helps maintain cell membrane pliability and ion transport capabilities. NADPH also helps preserve iron in the cell's hemoglobin and prevent premature breakdown of the cell's proteins.[9]

1   Berg JM, Tymoczko JL, Stryer L. *Biochemistry.* 6th ed. New York: WH Freeman, 2007.

2   Guyton AC, Hall JE. *Textbook of Medical Physiology.* 10th ed. Philadelphia: WB Saunders, 2000.

3   Berg, Tymoczko, Stryer. *Biochemistry.*

4   Guyton, Hall. *Textbook of Medical Physiology.*

5   Ibid.

6   Schaap FG, van der Vusse GJ, Glatz JF. Fatty acid-binding proteins in the heart. *Mol Cell Biochem.* 1998;180:1–2, 43–51.

7   Murray RK, et al. *Harper's Biochemistry.* 25th ed. Stamford, CT: Appleton & Lange, 1999.

8   Guyton, Hall. *Textbook of Medical Physiology.*

9   Ibid.

SHORT-TERM FASTING

OFF		
	Insulin	

ON		
Glucagon: liver glycogen ⟶	glucose	
Epinephrine: muscle glycogen ⟶	glucose	
Cortisol: amino acid breakdown ⟶	glucose	

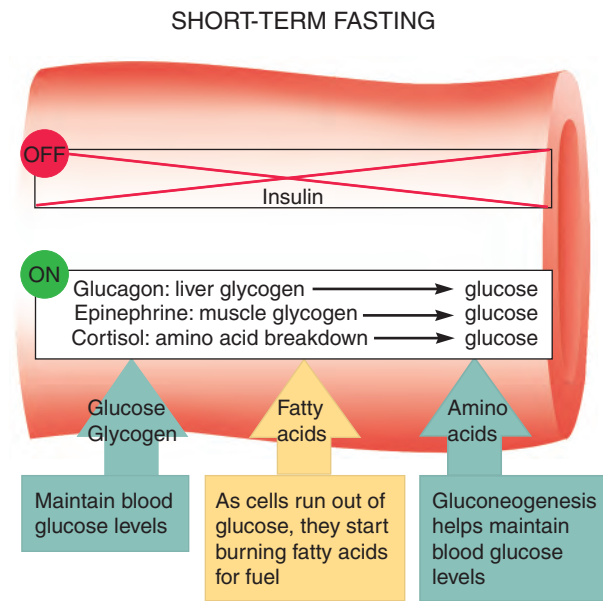| Glucose Glycogen	Fatty acids	Amino acids
Maintain blood glucose levels	As cells run out of glucose, they start burning fatty acids for fuel	Gluconeogenesis helps maintain blood glucose levels

Figure 7.23 **Fasting.** During a short fast, cells first break down liver glycogen to maintain blood glucose levels. They also burn fatty acids and ramp up the production of glucose from amino acids.

carbohydrate? Can it conserve its energy reserves? Which tissues should it sacrifice to ensure survival?

Your body's first priority is to preserve glucose-dependent tissue: red blood cells, brain cells, and the rest of the central nervous system. Your brain will not tolerate even a short interruption in the supply of adequate energy. Once your body depletes its carbohydrate reserves, it begins sacrificing readily available circulating amino acids to make glucose and ATP.

Your body's second priority is to maintain muscle mass. In the face of danger, we rely upon our ability to mount a fight-or-flight response. This survival mechanism requires a large muscle mass, allowing us to move quickly and effectively. Your body grudgingly uses muscle protein for energy and breaks it down rapidly only in the final stages of starvation.

Although your body stores most of its energy reserve in adipose tissue, triglycerides are a poor source of glucose. Although your body can make a small amount of glucose from the glycerol backbone, it cannot make any glucose from fatty acids. As a consequence, your body's primary energy stores—fat—are incompatible with your body's paramount energy priority—glucose for your brain. To meet this metabolic challenge, your body's antistarvation strategies include a glucose-sparing mechanism. It shifts to fatty acids and ketone bodies to fuel its needs. In time, even your brain adapts as most, but not all, brain cells come to rely on ketone bodies for fuel.

