4 Energy and Cellular Metabolism

There is no good evidence that … life evades the second law of thermodynamics, but in the downward course of the energy-flow it interposes a barrier and dams up a reservoir which provides potential for its own remarkable activities.

F. G. Hopkins, 1933. "Some Chemical Aspects of Life," presidential address to the 1933 meeting of British Association for the Advancement of Science.

BACKGROUND BASICS

35 DNA and RNA
65 Organelles
30 Lipids
39 Hydrogen bonds
32 Protein structure
46 Protein interactions
33 Covalent bonds
31 Carbohydrates
20 Graphing
34 ATP

Glucose crystals

Christine Schmidt, Ph.D., and her graduate students seed isolated endothelial cells onto an engineered matrix and watch them grow. They know that if their work is successful, the tissue that results might someday help replace a blood vessel in the body. Just as a child playing with building blocks assembles them into a house, the bioengineer and her students create tissue from cells. In both cases someone familiar with the starting components, building blocks or cells, can predict what the final product will be: blocks make buildings; cells make tissues.

Why then can't biologists, knowing the characteristics of nucleic acids, proteins, lipids, and carbohydrates, explain how combinations of these molecules acquire the remarkable attributes of a living cell? How can living cells carry out processes that far exceed what we would predict from understanding their individual components? The answer is *emergent properties* [p. 2], those distinctive traits that cannot be predicted from the simple sum of the component parts. For example, if you came across a collection of metal pieces and bolts from a disassembled car motor, could you predict (without prior knowledge) that, given an energy source and properly arranged, this collection could create the power to move thousands of pounds?

The emergent properties of biological systems are of tremendous interest to scientists trying to explain how a simple compartment, such as a phospholipid liposome [p. 62], could have evolved into the first living cell. Pause for a moment and see if you can list the properties of life that characterize all living creatures. If you were a scientist looking at pictures and samples sent back from Mars, what would you look for to determine whether life exists there?

Now compare your list with the one in **TABLE 4.1**. Living organisms are highly organized and complex entities. Even a one-celled bacterium, although it appears simple under a microscope, has incredible complexity at the chemical level of organization. It uses intricately interconnected biochemical reactions to acquire, transform, store, and use energy and information. It senses and responds to changes in its internal and external environments and adapts so that it can maintain homeostasis. It reproduces, develops, grows, and dies; and over time, its species evolves.

TABLE 4.1 Properties of Living Organisms

1. Have a complex structure whose basic unit of organization is the cell
2. Acquire, transform, store, and use energy
3. Sense and respond to internal and external environments
4. Maintain homeostasis through internal control systems with feedback
5. Store, use, and transmit information
6. Reproduce, develop, grow, and die
7. Have emergent properties that cannot be predicted from the simple sum of the parts
8. Individuals adapt and species evolve

Energy is essential for the processes we associate with living things. Without energy for growth, repair, and maintenance of the internal environment, a cell is like a ghost town filled with buildings that are slowly crumbling into ruin. Cells need energy to import raw materials, make new molecules, and repair or recycle aging parts. The ability of cells to extract energy from the external environment and use that energy to maintain themselves as organized, functioning units is one of their most outstanding characteristics. In this chapter, we look at the cell processes through which the human body obtains energy and maintains its ordered systems. You will learn how protein interactions [p. 46] apply to enzyme activity and how the subcellular compartments [p. 8] separate various steps of energy metabolism.

RUNNING **PROBLEM** **Tay-Sachs Disease: A Deadly Inheritance**

In many American ultra-orthodox Jewish communities—in which arranged marriages are the norm—the rabbi is entrusted with an important, life-saving task. He keeps a confidential record of individuals known to carry the gene for Tay-Sachs disease, a fatal, inherited condition that strikes one in 3600 American Jews of Eastern European descent. Babies born with this disease rarely live beyond age 4, and there is no cure. Based on the family trees he constructs, the rabbi can avoid pairing two individuals who carry the deadly gene.

Sarah and David, who met while working on their college newspaper, are not orthodox Jews. Both are aware, however, that their Jewish ancestry might put any children they have at risk for Tay-Sachs disease. Six months before their wedding, they decide to see a genetic counselor to determine whether they are carriers of the gene for Tay-Sachs disease.

93 99 101 104 111 118

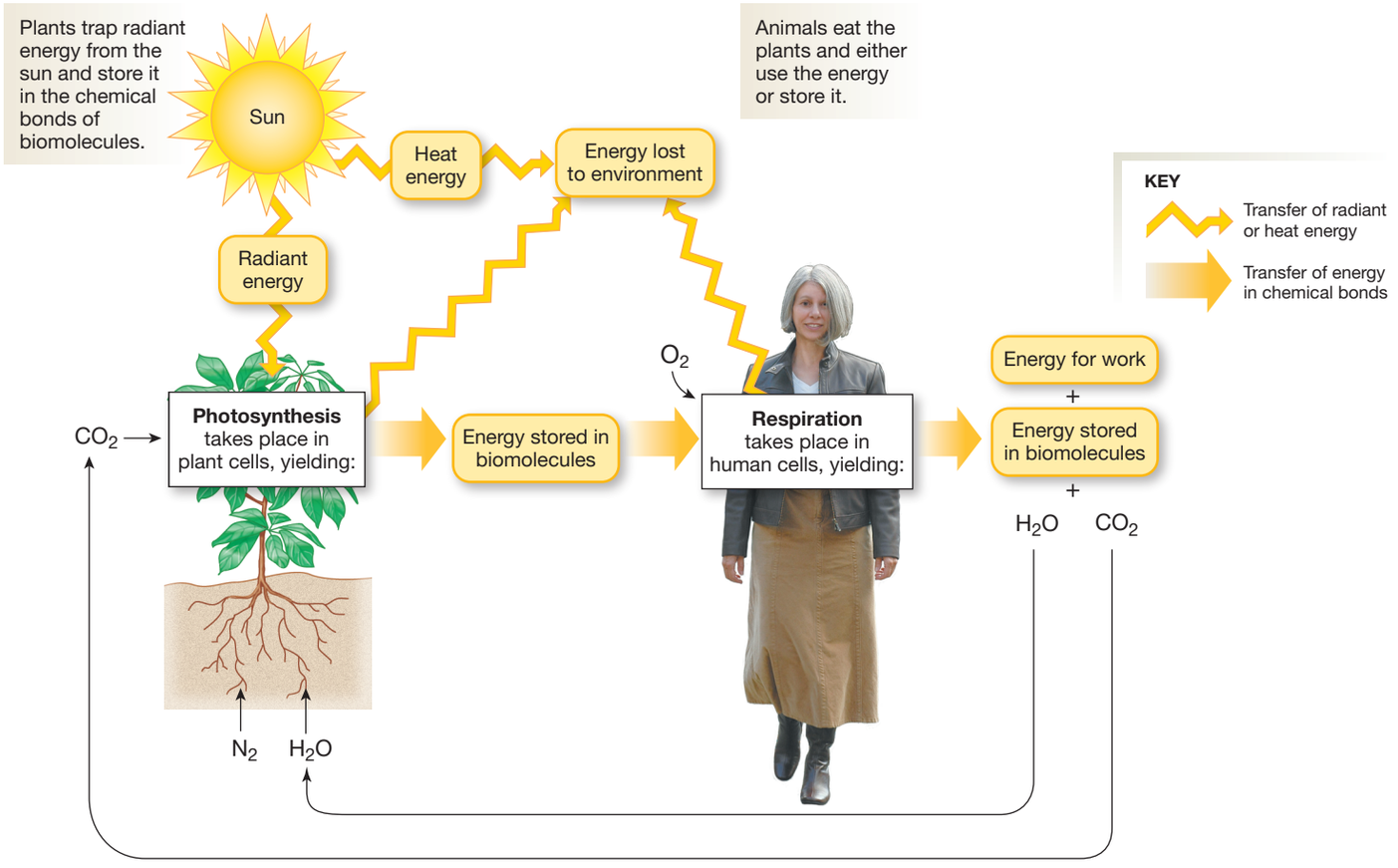
ENERGY IN BIOLOGICAL SYSTEMS

Energy cycling between the environment and living organisms is one of the fundamental concepts of biology. All cells use energy from their environment to grow, make new parts, and reproduce. Plants trap radiant energy from the sun and store it as chemical-bond energy through the process of photosynthesis (**FIG. 4.1**). They extract carbon and oxygen from carbon dioxide, nitrogen from the soil, and hydrogen and oxygen from water to make biomolecules such as glucose and amino acids.

Animals, on the other hand, cannot trap energy from the sun or use carbon and nitrogen from the air and soil to synthesize biomolecules. They must import chemical-bond energy by ingesting the biomolecules of plants or other animals. Ultimately, however, energy trapped by photosynthesis is the energy source for all animals, including humans.

Animals extract energy from biomolecules through the process of *respiration,* which consumes oxygen and produces carbon dioxide and water. If animals ingest more energy than they need

FIG. 4.1 Energy transfer in the environment



for immediate use, the excess energy is stored in chemical bonds, just as it is in plants. Glycogen (a glucose polymer) and lipid molecules are the main energy stores in animals [p. 31]. These storage molecules are available for use at times when an animal's energy needs exceed its food intake.

CONCEPT CHECK

1. Which biomolecules always include nitrogen in their chemical makeup?

Energy Is Used to Perform Work

All living organisms obtain, store, and use energy to fuel their activities. **Energy** can be defined as the capacity to do work, but what is *work*? We use this word in everyday life to mean various things, from hammering a nail to sitting at a desk writing a paper. In biological systems, however, the word means one of three specific things: chemical work, transport work, or mechanical work.

Chemical work is the making and breaking of chemical bonds. It enables cells and organisms to grow, maintain a suitable internal environment, and store information needed for reproduction and other activities. Forming the chemical bonds of a protein is an example of chemical work.

Transport work enables cells to move ions, molecules, and larger particles through the cell membrane and through the membranes of organelles in the cell. Transport work is particularly useful for creating **concentration gradients,** distributions of molecules in which the concentration is higher on one side of a membrane than on the other. For example, certain types of endoplasmic reticulum [p. 71] use energy to import calcium ions from the cytosol. This ion transport creates a high calcium concentration inside the organelle and a low concentration in the cytosol. If calcium is then released back into the cytosol, it creates a "calcium signal" that causes the cell to perform some action, such as muscle contraction.

Mechanical work in animals is used for movement. At the cellular level, movement includes organelles moving around in a cell, cells changing shape, and cilia and flagella beating [p. 68]. At the macroscopic level in animals, movement usually involves muscle contraction. Most mechanical work is mediated by motor proteins that make up certain intracellular fibers and filaments of the cytoskeleton [p. 68].

Energy Comes in Two Forms: Kinetic and Potential

Energy can be classified in various ways. We often think of energy in terms we deal with daily: thermal energy, electrical energy,

mechanical energy. We speak of energy stored in chemical bonds. Each type of energy has its own characteristics. However, all types of energy share an ability to appear in two forms: as kinetic energy or as potential energy.

Kinetic energy is the energy of motion {*kinetikos,* motion}. A ball rolling down a hill, perfume molecules spreading through the air, electric charge flowing through power lines, heat warming a frying pan, and molecules moving across biological membranes are all examples of bodies that have kinetic energy.

Potential energy is stored energy. A ball poised at the top of a hill has potential energy because it has the potential to start moving down the hill. A molecule positioned on the high-concentration side of a concentration gradient stores potential energy because it has the potential energy to move down the gradient. In chemical bonds, potential energy is stored in the position of the electrons that form the bond [p. 33]. [To learn more about kinetic and potential energy, see Appendix B.]

A key feature of all types of energy is the ability of potential energy to become kinetic energy and vice versa.

Energy Can Be Converted from One Form to Another

Recall that a general definition of energy is the capacity to do work. Work always involves movement and therefore is associated with kinetic energy. Potential energy can also be used to perform work, but the potential energy must first be converted to kinetic energy. The conversion from potential energy to kinetic energy is never 100% efficient, and a certain amount of energy is lost to the environment, usually as heat.

The amount of energy lost in the transformation depends on the *efficiency* of the process. Many physiological processes in the human body are not very efficient. For example, 70% of the energy used in physical exercise is lost as heat rather than transformed into the work of muscle contraction.

FIGURE 4.2 summarizes the relationship of kinetic energy and potential energy:

1. Kinetic energy of the moving ball is transformed into potential energy as work is used to push the ball up the ramp (Fig. 4.2a).
2. Potential energy is stored in the stationary ball at the top of the ramp (Fig. 4.2b). No work is being performed, but the capacity to do work is stored in the position of the ball.
3. The potential energy of the ball becomes kinetic energy when the ball rolls down the ramp (Fig. 4.2c). Some kinetic energy is lost to the environment as heat due to friction between the ball and the air and ramp.

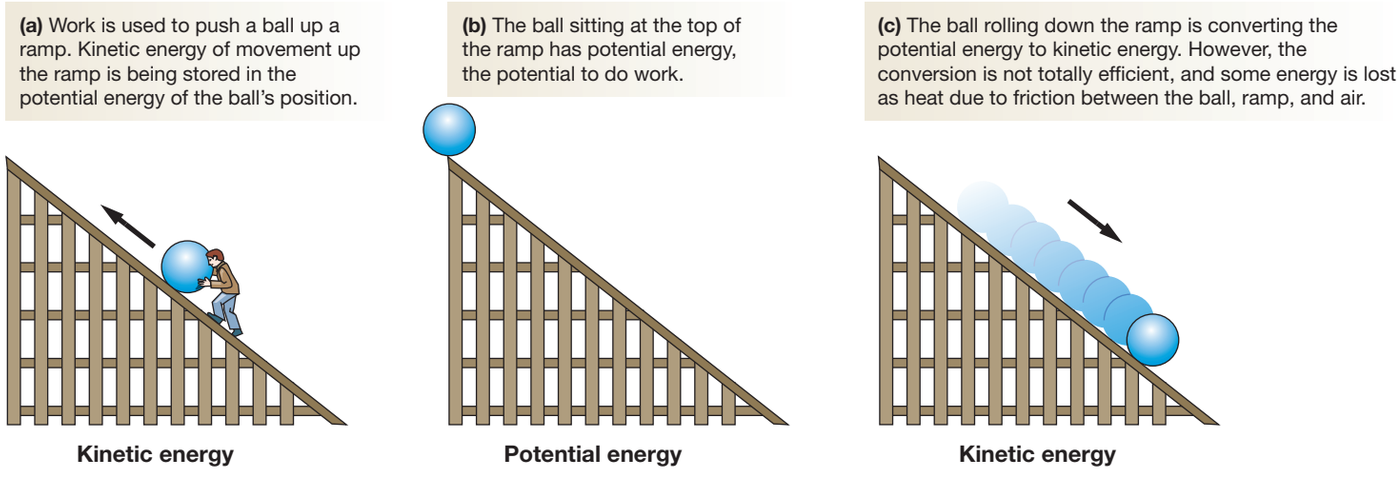
In biological systems, potential energy is stored in concentration gradients and chemical bonds. It is transformed into kinetic energy when needed to do chemical, transport, or mechanical work.

Thermodynamics Is the Study of Energy Use

Two basic rules govern the transfer of energy in biological systems and in the universe as a whole. The **first law of thermodynamics,** also known as the *law of conservation of energy,* states that the total amount of energy in the universe is constant. The universe is considered to be a *closed system*—nothing enters and nothing leaves. Energy can be converted from one type to another, but the total amount of energy in a closed system never changes.

The human body is not a closed system, however. As an *open system,* it exchanges materials and energy with its surroundings. Because our bodies cannot create energy, they import it from outside in the form of food. By the same token, our bodies lose energy, especially in the form of heat, to the environment. Energy that stays within the body can be changed from one type to another or can be used to do work.

FIG. 4.2 Kinetic and potential energy



The **second law of thermodynamics** states that natural spontaneous processes move from a state of order (nonrandomness) to a condition of randomness or disorder, also known as **entropy.** Creating and maintaining order in an open system such as the body requires the input of energy. Disorder occurs when open systems lose energy to their surroundings without regaining it. When this happens, we say that the entropy of the open system has increased.

The ghost-town analogy mentioned earlier illustrates the second law. When people put all their energy into activities away from town, the town slowly falls into disrepair and becomes less organized (its entropy increases). Similarly, without continual input of energy, a cell is unable to maintain its ordered internal environment. As the cell loses organization, its ability to carry out normal functions disappears, and it dies.

In the remainder of this chapter, you will learn how cells obtain energy from and store energy in the chemical bonds of biomolecules. Using chemical reactions, cells transform the potential energy of chemical bonds into kinetic energy for growth, maintenance, reproduction, and movement.

CONCEPT CHECK

2. Name two ways animals store energy in their bodies.
3. What is the difference between potential energy and kinetic energy?
4. What is entropy?

CHEMICAL REACTIONS

Living organisms are characterized by their ability to extract energy from the environment and use it to support life processes. The study of energy flow through biological systems is a field known as **bioenergetics** {*bios,* life + *en-,* in + *ergon,* work}. In a biological system, chemical reactions are a critical means of transferring energy from one part of the system to another.

Energy Is Transferred between Molecules during Reactions

In a **chemical reaction,** a substance becomes a different substance, usually by the breaking and/or making of covalent bonds. A reaction begins with one or more molecules called **reactants** and ends with one or more molecules called **products** (TBL. 4.2). In this discussion, we consider a reaction that begins with two reactants and ends with two products:

$$A + B \rightarrow C + D$$

The speed with which a reaction takes place, the **reaction rate**, is the disappearance rate of the reactants (A and B) or the appearance rate of the products (C and D). Reaction rate is measured as change in concentration during a certain time period and is often expressed as molarity per second (M/sec).

TABLE 4.2 Chemical Reactions

Reaction Type	Reactants (Substrates)		Products
Combination	A + B	⟶	C
Decomposition	C	⟶	A + B
Single displacement*	L + MX	⟶	LX + M
Double displacement*	LX + MY	⟶	LY + MX

*X and Y represent atoms, ions, or chemical groups.

The purpose of chemical reactions in cells is either to transfer energy from one molecule to another or to use energy stored in reactant molecules to do work. The potential energy stored in the chemical bonds of a molecule is known as the **free energy** of the molecule. Generally, complex molecules have more chemical bonds and therefore higher free energies.

For example, a large glycogen molecule has more free energy than a single glucose molecule, which in turn has more free energy than the carbon dioxide and water from which it was synthesized. The high free energy of complex molecules such as glycogen is the reason that these molecules are used to store energy in cells.

To understand how chemical reactions transfer energy between molecules, we should answer two questions. First, how do reactions get started? The energy required to initiate a reaction is known as the *activation energy* for the reaction. Second, what happens to the free energy of the products and reactants during a reaction? The difference in free energy between reactants and products is the *net free energy change of the reaction.*

Activation Energy Gets Reactions Started

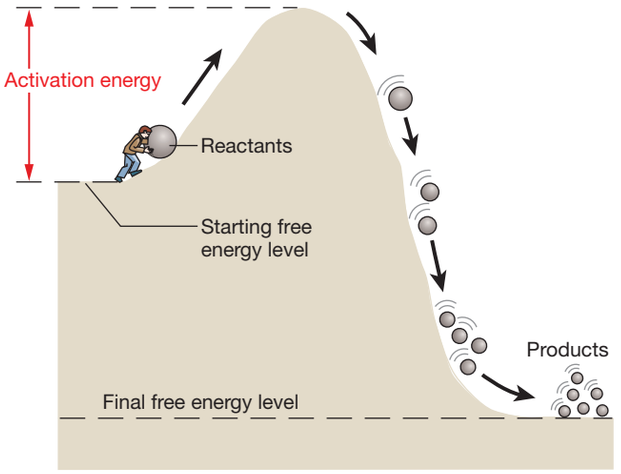
Activation energy is the initial input of energy required to bring reactants into a position that allows them to react with one another. This "push" needed to start the reaction is shown in FIGURE 4.3a as the little hill up which the ball must be pushed before it can roll by itself down the slope. A reaction with low activation energy proceeds spontaneously when the reactants are brought together. You can demonstrate a *spontaneous reaction* by pouring a little vinegar onto some baking soda and watching the two react to form carbon dioxide. Reactions with high activation energies either do not proceed spontaneously or else proceed too slowly to be useful. For example, if you pour vinegar over a pat of butter, no observable reaction takes place.

Energy Is Trapped or Released during Reactions

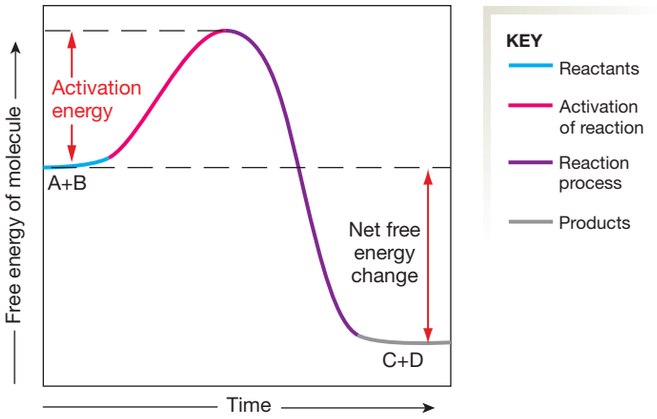
One characteristic property of any chemical reaction is the free energy change that occurs as the reaction proceeds. The products of a reaction have either a lower free energy than the reactants

FIG. 4.3 Activation energy in exergonic and endergonic reactions

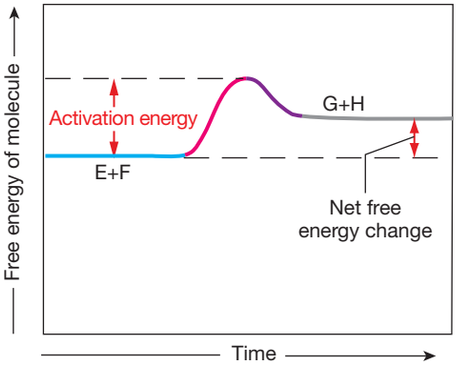
(a) Activation energy is the "push" needed to start a reaction.



(b) Exergonic reactions release energy because the products have less energy than the reactants.



(c) Endergonic reactions trap some activation energy in the products, which then have more free energy than the reactants.



or a higher free energy than the reactants. A change in free energy level means that the reaction has either released or trapped energy.

If the free energy of the products is lower than the free energy of the reactants, as in Figure 4.3b, the reaction releases energy and is called an **exergonic reaction** {*ex-*, out + *ergon,* work}. The energy released by an exergonic, or *energy-producing,* reaction may be used by other molecules to do work or may be given off as heat. In a few cases, the energy released in an exergonic reaction is stored as potential energy in a concentration gradient.

An important biological example of an exergonic reaction is the combination of ATP and water to form ADP, inorganic phosphate (P_i) and H^+. Energy is released during this reaction when the high-energy phosphate bond of the ATP molecule is broken:

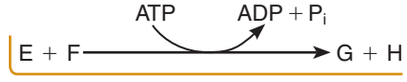
$$ATP + H_2O \rightarrow ADP + P_i + H^+ + \text{energy}$$

Now contrast the exergonic reaction of Figure 4.3b with the reaction represented in Figure 4.3c. In the latter, products retain part of the activation energy that was added, making their free energy greater than that of the reactants. These reactions that require a net input of energy are said to be **endergonic** {*end(o),* within + *ergon,* work}, or *energy-utilizing,* reactions.

Some of the energy added to an endergonic reaction remains trapped in the chemical bonds of the products. These energy-consuming reactions are often *synthesis* reactions, in which complex molecules are made from smaller molecules. For example, an endergonic reaction links many glucose molecules together to create the glucose polymer glycogen. The complex glycogen molecule has more free energy than the simple glucose molecules used to make it.

If a reaction traps energy as it proceeds in one direction ($A + B \rightarrow C + D$), it releases energy as it proceeds in the reverse direction ($C + D \rightarrow A + B$). (The naming of forward and reverse directions is arbitrary.) For example, the energy trapped in the bonds of glycogen during its synthesis is released when glycogen is broken back down into glucose.