THINK About It 4

The Prolonged Fast: In the Beginning

What happens during the fasting state? Let's take a metabolic look at Fasting Frank, a political activist determined to make a dramatic statement. Frank begins fasting at sundown, planning to drink only water and consume no other foods or liquids.

The first few hours are no different from your nightly fast between dinner and breakfast. As blood glucose drops to fasting baseline levels, the liver breaks down glycogen to glucose. Gluconeogenesis becomes highly active and begins churning out glucose from circulating amino acids. The liver pours glucose into the bloodstream to supply other organs and shifts to fatty acids for its own energy needs. Muscle cells also start burning fatty acids. After about 12 hours, the battle to maintain a constant supply of blood glucose exhausts nearly all carbohydrate stores.[25]

The First Few Days

During the next few days, fat and protein are the primary fuels. To preserve structural proteins, especially muscle mass, Frank's body first turns to easily metabolized amino acids. It uses some to produce ATP and others to make glucose. Glucogenic amino acids, especially alanine, furnish about 90 percent of the brain's glucose supply. Glycerol from triglyceride breakdown supplies the remaining 10 percent. After a couple of days, production of ketone bodies ramps up, augmenting the fuel supply. (See **Figure 7.24**.)

The Early Weeks

As starvation continues, Frank's body initiates several energy-conservation strategies. It ratchets down its energy use by lowering body temperature, pulse rate, blood pressure, and resting metabolism. Frank becomes lethargic,

reducing the amount of energy expended in activity. He also begins to have detectable signs of mild vitamin deficiencies as his body depletes its small reserves of vitamin C and most B vitamins.

If Frank's body continued to rapidly break down protein, he would survive less than three weeks. To avoid such a quick demise, protein breakdown slows drastically and gluconeogenesis drops by two-thirds or more.[26] To pick up the slack, Frank's body doubles the rate of fat catabolism to supply fatty acids for fuel and glycerol for glucose. Ketone bodies pour into the bloodstream and provide an important glucose-sparing energy source for the brain and red blood cells. After about 10 days of fasting, ketone bodies meet most of the nervous system's energy needs. Some brain cells, however, can use only glucose. To maintain a small, but essential, supply of blood glucose, protein breakdown crawls along, supplying small amounts of amino acids for gluconeogenesis.

Several Weeks of Fasting

After several weeks of fasting, Frank is increasingly susceptible to disease and infection. His severe micronutrient deficiencies add to his overall poor health.

The average person has about three weeks of fat stores, and the rate of fat depletion is fairly constant. As the later stages of starvation exhaust the final fat stores, the body turns again to protein, its sole remaining fuel source. Normally, Frank's body breaks down about 30 to 55 grams of protein each day, but now it accelerates the rate to several hundred grams daily. (See **Figure 7.25**.) You can see some of the effects of accelerated protein breakdown in

Figure 7.24 Shifting fuel selection during starvation. To fuel its needs as blood glucose levels decline, the body shifts from glucose to fatty acids and ketone bodies.