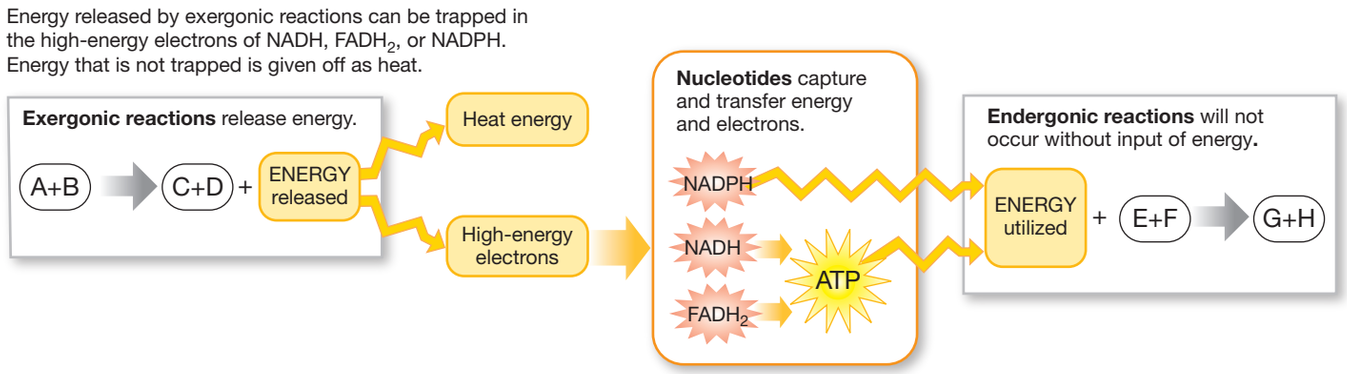
Coupling Endergonic and Exergonic Reactions Where does the activation energy for metabolic reactions come from? The simplest way for a cell to acquire activation energy is to couple an exergonic reaction to an endergonic reaction. Some of the most familiar coupled reactions are those that use the energy released by breaking the high-energy bond of ATP to drive an endergonic reaction:



In this type of coupled reaction, the two reactions take place simultaneously and in the same location, so that the energy from ATP can be used immediately to drive the endergonic reaction between reactants E and F.

However, it is not always practical for reactions to be directly coupled like this. Consequently, living cells have developed ways

FIG. 4.4 Energy in biological reactions



to trap the energy released by exergonic reactions and save it for later use. The most common method is to trap the energy in the form of high-energy electrons carried on nucleotides [p. 33]. The nucleotide molecules NADH, $FADH_2$, and NADPH all capture energy in the electrons of their hydrogen atoms (**FIG. 4.4**). NADH and $FADH_2$ usually transfer most of this energy to ATP, which can then be used to drive endergonic reactions.

Net Free Energy Change Determines Reaction Reversibility

The net free energy change of a reaction plays an important role in determining whether that reaction can be reversed, because the net free energy change of the forward reaction contributes to the activation energy of the reverse reaction. A chemical reaction that can proceed in both directions is called a **reversible reaction.** In a reversible reaction, the forward reaction $A + B \rightarrow C + D$ and its reverse reaction $C + D \rightarrow A + B$ are both likely to take place. If a reaction proceeds in one direction but not the other, it is an **irreversible reaction.**

For example, look at the activation energy of the reaction $C + D \rightarrow A + B$ in **FIGURE 4.5**. This reaction is the reverse of the reaction shown in Figure 4.3b. Because a lot of energy was released in the forward reaction $A + B \rightarrow C + D$, the activation energy of the reverse reaction is substantial (Fig. 4.5). As you will recall, the larger the activation energy, the less likely it is that the reaction will proceed spontaneously. Theoretically, all reactions can be reversed with enough energy input, but some reactions release so much energy that they are essentially irreversible.

In your study of physiology, you will encounter a few irreversible reactions. However, most biological reactions are reversible: if the reaction $A + B \rightarrow C + D$ is possible, then so is the reaction $C + D \rightarrow A + B$. Reversible reactions are shown with arrows that point in both directions: $A + B \rightleftarrows C + D$. One of the main reasons that many biological reactions are reversible is that they are aided by the specialized proteins known as enzymes.

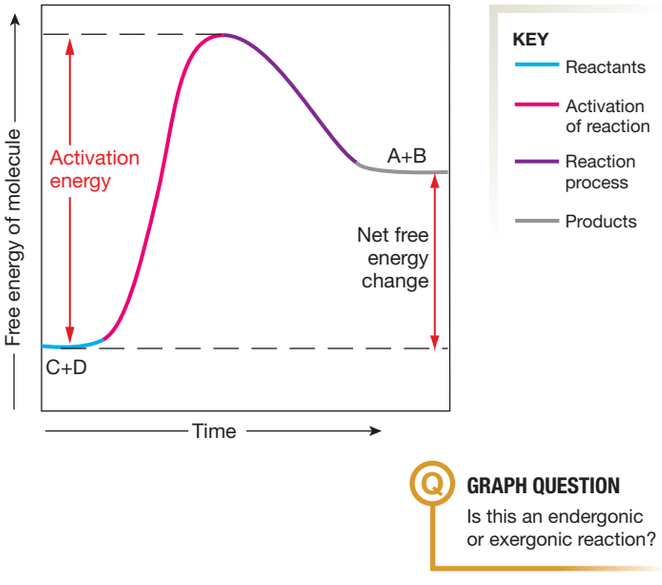
CONCEPT CHECK

5. What is the difference between endergonic and exergonic reactions?
6. If you mix baking soda and vinegar together in a bowl, the mixture reacts and foams up, releasing carbon dioxide gas. Name the reactant(s) and product(s) in this reaction.
7. Do you think the reaction of question 6 is endergonic or exergonic? Do you think it is reversible? Defend your answers.

ENZYMES

Enzymes are proteins that speed up the rate of chemical reactions. During these reactions, the enzyme molecules are not changed in any way, meaning they are biological *catalysts*. Without enzymes, most chemical reactions in a cell would go so slowly

FIG. 4.5 Some reactions have large activation energies



that the cell would be unable to live. Because an enzyme is not permanently changed or used up in the reaction it catalyzes, we might write it in a reaction equation this way:

$$A + B + \text{enzyme} \rightarrow C + D + \text{enzyme}$$

This way of writing the reaction shows that the enzyme participates with reactants A and B but is unchanged at the end of the reaction. A more common shorthand for enzymatic reactions shows the name of the enzyme above the reaction arrow, like this:

$$A + B \xrightarrow{enzyme} C + D$$

In enzymatically catalyzed reactions, the reactants A and B are called **substrates.**

Enzymes Are Proteins

Most enzymes are large proteins with complex three-dimensional shapes, although recently researchers discovered that RNA can sometimes act as a catalyst. Like other proteins that bind to substrates, protein enzymes exhibit specificity, competition, and saturation [p. 46].

A few enzymes come in a variety of related forms (isoforms) and are known as **isozymes** {*iso-*, equal} of one another. Isozymes are enzymes that catalyze the same reaction but under different conditions or in different tissues. The structures of related isozymes are slightly different from one another, which causes the variability in their activity. Many isozymes have complex structures with multiple protein chains.

For example, the enzyme *lactate dehydrogenase* (LDH) has two kinds of subunits, named H and M, that are assembled into *tetramers*—groups of four. LDH isozymes include H_4, H_2M_2, and M_4. The different LDH isozymes are tissue specific, including one found primarily in the heart and a second found in skeletal muscle and the liver.

Isozymes have an important role in the diagnosis of certain medical conditions. For example, in the hours following a heart attack, damaged heart muscle cells release enzymes into the blood. One way to determine whether a person's chest pain was indeed due to a heart attack is to look for elevated levels of heart isozymes in the blood. Some diagnostically important enzymes and the diseases of which they are suggestive are listed in **TABLE 4.3**.

Reaction Rates Are Variable

We measure the rate of an enzymatic reaction by monitoring either how fast the products are synthesized or how fast the substrates are consumed. Reaction rate can be altered by a number of factors, including changes in temperature, the amount of enzyme present, and substrate concentrations [p. 52]. In mammals, we consider temperature to be essentially constant. This leaves enzyme amount and substrate concentration as the two main variables that affect reaction rate.

In protein-binding interactions, if the amount of protein (in this case, enzyme) is constant, the reaction rate is proportional to the substrate concentration. One strategy cells use to control reaction rates is to regulate the amount of enzyme in the cell. In the absence of appropriate enzyme, many biological reactions go very slowly or not at all. If enzyme is present, the rate of the reaction is proportional to the amount of enzyme and the amount of substrate, unless there is so much substrate that all enzyme binding sites are saturated and working at maximum capacity [p. 51].

This seems simple until you consider a reversible reaction that can go in both directions. In that case, what determines in which direction the reaction goes? The answer is that reversible reactions go to a state of *equilibrium,* where the rate of the reaction in the forward direction ($A + B \rightarrow C + D$) is equal to the rate of the reverse reaction ($C + D \rightarrow A + B$). At equilibrium,

RUNNING **PROBLEM**

Tay-Sachs disease is a devastating condition. Normally, lysosomes in cells contain enzymes that digest old, worn-out parts of the cell. In Tay-Sachs and related lysosomal storage diseases, genetic mutations result in lysosomal enzymes that are ineffective or absent. Tay-Sachs disease patients lack *hexosaminidase A*, an enzyme that digests glycolipids called *gangliosides*. As a result, gangliosides accumulate in nerve cells in the brain, causing them to swell and function abnormally. Infants with Tay-Sachs disease slowly lose muscle control and brain function. There is currently no treatment or cure for Tay-Sachs disease, and affected children usually die before age 4.

Q1: *Hexosaminidase A is also required to remove gangliosides from the light-sensitive cells of the eye. Based on this information, what is another symptom of Tay-Sachs disease besides loss of muscle control and brain function?*

TABLE 4.3 Diagnostically Important Enzymes

Elevated blood levels of these enzymes are suggestive of the pathologies listed.

Enzyme	Related Diseases
Acid phosphatase*	Cancer of the prostate
Alkaline phosphatase	Diseases of bone or liver
Amylase	Pancreatic disease
Creatine kinase (CK)	Myocardial infarction (heart attack), muscle disease
Lactate dehydrogenase (LDH)	Tissue damage to heart, liver, skeletal muscle, red blood cells

*A newer test for a molecule called prostate specific antigen (PSA) has replaced the test for acid phosphatase in the diagnosis of prostate cancer.

BIOTECHNOLOGY

Seeing Isozymes

One way to determine which isozymes are present in a tissue sample is to use a technique known as **electrophoresis.** In this technique, a solution derived from the tissue sample is placed at one end of a container filled with a polyacrylamide polymer gel. An electric current passed through the gel causes the negatively charged proteins to move toward the positively charged end of the gel. The rate at which the proteins move depends on their size, their shape, and the electrical charge on their amino acids. As proteins move along the gel at different rates, they separate from one another and appear as individual bands of color when stained with a dye called Coomassie blue or with silver. Electrophoresis can separate mixtures of charged macromolecules, such as proteins and DNA.

there is no net change in the amount of substrate or product, and the ratio [C][D]/[A][B] is equal to the reaction's equilibrium constant, K_{eq} [p. 47].

If substrates or products are added or removed by other reactions in a pathway, the reaction rate increases in the forward or reverse direction as needed to restore the ratio [C][D]/[A][B]. According to the law of mass action, the ratio of [C] and [D] to [A] and [B] is always the same at equilibrium.

Enzymes May Be Activated, Inactivated, or Modulated

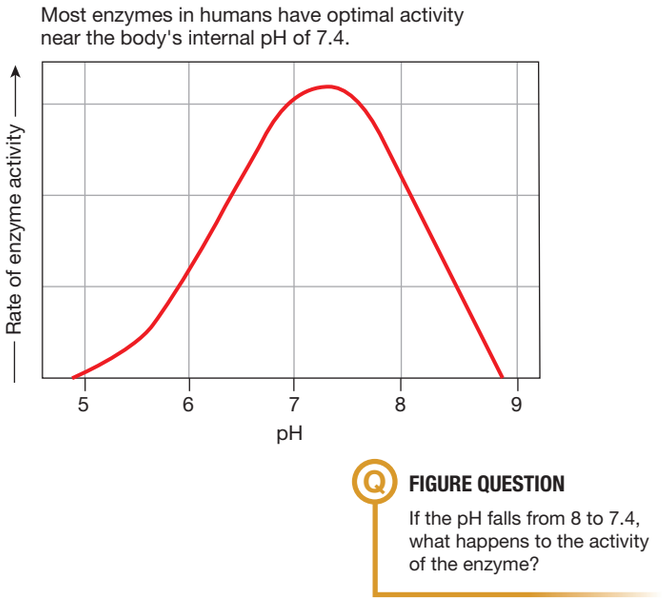
Enzyme activity, like the activity of other soluble proteins, can be altered by various factors. Some enzymes are synthesized as inactive molecules (*proenzymes* or *zymogens*) and activated on demand by proteolytic activation [p. 49]. Others require the binding of inorganic cofactors, such as Ca^{2+} or Mg^{2+} before they become active.

Organic cofactors for enzymes are called **coenzymes.** Coenzymes do not alter the enzyme's binding site as inorganic cofactors do. Instead, coenzymes act as receptors and carriers for atoms or functional groups that are removed from the substrates during the reaction. Although coenzymes are needed for some metabolic reactions to take place, they are not required in large amounts.

Many of the substances that we call **vitamins** are the precursors of coenzymes. The water-soluble vitamins, such as the B vitamins, vitamin C, folic acid, biotin, and pantothenic acid, become coenzymes required for various metabolic reactions. For example, vitamin C is needed for adequate collagen synthesis.

Enzymes may be inactivated by inhibitors or by becoming denatured. Enzyme activity can be modulated by chemical factors or by changes in temperature and pH. **FIGURE 4.6** shows how

FIG. 4.6 pH affects enzyme activity



enzyme activity can vary over a range of pH values. By turning reactions on and off or by increasing and decreasing the rate at which reactions take place, a cell can regulate the flow of biomolecules through different synthetic and energy-producing pathways.

CONCEPT CHECK

8. What is a biological advantage of having multiple isozymes for a given reaction rather than only one form of the enzyme?
9. The four protein chains of an LDH isozyme are an example of what level of protein structure? (a) primary (b) secondary (c) tertiary (d) quaternary

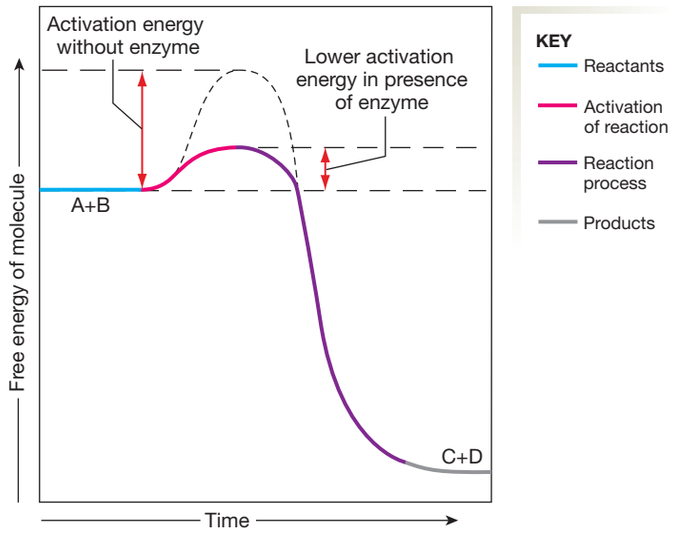
Enzymes Lower Activation Energy of Reactions

How does an enzyme increase the rate of a reaction? In thermodynamic terms, it lowers the activation energy, making it more likely that the reaction will start (**FIG. 4.7**). Enzymes accomplish this by binding to their substrates and bringing them into the best position for reacting with each other. Without enzymes, the reaction would depend on random collisions between substrate molecules to bring them into alignment.

The rate of a reaction catalyzed by an enzyme is much more rapid than the rate of the same reaction taking place without the enzyme. For example, consider *carbonic anhydrase,* which facilitates conversion of CO_2 and water to carbonic acid. This enzyme plays a critical role in the transport of waste CO_2 from cells to lungs. Each molecule of carbonic anhydrase takes one second to catalyze the conversion of 1 million molecules of CO_2 and water to carbonic acid. In the absence of enzyme, it takes more than a minute for one molecule of CO_2 and water to be converted to

FIG. 4.7 Enzymes lower the activation energy of reactions

In the absence of enzyme, the reaction (curved dashed line) would have much greater activation energy.



carbonic acid. Without carbonic anhydrase and other enzymes in the body, biological reactions would go so slowly that cells would be unable to live.

Enzymatic Reactions Can Be Categorized

Most reactions catalyzed by enzymes can be classified into four categories: oxidation-reduction, hydrolysis-dehydration, exchange-addition-subtraction, and ligation reactions. **TABLE 4.4** summarizes these categories and gives common enzymes for different types of reactions.

An enzyme's name can provide important clues to the type of reaction the enzyme catalyzes. Most enzymes are instantly recognizable by the suffix *-ase.* The first part of the enzyme's name (everything that precedes the suffix) usually refers to the type of reaction, to the substrate upon which the enzyme acts, or to both. For example, *glucokinase* has glucose as its substrate, and as a *kinase* it will add a phosphate group [p. 33] to the substrate. Addition of a phosphate group is called **phosphorylation.**

A few enzymes have two names. These enzymes were discovered before 1972, when the current standards for naming enzymes were first adopted. As a result, they have both a new name and a commonly used older name. Pepsin and trypsin, two digestive enzymes, are examples of older enzyme names.

RUNNING PROBLEM

Tay-Sachs disease is a *recessive* genetic disorder caused by a defect in the gene that directs synthesis of hexosaminidase A. *Recessive* means that for a baby to be born with Tay-Sachs disease, it must inherit two defective genes, one from each parent. People with one Tay-Sachs gene and one normal gene are called *carriers* of the disease. Carriers do not develop the disease but can pass the defective gene on to their children. People who have two normal genes have normal amounts of hexosaminidase A in their blood. Carriers have lower-than-normal levels of the enzyme, but this amount is enough to prevent excessive accumulation of gangliosides in cells.

Q2: *How could you test whether Sarah and David are carriers of the Tay-Sachs gene?*

Oxidation-Reduction Reactions

Oxidation-reduction reactions are the most important reactions in energy extraction and transfer in cells. These reactions transfer electrons from one molecule to another. A molecule that gains electrons is said to be **reduced.** One way to think of this is to remember that adding negatively charged electrons *reduces* the electric charge on the molecule. Conversely, molecules that lose electrons are said to be **oxidized.** Use the mnemonic OIL RIG to remember what happens: Oxidation Is Loss (of electrons), Reduction Is Gain.

Hydrolysis-Dehydration Reactions

Hydrolysis and dehydration reactions are important in the breakdown and synthesis of large biomolecules. In **dehydration reactions** {*de-*, out + *hydr-*, water}, a water molecule is one of the products. In many dehydration reactions, two molecules combine into one, losing water in the process. For example, the monosaccharides glucose and fructose join to make one sucrose molecule [p. 31]. In the process, one substrate molecule loses a hydroxyl group -OH and the other substrate molecule loses a hydrogen to create water, H_2O. When a dehydration reaction results in the synthesis of a new molecule, the process is known as *dehydration synthesis*.

In a **hydrolysis reaction** {*hydro,* water + *lysis,* to loosen or dissolve}, a substrate changes into one or more products through the addition of water. In these reactions, the covalent bonds of the water molecule are broken ("lysed") so that the water reacts as a hydroxyl group OH^- and a hydrogen ion H^+. For example, an amino acid can be removed from the end of a peptide chain through a hydrolysis reaction.

When an enzyme name consists of the substrate name plus the suffix *-ase,* the enzyme causes a hydrolysis reaction. One example is *lipase,* an enzyme that breaks up large lipids into smaller lipids by hydrolysis. A *peptidase* is an enzyme that removes an amino acid from a peptide.

Addition-Subtraction-Exchange Reactions

An **addition reaction** adds a functional group to one or more of the substrates. A **subtraction reaction** removes a functional group from one or more of the substrates. Functional groups are exchanged between or among substrates during **exchange reactions.**

For example, phosphate groups may be transferred from one molecule to another during addition, subtraction, or exchange reactions. The transfer of phosphate groups is an important means

TABLE 4.4 Classification of Enzymatic Reactions

Reaction Type	What Happens	Representative Enzymes
1. Oxidation-reduction (a) Oxidation (b) Reduction	Add or subtract electrons Transfer electrons from donor to oxygen Remove electrons and H+ Gain electrons	**Class:*** oxidoreductase Oxidase Dehydrogenase Reductase
2. Hydrolysis-dehydration (a) Hydrolysis (b) Dehydration	Add or subtract a water molecule Split large molecules by adding water Remove water to make one large molecule from several smaller ones	**Class:*** hydrolase Peptidases, saccharidases, lipases Dehydratases
3. Transfer chemical groups (a) Exchange reaction (b) Addition (c) Subtraction	Exchange groups between molecules Add or subtract groups Phosphate Amino group (*transamination*) Phosphate (*phosphorylation*) Amino group (*amination*) Phosphate (*dephosphorylation*) Amino group (*deamination*)	**Class:*** transferases **Class:*** lyases Kinase Transaminase Phosphorylase Aminase Phosphatase Deaminase
4. Ligation	Join two substrates using energy from ATP	**Class:*** ligases Synthetase

*Enzyme classes as defined by the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology, *www.chem.qmul.ac.uk/iubmb/enzyme*.

of covalent modulation [p. 49], turning reactions on or off or increasing or decreasing their rates. Several types of enzymes catalyze reactions that transfer phosphate groups. **Kinases** transfer a phosphate group from a substrate to an ADP molecule to create ATP, or from an ATP molecule to a substrate. For example, creatine kinase transfers a phosphate group from creatine phosphate to ADP, forming ATP and leaving behind creatine.

The addition, subtraction, and exchange of amino groups [p. 32] are also important in the body's use of amino acids. Removal of an amino group from an amino acid or peptide is a **deamination** reaction. Addition of an amino group is **amination,** and the transfer of an amino group from one molecule to another is **transamination.**

Ligation Reactions Ligation reactions join two molecules together using enzymes known as *synthetases* and energy from ATP. An example of a ligation reaction is the synthesis of *acetyl coenzyme A* (acetyl CoA) from fatty acids and coenzyme A. Acetyl CoA is an important molecule in the body, as you will learn in the next section.

CONCEPT CHECK

10. Name the substrates for the enzymes lactase, peptidase, lipase, and sucrase.

11. Match the reaction type or enzyme in the left column to the group or particle involved.

a. kinase	1. amino group
b. oxidation	2. electrons
c. hydrolysis	3. phosphate group
d. transaminase	4. water

METABOLISM

Metabolism refers to all chemical reactions that take place in an organism. These reactions (1) extract energy from nutrient biomolecules (such as proteins, carbohydrates, and lipids) and (2) either synthesize or break down molecules. Metabolism is often divided into **catabolism,** reactions that release energy through the breakdown of large biomolecules, and **anabolism,** energy-utilizing reactions that result in the synthesis of large biomolecules. Anabolic and catabolic reactions take place simultaneously in cells throughout the body, so that at any given moment, some biomolecules are being synthesized while others are being broken down.

The energy released from or stored in the chemical bonds of biomolecules during metabolism is commonly measured in kilocalories (kcal). A **kilocalorie** is the amount of energy needed to raise the temperature of 1 liter of water by 1 degree Celsius. One kilocalorie is the same as a Calorie, with a capital C, used for quantifying the energy content of food. One kilocalorie is also equal to 1000 calories (small c).

Much of the energy released during catabolism is trapped in the high-energy phosphate bonds of ATP or in the high-energy electrons of NADH, $FADH_2$, or NADPH. Anabolic reactions then transfer energy from these temporary carriers to the covalent bonds of biomolecules.

Metabolism is a network of highly coordinated chemical reactions in which the activities taking place in a cell at any given moment are matched to the needs of the cell. Each step in a metabolic pathway is a different enzymatic reaction, and the reactions of a pathway proceed in sequence. Substrate A is changed into

product B, which then becomes the substrate for the next reaction in the pathway. B is changed into C, and so forth:

$$A \rightarrow B \rightarrow C \rightarrow D$$

We call the molecules of the pathway **intermediates** because the products of one reaction become the substrates for the next. You will sometimes hear metabolic pathways called *intermediary metabolism*. Certain intermediates, called *key intermediates,* participate in more than one pathway and act as the branch points for channeling substrate in one direction or another. Glucose, for instance, is a key intermediate in several metabolic pathways.