Figure 7.25 Starvation and fuel sources. During starvation, carbohydrate is exhausted quickly, and fat becomes the primary fuel. Burning fat without available carbohydrate produces ketone bodies, a by-product that the body can use as fuel. Glucose produced from amino acids and the glycerol portion of fatty acids help fuel the brain. The body conserves protein and breaks it down rapidly only after most fat stores are depleted.
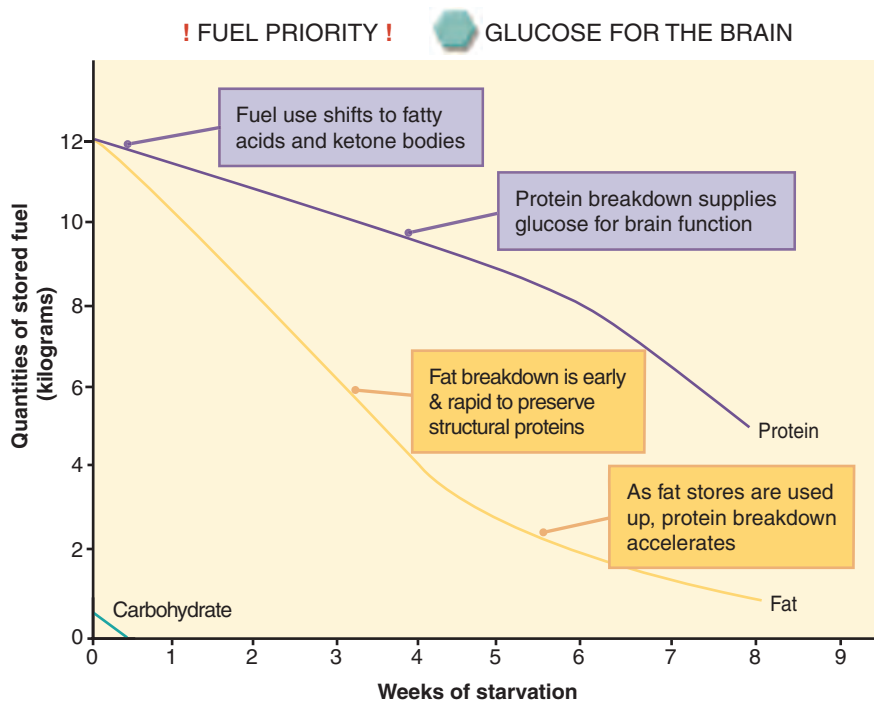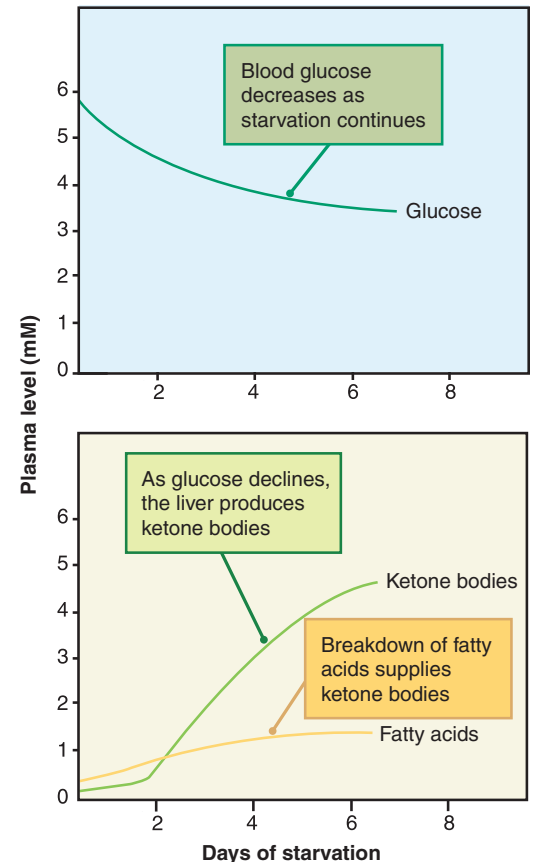
starving children suffering from kwashiorkor. The loss of blood proteins causes the swollen limbs and bulging stomachs that typify this type of protein-energy malnutrition (PEM). (For more detail on PEM, see Chapter 6, "Proteins and Amino Acids.").

The End Is Near

In the final stage of protein depletion, the body deteriorates rapidly. You can see the severe muscle atrophy and emaciation in photos of Holocaust victims. Their bodies sacrificed muscle tissue in attempts to preserve brain tissue. Even organ tissues were not spared. The final stage of starvation attacks the liver and intestines, greatly depleting them. It moderately depletes the heart and kidneys, and even mounts a small attack on the nervous system. Amazingly, starving people can cling to life until they lose about half their body proteins, after which death generally occurs.