In many ways, a group of metabolic pathways is similar to a detailed road map (**FIG. 4.8**). Just as a map shows a network of roads that connect various cities and towns, you can think of metabolism as a network of chemical reactions connecting various intermediate products. Each city or town is a different chemical intermediate. One-way roads are irreversible reactions, and big cities with roads to several destinations are key intermediates. Just as there may be more than one way to get from one place to another, there can be several pathways between any given pair of chemical intermediates.

Cells Regulate Their Metabolic Pathways

How do cells regulate the flow of molecules through their metabolic pathways? They do so in five basic ways:

1. By controlling enzyme concentrations
2. By producing modulators that change reaction rates
3. By using two different enzymes to catalyze reversible reactions
4. By compartmentalizing enzymes within intracellular organelles
5. By maintaining an optimum ratio of ATP to ADP

We discussed the effects of changing enzyme concentration in the discussion of protein-binding reactions: as enzyme concentration increases, the reaction rate increases [p. 51]. The sections that follow examine the remaining four items on the list.

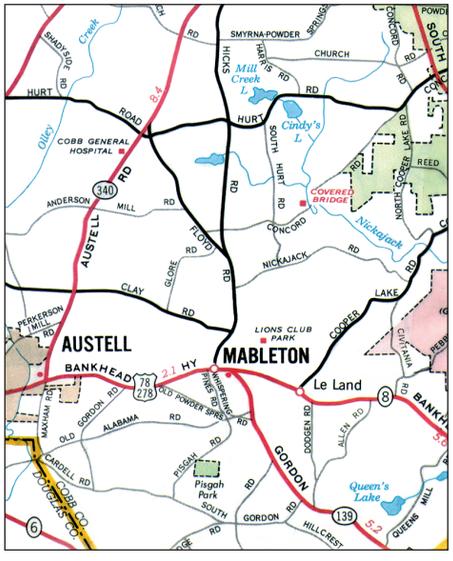
Enzyme Modulation Modulators, which alter the activity of a protein, were introduced in the discussion of protein binding [p. 49]. For enzymes, the production of modulators is frequently controlled by hormones and other signals coming from outside the cell. This type of outside regulation is a key element in the integrated control of the body's metabolism following a meal or during periods of fasting between meals.

In addition, some metabolic pathways have their own built-in form of modulation, called **feedback inhibition.** In this form of modulation, the end product of a pathway, shown as Z in **FIGURE 4.9**, acts as an inhibitory modulator of the pathway. As the pathway proceeds and Z accumulates, the enzyme catalyzing the conversion of A to B is inhibited. Inhibition of the enzyme slows down production of Z until the cell can use it up. Once the levels of Z fall, feedback inhibition on enzyme 1 is removed and

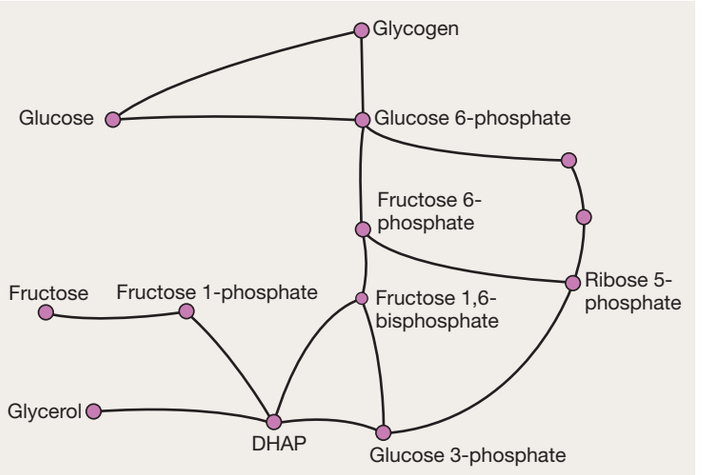
FIG. 4.8 Metabolic pathways resemble a road map

Cities on the map are equivalent to intermediates in metabolism. In metabolism, there may be more than one way to go from one intermediate to another, just as on the map, there may be many ways to get from one city to another.

(a) Section of Road Map



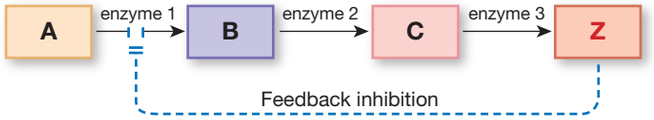
(b) Metabolic Pathways Drawn Like a Road Map



DHAP = dihydroxyacetone phosphate

FIG. 4.9 Feedback inhibition

The accumulation of end product Z inhibits the first step of the pathway. As the cell consumes Z in another metabolic reaction, the inhibition is removed and the pathway resumes.



the pathway starts to run again. Because Z is the end product of the pathway, this type of feedback inhibition is sometimes called *end-product inhibition*.

Reversible Reactions Cells can use reversible reactions to regulate the rate and direction of metabolism. If a single enzyme can catalyze the reaction in either direction, the reaction will go to a state of equilibrium, as determined by the law of mass action (**FIG. 4.10a**). Such a reaction, therefore, cannot be closely regulated except by modulators and by controlling the amount of enzyme.

However, if a reversible reaction requires two different enzymes, one for the forward reaction and one for the reverse reaction, the cell can regulate the reaction more closely (Fig. 4.10b). If no enzyme for the reverse reaction is present in the cell, the reaction is irreversible (Fig. 4.10c).

Compartmentalizing Enzymes in the Cell Many enzymes of metabolism are isolated in specific subcellular compartments. Some, like the enzymes of carbohydrate metabolism, are dissolved in the cytosol, whereas others are isolated within specific organelles. Mitochondria, endoplasmic reticulum, Golgi apparatus, and lysosomes all contain enzymes that are not found in the cytosol. This separation of enzymes means that the pathways controlled by the enzymes are also separated. That allows the cell to control metabolism by regulating the movement of substrate from one cellular compartment to another. The isolation of enzymes within organelles is an important example of structural and functional compartmentation [p. 8].

Ratio of ATP to ADP The energy status of the cell is one final mechanism that can influence metabolic pathways. Through complex regulation, the ratio of ATP to ADP in the cell determines whether pathways that result in ATP synthesis are turned on or off. When ATP levels are high, production of ATP decreases. When ATP levels are low, the cell sends substrates through pathways that result in more ATP synthesis. In the next section, we look further into the role of ATP in cellular metabolism.

ATP Transfers Energy between Reactions

The usefulness of metabolic pathways as suppliers of energy is often measured in terms of the net amount of ATP the pathways can yield. ATP is a nucleotide containing three phosphate groups [p. 34]. One of the three phosphate groups is attached to ADP by a covalent bond in an energy-requiring reaction. Energy is stored in this **high-energy phosphate bond** and then released when the bond is broken during removal of the phosphate group. This relationship is shown by the following reaction:

$$ADP + P_i + \text{energy} \rightleftharpoons ADP \sim P (= ATP)$$

RUNNING PROBLEM

In 1989, researchers discovered three genetic mutations responsible for Tay-Sachs disease. This discovery paved the way for a new carrier screening test that detects the presence of one of the three genetic mutations in blood cells rather than testing for lower-than-normal hexosaminidase A levels. David and Sarah will undergo this genetic test.

Q3: *Why might the genetic test for mutations in the Tay-Sachs gene be more accurate than the test that detects decreased amounts of hexosaminidase A?*

Q4: *Can you think of a situation in which the enzyme test might be more accurate than the genetic test?*

93 99 101 104 111 118

FIG. 4.10 Enzymes control reversibility of metabolic reactions

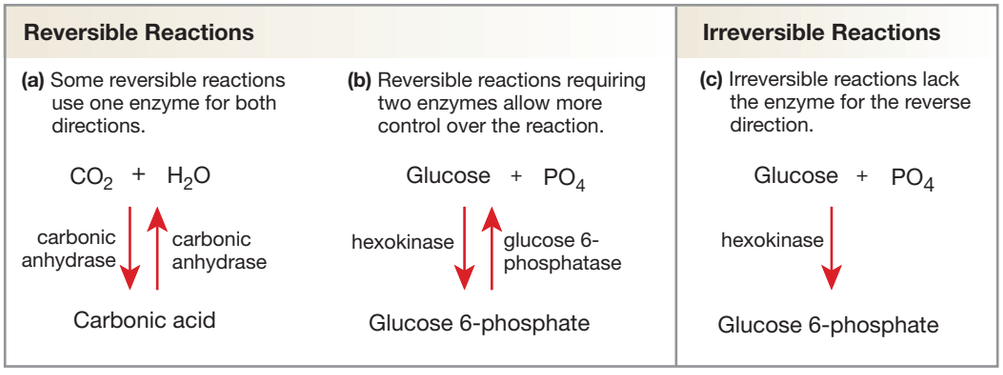


FIGURE QUESTION
What is the difference between a kinase and a phosphatase? (*Hint:* See Tbl. 4.4.)

The squiggle ~ indicates a high-energy bond, and P_i is the abbreviation for an inorganic phosphate group. Estimates of the amount of free energy released when a high-energy phosphate bond is broken range from 7 to 12 kcal per mole of ATP.

ATP is more important as a carrier of energy than as an energy-storage molecule. For one thing, cells can contain only a limited amount of ATP. A resting adult human needs 40 kg (88 pounds!) of ATP to supply the energy required to support one day's worth of metabolic activity, far more than our cells could store. Instead, the body acquires most of its daily energy requirement from the chemical bonds of complex biomolecules. Metabolic reactions transfer that chemical bond energy to the high-energy bonds of ATP, or in a few cases, to the high-energy bonds of the related nucleotide *guanosine triphosphate,* **GTP.**

The metabolic pathways that yield the most ATP molecules are those that require oxygen—the **aerobic,** or *oxidative,* pathways. **Anaerobic** {*an-,* without + *aer,* air} pathways, which are those that can proceed without oxygen, also produce ATP molecules but in much smaller quantities. The lower ATP yield of anaerobic pathways means that most animals (including humans) are unable to survive for extended periods on anaerobic metabolism alone. In the next section, we consider how biomolecules are metabolized to transfer energy to ATP.

CONCEPT CHECK

12. Name five ways in which cells regulate the movement of substrates through metabolic pathways.

13. In which part of an ATP molecule is energy trapped and stored? In which part of a NADH molecule is energy stored?

14. What is the difference between aerobic and anaerobic pathways?

Catabolic Pathways Produce ATP

FIGURE 4.11 summarizes the catabolic pathways that extract energy from biomolecules and transfer it to ATP. Aerobic production of ATP from glucose commonly follows two pathways: **glycolysis** {*glyco-,* sweet + *lysis,* dissolve} and the **citric acid cycle** (also known as the tricarboxylic acid cycle). The citric acid cycle was first described by Hans A. Krebs, so it is sometimes called the *Krebs cycle*. Because Dr. Krebs described other metabolic cycles, we will avoid confusion by using the term *citric acid cycle*.

Carbohydrates enter glycolysis in the form of glucose (top of Fig. 4.11). Lipids are broken down into glycerol and fatty acids [p. 30], which enter the pathway at different points: glycerol feeds into glycolysis, and fatty acids are metabolized to acetyl CoA. Proteins are broken down into amino acids, which also enter at various points. Carbons from glycolysis and other nutrients enter the citric acid cycle, which makes a never-ending circle. At each turn, the cycle adds carbons and produces ATP, high-energy electrons, and carbon dioxide.

Both glycolysis and the citric acid cycle produce small amounts of ATP directly, but their most important contribution to ATP synthesis is trapping energy in electrons carried by NADH and $FADH_2$. These compounds transfer the electrons to the **electron transport system** (ETS) in the mitochondria. The electron transport system, in turn, uses energy from those electrons to make the high-energy phosphate bond of ATP. At various points, the process produces carbon dioxide and water. Cells can use the water, but carbon dioxide is a waste product and must be removed from the body.

Because glucose is the only molecule that follows both pathways in their entirety, in this chapter, we look at only glucose catabolism.

- **FIGURE 4.12** summarizes the key steps of glycolysis, the conversion of glucose to pyruvate.
- **FIGURE 4.13** shows how pyruvate is converted to acetyl CoA and how carbons from acetyl CoA go through the citric acid cycle.
- **FIGURE 4.14** illustrates the energy-transferring pathway of the electron transport system.

We will examine protein and lipid catabolism and synthetic pathways for lipids and glucose when we look at the fate of the nutrients we eat [Chapter 22].

The aerobic pathways for ATP production are a good example of compartmentation within cells. The enzymes of glycolysis are located in the cytosol, and the enzymes of the citric acid cycle are in the mitochondria. Within mitochondria, concentration of H^+ in the intermembrane compartment stores the energy needed to make the high-energy bond of ATP.

CONCEPT CHECK

15. Match each component on the left to the molecule(s) it is part of:

(a) amino acids	1. carbohydrates
(b) fatty acids	2. lipids
(c) glycerol	3. polysaccharides
(d) glucose	4. proteins
	5. triglycerides

16. Do endergonic reactions release energy or trap it in the products?

One Glucose Molecule Can Yield 30–32 ATP

Recall from Figure 4.11 that the aerobic metabolism of one glucose molecule produces carbon dioxide, water, and 30–32 ATP. Let's review the role of glycolysis and the citric acid cycle in that ATP production.

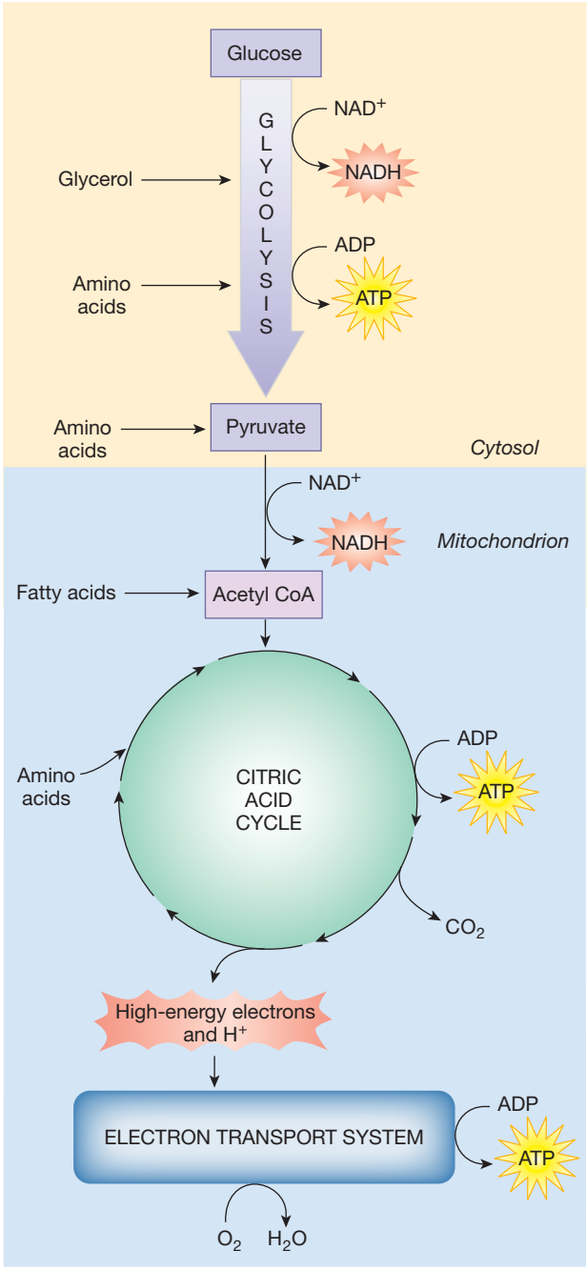
In glycolysis (Fig. 4.12), metabolism of one glucose molecule $C_6H_{12}O_6$ has a net yield of two 3-carbon pyruvate molecules, 2 ATPs, and high-energy electrons carried on 2 NADH:

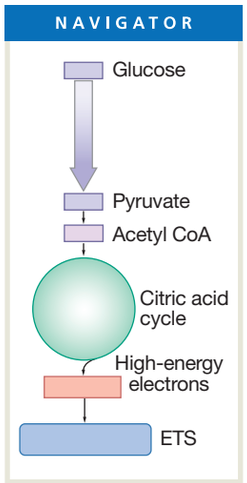
$$\text{Glucose} + 2\,NAD^+ + 2\,ADP + 2\,P_i \rightarrow$$
$$2\,\text{Pyruvate} + 2\,ATP + 2\,NADH + 2\,H^+ + 2\,H_2O$$

ATP Production

The catabolic pathways that extract energy from biomolecules and transfer it to ATP are summarized in this overview figure of aerobic respiration of glucose.

Glycolysis and the **citric acid cycle** produce small amounts of ATP directly, but their most important contributions to ATP synthesis are high-energy electrons carried by NADH and FADH2 to the electron transport system in the mitochondria.





This icon represents the different steps in the metabolic summary figure. Look for it in the figures that follow to help you navigate your way through metabolism.

Aerobic Metabolism of Glucose

The energy production from one glucose molecule can be summarized in the following two equations.

$$\text{Glucose} + O_2 + \text{ADP} + P_i \rightarrow CO_2 + H_2O + \text{ATP}$$

$$C_6H_{12}O_6 + 6\,O_2 \xrightarrow{30\text{–}32\ \text{ADP} + P_i \;\rightarrow\; 30\text{–}32\ \text{ATP}} 6\,CO_2 + 6\,H_2O$$

In the next phase, the conversion of pyruvate to acetyl CoA produces one NADH (Fig. 4.13). Carbons from one acetyl CoA going through the citric acid cycle trap energy in 3 NADH molecules, 1 $FADH_2$ and 1 ATP. These steps happen twice for each glucose, giving a total yield of 8 NADH, 2 $FADH_2$, and 2 ATP for the pyruvate-citric acid cycle phase of glucose metabolism.

In the final step, high-energy electrons of NADH and $FADH_2$ passing along the proteins of the electron transport system use their energy to concentrate H^+ in the intermembrane compartment of the mitochondria (Fig. 4.14). When the H^+ move down their concentration gradient through a channel in the ATP synthase, the energy released is transferred to the high-energy phosphate bond of ATP. On average, the NADH and $FADH_2$ from one glucose produce 26–28 ATPs.

When we tally the maximum potential energy yield for the catabolism of one glucose molecule through aerobic pathways, the total comes to 30–32 ATP (**FIG. 4.15b**). These numbers are the *potential* maximum because often the mitochondria do not

Glycolysis

During glycolysis, one molecule of glucose is converted by a series of enzymatically catalyzed reactions into two pyruvate molecules, producing a net release of energy.