How long can a person survive total starvation? A while ago, some Irish prisoners starved themselves to death—the average time was 60 days.[27] Most people survive total starvation for one to three months. Starvation survival factors include the following:

- *Starting percentage of body fat:* Ample adipose tissue prolongs survival.
- *Age:* Middle-aged people survive longer than children and the elderly.
- *Sex:* Women fare better due to their higher proportion of body fat.
- *Energy expenditure levels:* Increased activity leads to an earlier demise.

Key Concepts *Fasting, or underconsumption of energy (calories), favors catabolic pathways. The body first obtains fuel from stored glycogen, and then from stored fat and functional proteins, such as muscle. Over time, the body adapts to using increasing amounts of ketone bodies as fuel because limited carbohydrate is available. Larger stores of fat in adipose tissue extend survival time during starvation. In prolonged starvation, the body catabolizes muscle tissue to continue minimal production of glucose from amino acids.*

Psychological Stress

Our bodies respond to stress in the same way that they respond to danger—we mobilize for "fight or flight." In primitive times, this response would culminate in intense physical activity; we actually did fight or flee. In modern times, there often is no such physical outlet. Also, the specific short-term triggering event, such as an attack by a lion, has been largely replaced by a never-ending assault from noise, overcrowding, competition, and economic pressures. Today, many people suffer from chronic stress—a condition that scientists have linked to diseases such as hypertension and heart disease that are common in the modern world.

Chronic psychological stress can increase glucose production while impairing glucose uptake, so that a person needs more insulin for glucose to enter cells. When stressed, our bodies increase the availability of biological building blocks and ramp up energy production, especially in muscle tissues that are related to movement. Stress hormones, including epinephrine, cortisol, growth hormone, and glucagon, stimulate the breakdown of glycogen and the production of glucose. The elevated levels of blood glucose and increased metabolic rate provide energy to help us respond to threats, whether real or perceived.

Cells prepare for action by taking up glucose at a near maximal rate.[28] This uptake slows the assimilation of new glucose. When the danger passes, cells need higher than normal amounts of insulin to return blood glucose to baseline levels. This condition, called glucose intolerance, is a known complication of chronic stress.[29]

Diabetes and Obesity

In type 1 diabetes mellitus, a lack of insulin limits the cellular uptake of glucose. The starving, glucose-deprived cells signal the liver to make more glucose. This combination of limited uptake and increased production causes abnormally high blood glucose levels. The starving cells turn to fatty acids for energy. Inside the cells, the increased rate of fatty acid oxidation, along with a lack of glucose, leads to the production of ketone bodies. In untreated type 1 diabetes mellitus, ketone bodies accumulate rapidly, causing ketosis and producing the characteristic smell of acetone on the breath. The blood becomes acidic, and the condition of a person with untreated type 1 diabetes mellitus can progress quickly to coma and death.

Obese people and individuals with type 2 diabetes mellitus often have only mildly elevated blood glucose levels, elevated fasting insulin levels, and glucose intolerance. Although insulin levels are adequate, their cells have difficulty taking up glucose, possibly due to a problem with insulin receptors. Because some glucose enters the cells, ketosis is less common among people with type 2 diabetes. (For more details on diabetes, see Chapter 14, "Diet and Health.")

Exercise

Exercise increases not only muscle fitness but also "cell fitness" by enhancing the ability of cells to take up glucose. In fact, regular exercise often can reduce the need for insulin in a person with diabetes.

Carbohydrate and fat are the primary fuels for physical activity, providing more than 90 percent of the energy used by contracting skeletal muscle. During low-intensity aerobic activities, such as walking, fat is a good fuel source. Carbohydrate is better suited to fuel high-intensity anaerobic efforts, such as fast running, that can be maintained for only a few minutes. As exercise intensity moves from low to high, the mix of fuels burned moves gradually from mostly fat to mostly carbohydrate. Which fuel predominates has important implications for how long an activity can be maintained. (See the Nutrition Science in Action feature "Fuel for Distance Walking.")

Key Concepts *Chronic psychological stress can cause glucose intolerance, so that a person needs more insulin for glucose to enter cells. In uncontrolled diabetes mellitus, cells react much as they do in starvation. Untreated type 1 diabetes mellitus can cause a dangerous accumulation of ketone bodies and acidification of the blood. Exercise enhances glucose uptake. Depending on the duration and intensity of exercise, your body chooses different mixes of metabolic fuels.*

Quick Bite

Sweet Urine
The word *diabetes* is Greek for "siphon," from *dia*, meaning "through," and *bainein*, meaning "to go." The word *mellitus* is Latin for "sweetened with honey." Diabetes mellitus means the flow of sweetened water. The disease causes a rise in blood sugar that spills into the urine. As early as the 1600s, some doctors would taste a patient's urine to confirm a diagnosis of diabetes mellitus.

Nutrition Science *in Action*

Fuel for Distance Walking

Observations: Humans naturally select a preferred walking speed (PWS), and the body's fuel selection can be critical to the total distance traveled. The body primarily uses carbohydrate (CHO) to fuel short, intense bursts of activity and uses fat to fuel endurance exercise. Lean humans store far more energy as fat than as CHO, and the choice of fuel may produce a 30-fold difference in the distance traveled.

Hypothesis: Humans select a preferred walking speed that primarily uses fat as fuel and does not deplete carbohydrate stores.

Experimental Plan: Recruit 12 healthy adults. Time the subjects as they walk four laps at their natural rate around a 53-meter track. After resting 10 minutes, subjects walk on a level treadmill for 10-minute increments at 3.2, 4.0, 4.8, 5.6, 6.4, and 7.2 kilometers per hour (kph). Using indirect calorimetry, estimate fat and CHO oxidation during each increment.

Results: The hypothesis is confirmed. The subjects' natural PWS was 4.7 kph. At speeds less than 4.8 kph, CHO oxidation rates remain low and fat oxidation is the primary fuel. At about 4.8 kph and beyond, CHO oxidation increases abruptly and rises rapidly.

Conclusion and Discussion: The major finding of this study was that able-bodied subjects naturally selected a walking speed just below the speed preceding an abrupt rise in CHO oxidation that would deplete the body's small stores of CHO quickly.

In a historical context, people able to naturally select the walking speed resulting in the greatest range would have a survival advantage when challenged with walking away from a region of food scarcity. Moreover, minimizing CHO depletion would defend the person's ability to engage in burst activity to escape predators or capture prey during the trek.

Source: Based on Willis WT, Ganley KJ, Herman RM. Fuel oxidation during human walking. *Metabolism.* 2005;54(6):793–799.
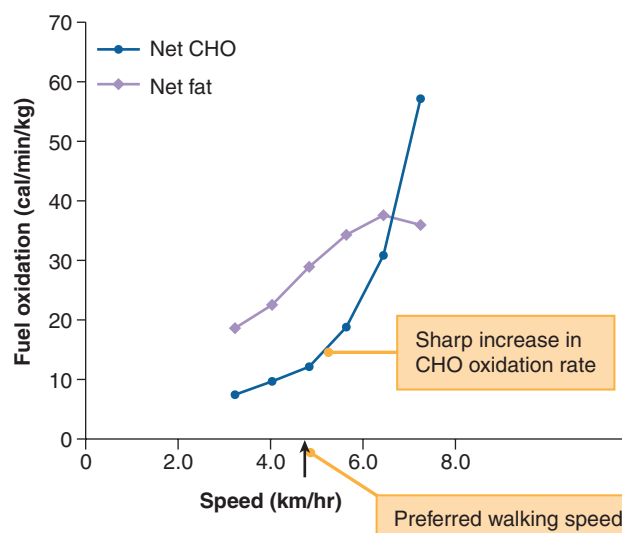
Learning Portfolio
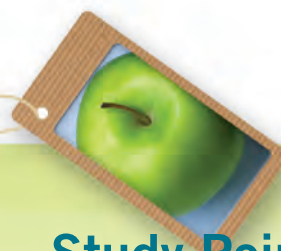
Key Terms