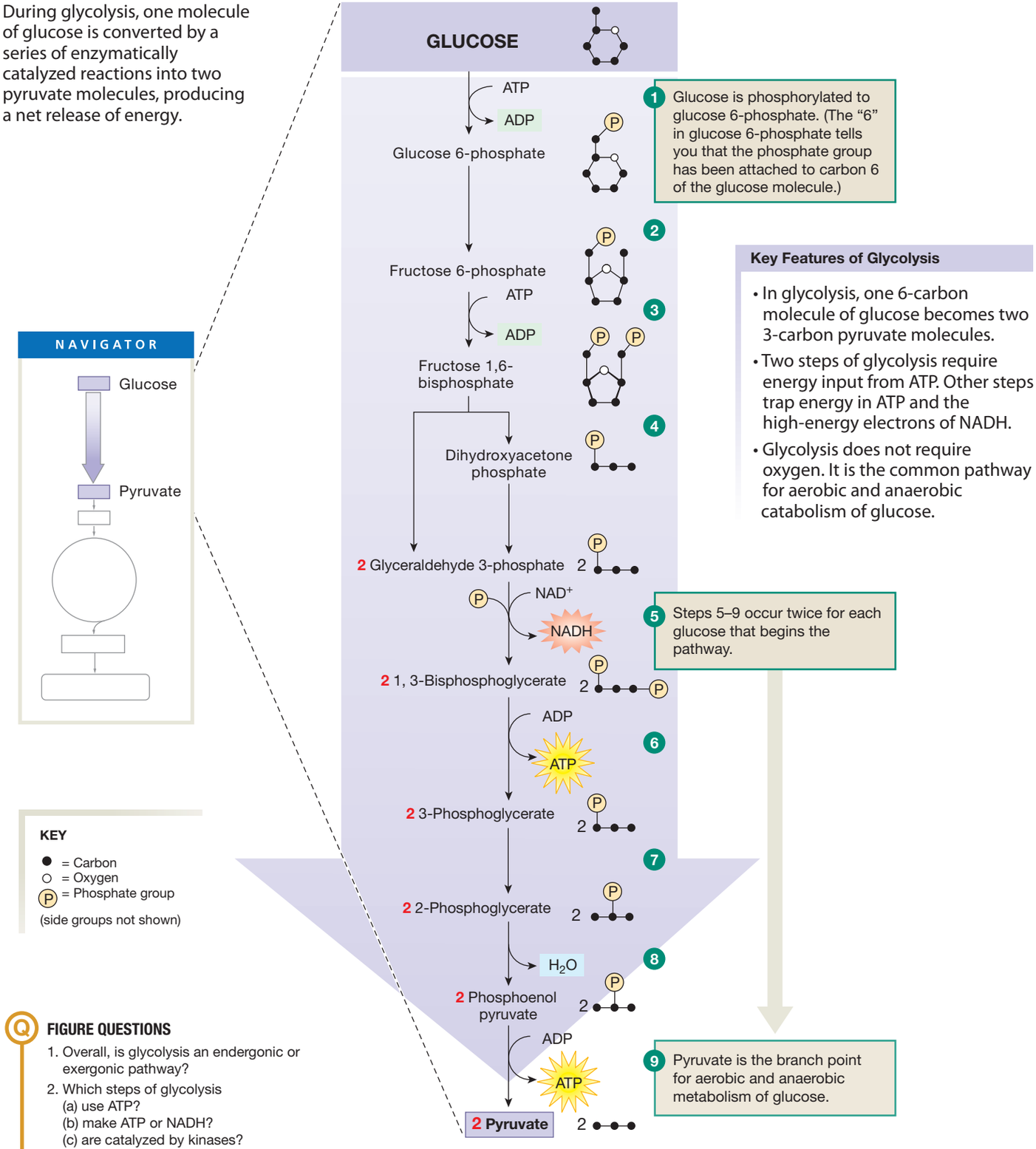


FIGURE QUESTIONS

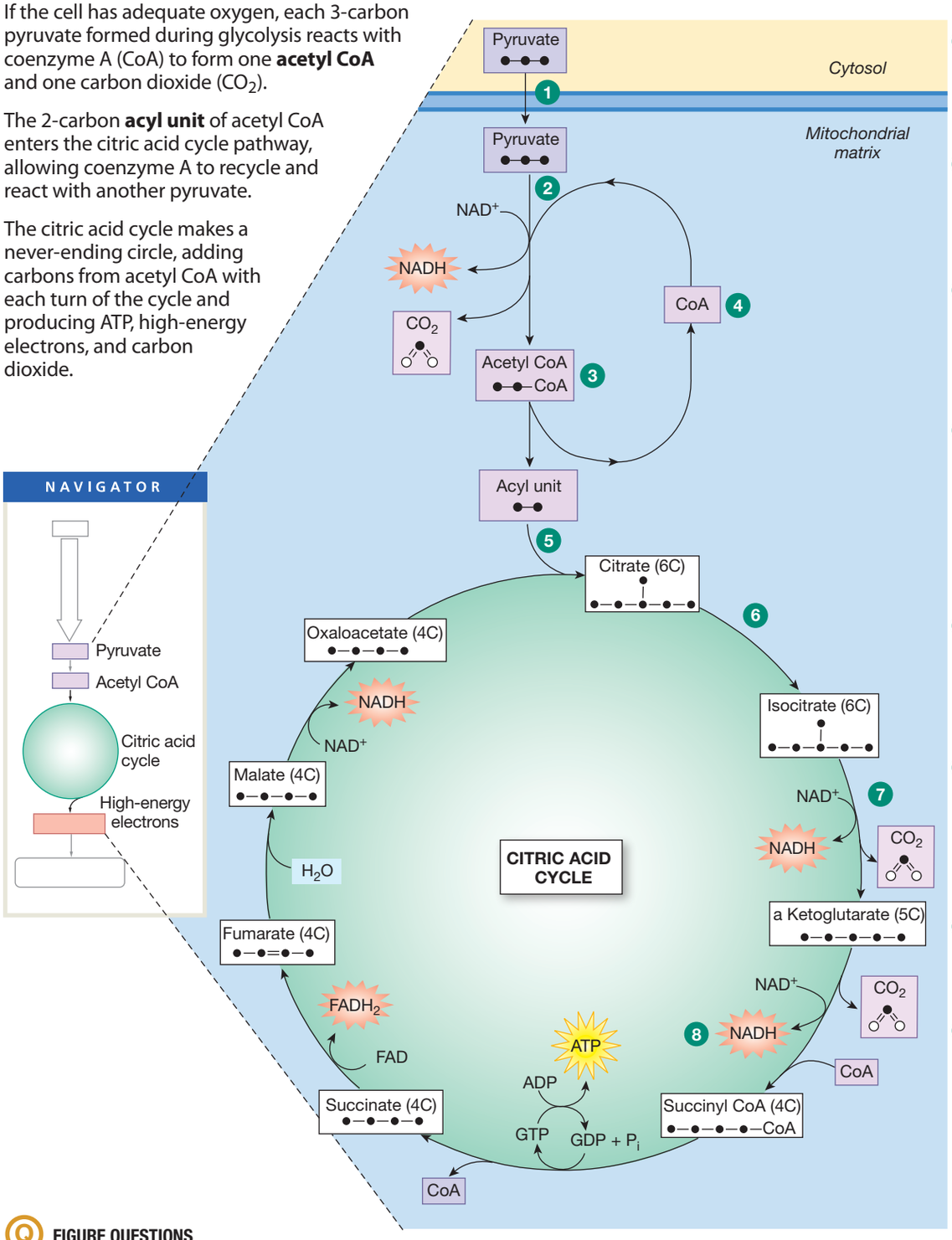
1. Overall, is glycolysis an endergonic or exergonic pathway?
2. Which steps of glycolysis
   (a) use ATP?
   (b) make ATP or NADH?
   (c) are catalyzed by kinases?
   (d) are catalyzed by dehydrogenases? (*Hint:* See Tbl. 4.4.)
3. What is the net energy yield (ATP and NADH) for one glucose?

Pyruvate, Acetyl CoA, and the Citric Acid Cycle

If the cell has adequate oxygen, each 3-carbon pyruvate formed during glycolysis reacts with coenzyme A (CoA) to form one **acetyl CoA** and one carbon dioxide (CO_2).

The 2-carbon **acyl unit** of acetyl CoA enters the citric acid cycle pathway, allowing coenzyme A to recycle and react with another pyruvate.

The citric acid cycle makes a never-ending circle, adding carbons from acetyl CoA with each turn of the cycle and producing ATP, high-energy electrons, and carbon dioxide.



1. If the cell has adequate oxygen, pyruvate is transported into the mitochondria.
2. Pyruvate reacts with coenzyme A to produce acetyl CoA, one NADH, and one CO_2.
3. Acetyl CoA has two parts: a 2-carbon acyl unit, derived from pyruvate, and coenzyme A.
4. Coenzyme A is made from the vitamin *pantothenic acid*. Coenzymes, like enzymes, are not changed during reactions and can be reused.
5. The 2-carbon acyl unit enters the cycle by combining with a 4-carbon oxaloacetate molecule.
6. The 6-carbon citrate molecule goes through a series of reactions until it completes the cycle as another oxaloacetate molecule.
7. Two carbons are removed in the form of CO_2.
8. Most of the energy released is captured as high-energy electrons on three NADH and one $FADH_2$. Some energy goes into the high-energy phosphate bond of one ATP. The remaining energy is given off as heat.

FIGURE QUESTIONS

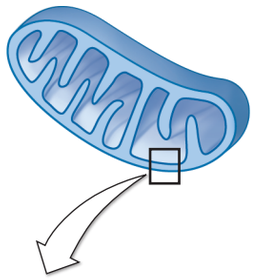
1. Overall, is the citric acid cycle an endergonic or exergonic pathway?
2. What is the net energy yield (ATP, $FADH_2$, and NADH) for one pyruvate completing the cycle?
3. How many CO_2 are formed from one pyruvate? Compare the number of carbon atoms in the pyruvate and CO_2s.

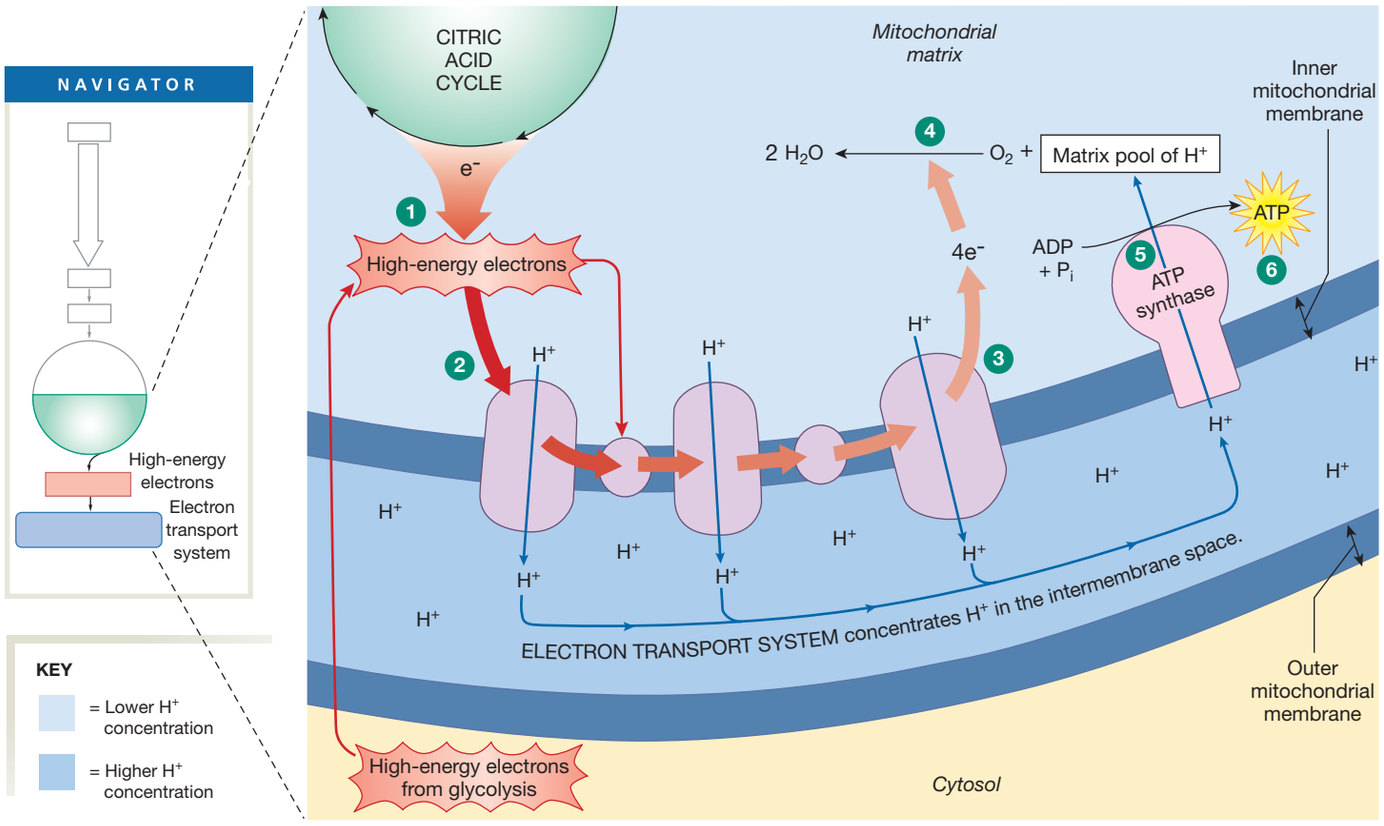
KEY

● = Carbon
○ = Oxygen
CoA = Coenzyme A
Side groups not shown

The Electron Transport System

The final step in aerobic ATP production is energy transfer from high-energy electrons of NADH and $FADH_2$ to ATP. This energy transfer requires mitochondrial proteins known as the **electron transport system (ETS),** located in the inner mitochondrial membrane. ETS proteins include enzymes and iron-containing **cytochromes.** The synthesis of ATP using the ETS is called **oxidative phosphorylation** because the system requires oxygen to act as the final acceptor of electrons and H^+. The **chemiosmotic theory** says that potential energy stored by concentrating H^+ in the intermembrane space is used to make the high-energy bond of ATP.





1. $NADH$ and $FADH_2$ release high-energy electrons and H^+ to the ETS. NAD^+ and FAD are coenzymes that recycle.
2. Energy released when pairs of high-energy electrons pass along the transport system is used to concentrate H^+ from the mitochondrial matrix in the intermembrane space. The H^+ concentration gradient is a source of potential energy.
3. By the end of the ETS, the electrons have given up their stored energy.
4. Each pair of electrons released by the ETS combines with two H^+ and an oxygen atom, creating a molecule of water, H_2O.
5. H^+ flow back into the matrix through a protein known as **ATP synthase.** As the H^+ move down their concentration gradient, the synthase transfers their kinetic energy to the high-energy phosphate bond of ATP. Because energy conversions are never completely efficient, a portion of the energy is released as heat.
6. Each three H^+ that shuttle through the ATP synthase make a maximum of one ATP.

FIGURE QUESTIONS

1. What is phosphorylation? What is phosphorylated in oxidative phosphorylation?
2. Is the movement of electrons through the electron transport system endergonic or exergonic?
3. What is the role of oxygen in oxidative phosphorylation?