	page		page
acetyl CoA	000	glycogenolysis	000
adenosine diphosphate (ADP)	000	glycolysis [gligh-COLL-ih-sis]	000
adenosine monophosphate		guanosine triphosphate (GTP)	000
(AMP)	000	hydrogen ions	000
adenosine triphosphate		ketoacidosis	000
(ATP) [ah-DEN-oh-seen		ketogenesis	000
try-FOS-fate]	000	ketogenic	000
aerobic [air-ROW-bic]	000	ketones [KEE-tones]	000
anabolism [an-A-bol-iz-um]	000	Krebs cycle	000
anaerobic [AN-ah-ROW-bic]	000	lactate	000
beta-oxidation	000	lipogenesis	
biosynthesis	000	[lye-poh-JEN-eh-sis]	000
carnitine [CAR-nih-teen]	000	metabolic pathway	000
catabolism [ca-TA-bol-iz-um]	000	metabolism	000
cells	000	metabolites	000
chemical energy	000	mitochondria (mitochondrion)	000
citric acid cycle	000	mitochondrial membrane	000
coenzyme A	000	NADH	000
coenzymes	000	NADPH	000
cofactors	000	nicotinamide adenine	
Cori cycle	000	dinucleotide (NAD+)	000
cytoplasm	000	nucleus	000
cytosol	000	organelles	000
electron transport chain	000	oxaloacetate	000
FADH$_2$	000	oxidative phosphorylation	000
flavin adenine dinucleotide		photosynthesis	000
(FAD)	000	pyrophosphate (Pi)	000
glucogenic	000	pyruvate	000
gluconeogenesis [gloo-ko-		transamination	
nee-oh-JEN-uh-sis]	000	[TRANS-am-ih-NAY-shun]	000
glycogenesis	000	tricarboxylic acid (TCA) cycle	000

Study Points

- Energy is necessary to do any kind of work. The body converts chemical energy from food sources—carbohydrates, proteins, and fats—into a form usable by cells.

- Anabolic reactions (anabolism) build compounds. These reactions require energy.

- Catabolic reactions (catabolism) break compounds into smaller units. These reactions produce energy.

- Adenosine triphosphate (ATP) is the energy currency of the body.

- NADH, FADH$_2$, and NADPH are important carriers of hydrogen and high-energy electrons. NADH and FADH$_2$ are used in making ATP, while NADPH is used in biosynthetic reactions.

- Cells extract energy from carbohydrate via four main pathways: glycolysis, conversion of pyruvate to acetyl CoA, the citric acid cycle, and the electron transport chain.

- The citric acid cycle and electron transport chain require oxygen. Glycolysis does not.

- The electron transport chain produces more ATP than other catabolic pathways.

- To extract energy from fat, first triglycerides are separated into glycerol and fatty acids. Next, beta-oxidation breaks down the fatty acids to yield acetyl CoA, NADH, and FADH$_2$. The acetyl CoA enters the citric acid cycle, producing more NADH and FADH$_2$. The NADH and FADH$_2$ molecules deliver their high-energy electrons to the electron transport chain to make ATP.

- To extract energy from an amino acid, first it is deaminated (the amino group is removed). Depending on the structure of the remaining carbon skeleton, it enters the catabolic pathways as pyruvate, acetyl CoA, or a citric acid cycle intermediate. The citric acid cycle and the electron transport chain complete the production of ATP.

- The liver converts the nitrogen portion of amino acids to urea, which the kidneys excrete.

- Tissues differ in their preferred source of fuel. The brain, nervous system, and red blood cells rely primarily on glucose, whereas other tissues use a mix of glucose, fatty acids, and ketone bodies as fuel sources.

- When carbohydrate is available, glucose can be stored as glycogen in liver and muscle tissue.

- Glucose can be produced from the noncarbohydrate precursors glycerol and some (glucogenic) amino acids, but not from fatty acids.

- The hormone insulin regulates metabolism by favoring anabolic pathways. It promotes the uptake of glucose by cells, thus removing it from the bloodstream.

- Glucagon, cortisol, and epinephrine stimulate catabolic pathways. These hormones promote the breakdown of glycogen to glucose and of amino acids to make glucose via gluconeogenesis. The breakdown of liver glycogen increases the amount of glucose in the blood.

- Feasting, or overconsumption of energy, leads to glycogen and triglyceride storage.

- Fasting, or underconsumption of energy, leads to the mobilization of liver glycogen and stored triglycerides. Starvation, the state of prolonged fasting, leads to protein breakdown as well and can be fatal.

Study Questions

1. What is the "universal energy currency"? Where is most of it produced?

2. Name the two energy-equivalent molecules that contain three phosphates as part of their structure. What makes these two molecules different? How many high-energy phosphate bonds do they contain?

3. In the catabolic pathways, which two molecules are major electron acceptors? After they accept electrons, which electron carriers do they become? What is the primary function of the electron carriers?

4. How many pyruvate molecules does glycolysis produce from one glucose molecule? What does the oxidative step after glycolysis produce? What does the citric acid cycle produce from a single glucose molecule?

5. Which two-carbon molecules does beta-oxidation form as it "clips" the links of a fatty acid chain? Which other molecules important to the production of ATP does beta-oxidation produce?

6. What dictates whether an amino acid is considered ketogenic or glucogenic?

7. What are ketone bodies and when are they produced?

8. Name the three tissues where energy is stored. Which contains the largest store of energy?

9. Define gluconeogenesis and lipogenesis. Under what conditions do they predominantly occur? What are their primary inputs and outputs?

Try This

Comparing Fad Diets

The purpose of this exercise is to have you evaluate two fad diets in regard to their metabolic consequences. The two diets, Cabbage Soup and Super Protein, are described below. Once you've reviewed them, answer the following questions: Will these diets result in weight loss? Why or why not? On the seventh day of each diet, which of the following metabolic pathways will be highly active?

- Glycogen breakdown
- Fat breakdown
- Gluconeogenesis
- Ketogenesis

Diet 1: The Cabbage Soup Diet

A person following the Cabbage Soup diet eats only a water-based soup made out of cabbage and a few other vegetables. Three to four meals per day of this restricted diet supply approximately 500 kilocalories per day. The diet is devoid of protein and fat and gets its calories from the small amount of carbohydrate in the vegetables. Think about what happens during starvation.

Diet 2: The Super Protein Diet

In the Super Protein diet, a person can eat an unlimited amount of protein-rich foods such as meat, poultry, eggs, and seafood, but no added fats or carbohydrates are allowed. The average person can consume about 1,400 kilocalories if he or she eats three or four small meals each

day. Think about what happens when little carbohydrate is available as a person metabolizes fat and protein.

Fasting for Ketones

The purpose of this experiment is to see whether a day without eating will cause your body to produce measurable ketones in your urine. Before starting your fast, check with your physician to be sure this won't pose any health risks. Go to your local pharmacy and ask the pharmacist for urine ketone strips (often called Ketostix). Bring them home and read the directions. Before you start your one-day fast, test your urine to see whether it has a detectable amount of ketones. Start a 24-hour fast (or fast for as long as you can go without food or calorie-containing fluids, but no longer than 24 hours) and test your urine at 6-hour intervals. Do you detect a color change on the strips as the day goes on? Why? What has happened metabolically as the day progresses?

Remember to drink lots of water!

References

1. Alberts B, Johnson A, Lewis J, et al. *Molecular Biology of the Cell*. 5th ed. New York: Garland, 2008.

2. Butte NF, Cabellero B. Energy needs: assessments and requirements. In: Shils ME, Shike M, Ross AC, et al., eds. *Modern Nutrition in Health and Disease*. 10th ed. Philadelphia: Lippincott Williams & Wilkins, 2006:136–148.

3. Stipanuk MH. *Biochemical and Physiological Aspects of Human Nutrition*. 2nd ed. Philadelphia: WB Saunders, 2006.

4. Nelson DL, Cox MM. *Lehninger Principles of Biochemistry*. 5th ed. New York: WH Freeman, 2008.

5. Berg JM, Tymoczko JL, Stryer L. *Biochemistry*. 6th ed. New York: WH Freeman, 2007.

6. Gropper SS, Smith JL, Groff JL. *Advanced Nutrition and Human Metabolism*. 5th ed. Belmont, CA: Wadsworth, 2009.

7. Nelson, Cox. *Lehninger Principles of Biochemistry*; and Berg, Tymoczko, Stryer. *Biochemistry*.

8. Burge B. Carnitine in energy production. *Healthline*. July 1999.

9. Sarubin-Fragakis A. *The Health Professional's Guide to Popular Dietary Supplements*. 3rd ed. Chicago: American Dietetic Association, 2007.

10. Gropper, Smith, Groff. *Advanced Nutrition and Human Metabolism*.

11. Berg, Tymoczko, Stryer. *Biochemistry*.

12. Stein JH. *Internal Medicine*. 4th ed. St. Louis, MO: Mosby-Yearbook, 1994.

13. Nelson, Cox. *Lehninger Principles of Biochemistry*.

14. Martini FH. *Fundamentals of Anatomy and Physiology*. 6th ed. San Francisco: Benjamin Cummings, 2004.

15. Anderson JW. Prevention and management of diabetes mellitus. In: Shils ME, Shike M, Ross CA, et al., eds. *Modern Nutrition in Health and Disease*. 10th ed. Philadelphia: Lippincott Williams & Wilkins, 2006:1043–1066.

16. Guyton AC, Hall JE. *Textbook of Medical Physiology*. 10th ed. Philadelphia: WB Saunders, 2000.

17. Nelson, Cox. *Lehninger Principles of Biochemistry*.

18. Griffin JE, Ojeda SR. *Textbook of Endocrine Physiology*. 4th ed. New York: Oxford University Press, 2000.

19. Joosen AMCP, Westerterp KR. Energy expenditure during overfeeding. *Nutr Metab*. 2006;3:25.

20. Minehira K, Vega N, Vidal H, et al. Effect of metabolism and expression of lipogenic enzymes in adipose tissue of lean and overweight humans. *Int J Obes*. 2004;28:1291–1298.

21. Nelson, Cox. *Lehninger Principles of Biochemistry*.

22. Martini. *Fundamentals of Anatomy and Physiology*.

23. Scheele JS. A comparison of the concentrations of certain pesticides and polychlorinated hydrocarbons in bone marrow and fat tissue. *J Environ Pathol Toxicol Oncol*. 1998:17(1):65–68.

24. Gower T. The fasting cure. *Health*. April 1999:61–63.

25. Guyton, Hall. *Textbook of Medical Physiology*.

26. Ibid.

27. Ganong WF. *Review of Medical Physiology*. 24th ed. Stamford, CT: McGraw-Hill, 2005.

28. Battilana P, Seematter G, Schneiter P, et al. Effects of free fatty acids on insulin sensitivity and hemodynamics during mental stress. *J Clin Endocrinol Metab*. 2001;86:124–128.

29. Summers RL, Woodward LH, Sanders DY, Hall JE. Graphic analysis for the study of metabolic states. *Adv Physiol Ed*. 1996;15(1):S81–S87.