FIG. 4.15 Energy yields from catabolism of one glucose molecule

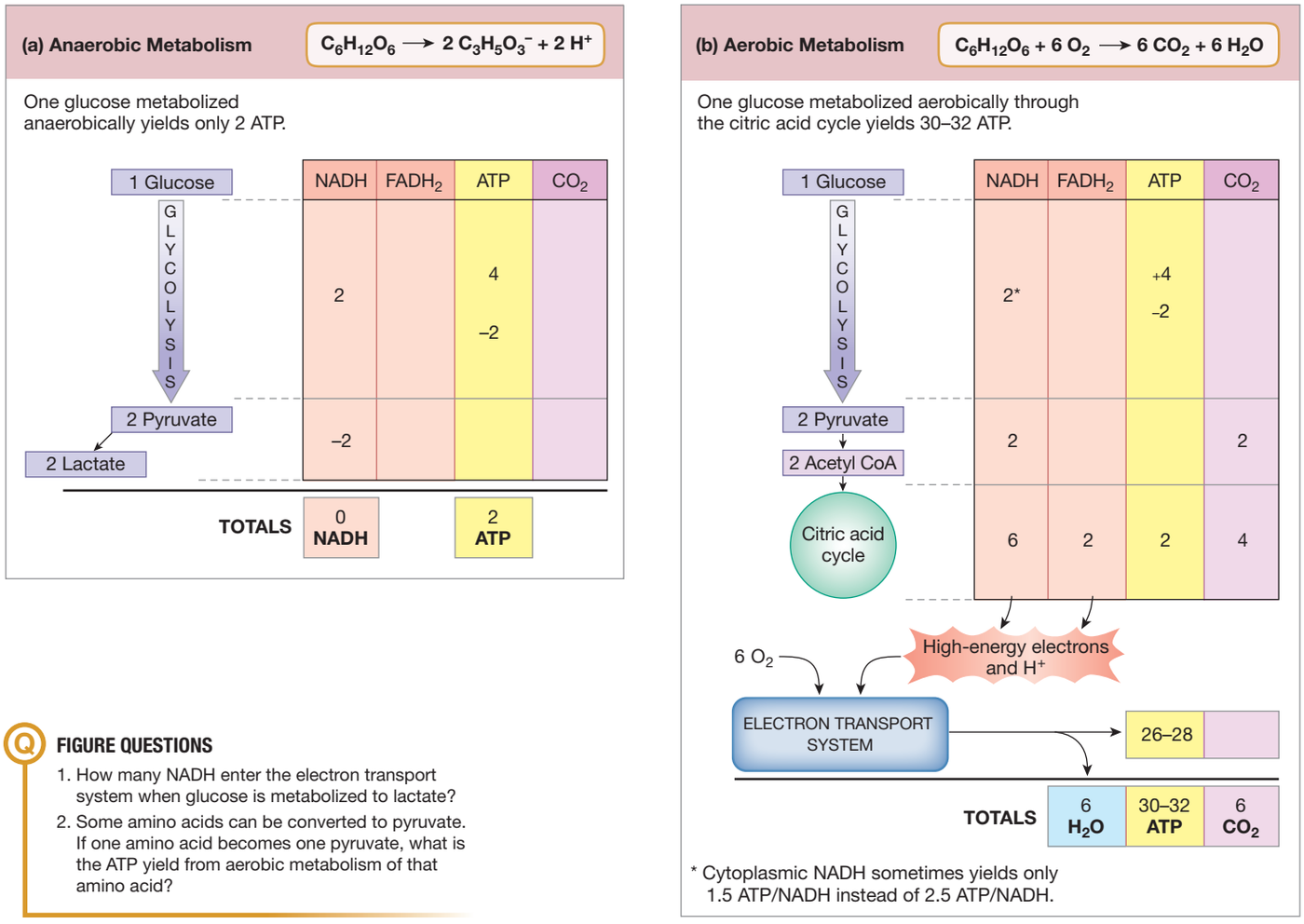


FIGURE QUESTIONS

1. How many NADH enter the electron transport system when glucose is metabolized to lactate?
2. Some amino acids can be converted to pyruvate. If one amino acid becomes one pyruvate, what is the ATP yield from aerobic metabolism of that amino acid?

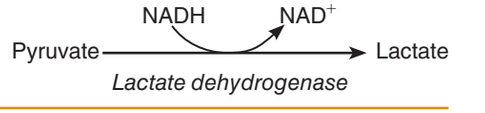
work up to capacity. There are various reasons for this, including the fact that a certain number of H^+ ions leak from the intermembrane space back into the mitochondrial matrix without producing an ATP.

A second source of variability in the number of ATP produced per glucose comes from the two cytosolic NADH molecules produced during glycolysis. These NADH molecules are unable to enter mitochondria and must transfer their electrons through membrane carriers. Inside a mitochondrion, some of these electrons go to $FADH_2$, which has a potential average yield of only 1.5 ATP rather than the 2.5 ATP made by mitochondrial NADH. If cytosolic electrons go to mitochondrial NADH instead, they produce two additional ATP molecules.

Anaerobic Metabolism Makes 2 ATP

The metabolism of glucose just described assumes that the cells have adequate oxygen to keep the electron transport system functioning. But what happens to a cell whose oxygen supply cannot keep pace with its ATP demand, such as often happens during strenuous exercise? In that case, the metabolism of glucose shifts from aerobic to anaerobic metabolism, starting at pyruvate (**FIG. 4.16**).

In anaerobic glucose metabolism, pyruvate is converted to lactate instead of being transported into the mitochondria:

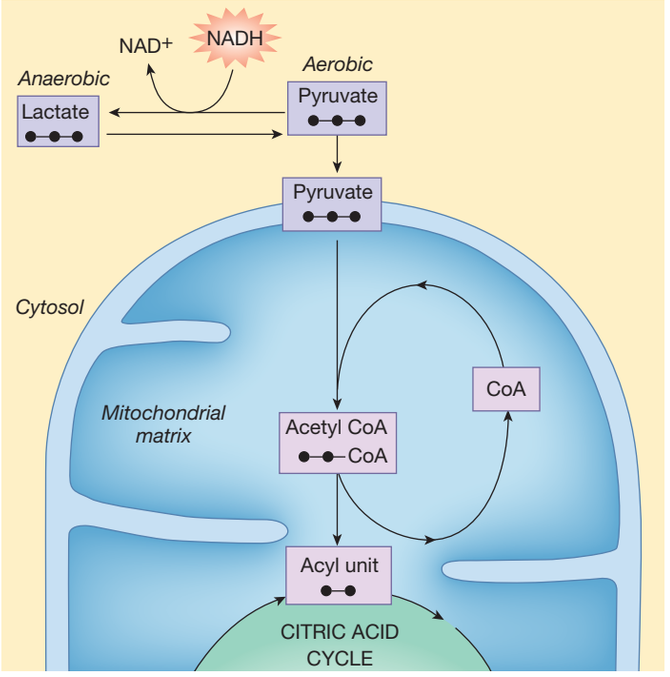


Pyruvate is a branch point for metabolic pathways, like a hub city on a road map. Depending on a cell's needs and oxygen content, pyruvate can be shuttled into the citric acid cycle or diverted into lactate production until oxygen supply improves.

The conversion of pyruvate to lactate changes one NADH back to NAD^+ when a hydrogen atom and an electron are transferred to the lactate molecule. As a result, the net energy yield for

FIG. 4.16 Aerobic and anaerobic metabolism

Pyruvate is the branch point between aerobic and anaerobic metabolism of glucose.



the anaerobic metabolism of one glucose molecule is 2 ATP and 0 NADH (Fig. 4.15a), a very puny yield when compared to the 30–32 ATP/glucose that result from aerobic metabolism (Fig. 4.15b). The low efficiency of anaerobic metabolism severely limits its usefulness in most vertebrate cells, whose metabolic energy demand is greater than anaerobic metabolism can provide. Some cells, such as exercising muscle cells, can tolerate anaerobic metabolism for a limited period of time. Eventually, however, they must shift back to aerobic metabolism. [Aerobic and anaerobic metabolism in muscle are discussed further in Chapters 12 and 25.]

CONCEPT CHECK

17. How is the separation of mitochondria into two compartments essential to ATP synthesis?

18. Lactate dehydrogenase acts on lactate by (adding or removing?) a(n) _____ and a(n) _____. This process is called (oxidation or reduction?).

19. Describe two differences between aerobic and anaerobic metabolism of glucose.

Proteins Are the Key to Cell Function

As you have seen, proteins are the molecules that run a cell from day to day. Protein enzymes control the synthesis and breakdown of carbohydrates, lipids, structural proteins, and signal molecules. Protein transporters and pores in the cell membrane and in organelle membranes regulate the movement of molecules into and out of compartments. Other proteins form the structural skeleton of cells and tissues. In these and other ways, protein synthesis is critical to cell function.

The power of proteins arises from their tremendous variability and specificity. Protein synthesis using 20 amino acids can be compared to creating a language with an alphabet of 20 letters. The "words" vary in length from three letters to hundreds of letters, spelling out the structure of thousands of different proteins with different functions. A change in one amino acid during protein synthesis can alter the protein's function, just as changing one letter turns the word "foot" into "food."

The classic example of an amino acid change causing a problem is sickle cell disease. In this inherited condition, when the amino acid valine replaces one glutamic acid in the protein chain, the change alters the shape of hemoglobin. As a result, red blood cells containing the abnormal hemoglobin take on a crescent (sickle) shape, which causes them to get tangled up and block small blood vessels.

The Protein "Alphabet" One of the mysteries of biology until the 1960s was the question of how only four nitrogenous bases in the DNA molecule—adenine (A), guanine (G), cytosine (C), and thymine (T)—could code for more than 20 different amino acids. If each base controlled the synthesis of one amino acid, a cell could make only four different amino acids. If pairs of bases represented different amino acids, the cell could make 4^2 or 16 different amino acids. Because we have 20 amino acids, this is still not satisfactory. If triplets of bases were the codes for different molecules, however, DNA could create 4^3 or 64 different amino acids. These triplets, called **codons,** are indeed the way information is encoded in DNA and RNA. **FIGURE 4.17** shows the genetic code as it appears in one form of RNA. Remember that RNA substitutes the base uracil (U) for the DNA base thymine [p. 35].

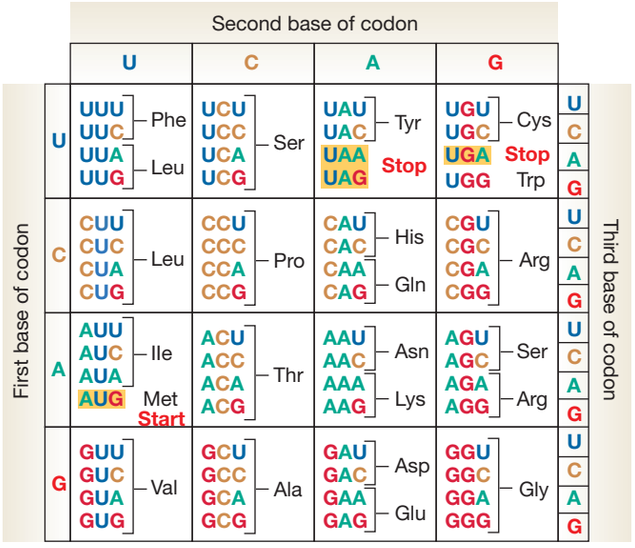
RUNNING **PROBLEM**

David and Sarah had their blood drawn for the genetic test several weeks ago and have been anxiously awaiting the results. Today, they returned to the hospital to hear the news. The tests show that Sarah carries the gene for Tay-Sachs disease but David does not. This means that although some of their children may be carriers of the Tay-Sachs gene like Sarah, none of the children will develop the disease.

Q5: *The Tay-Sachs gene is a recessive gene (t). If Sarah is a carrier of the gene (Tt) but David is not (TT), what is the chance that any child of theirs will be a carrier? (Consult a general biology or genetics text if you need help solving this problem.)*

FIG. 4.17 The genetic code as it appears in the codons of mRNA

The three-letter abbreviations to the right of the brackets indicate the amino acid each codon represents. The start and stop codons are also marked.



Of the 64 possible triplet combinations, one DNA codon (TAC) acts as the initiator or "start codon" that signifies the beginning of a coding sequence. Three codons serve as terminator or "stop codons" that show where the sequence ends. The remaining 60 triplets all code for amino acids. Methionine and tryptophan have only one codon each, but the other amino acids have between two and six different codons each. Thus, like letters spelling words, the DNA base sequence determines the amino acid sequence of proteins.

Unlocking DNA's Code How does a cell know which of the thousands of bases present in its DNA sequence to use in making a protein? It turns out that the information a cell needs to make a particular protein is contained in a segment of DNA known as a gene. What exactly is a gene? The definition keeps changing, but for this text we will say that a **gene** is a region of DNA that contains the information needed to make a functional piece of RNA, which in turn can make a protein.

FIGURE 4.18 shows the five major steps from gene to RNA to functional protein. First, a section of DNA containing a gene must be activated so that its code can be read 1. Genes that are continuously being read and converted to RNA messages are said to be *constitutively active*. Usually these genes code for proteins that are essential to ongoing cell functions. Other genes are *regulated*—that is, their activity can be turned on (*induced*) or turned off (*repressed*) by regulatory proteins.

Once a gene is activated, the DNA base sequence of the gene is used to create a piece of RNA in the process known as **transcription** {*trans*, over + *scribe*, to write} (Fig. 4.18 2). Human cells have three major forms of RNA: **messenger RNA** (mRNA), **transfer RNA** (tRNA), and **ribosomal RNA** (rRNA). Messenger RNA is processed in the nucleus after it is made 3. It may either undergo *alternative splicing* (discussed shortly) before leaving the nucleus or be "silenced" and destroyed by enzymes through *RNA interference*. Processed mRNA leaves the nucleus and enters the cytosol. There it works with tRNA and rRNA to direct **translation,** the assembly of amino acids into a protein chain 4.

Newly synthesized proteins are then subject to **posttranslational modification** (Fig. 4.18 5). They fold into complex shapes, may be split by enzymes into smaller peptides, or have various chemical groups added to them. The remainder of this chapter looks at transcription, RNA processing, translation, and posttranslational modification in more detail.

DNA Guides the Synthesis of RNA

The first steps in protein synthesis are compartmentalized within the nucleus because DNA is a very large molecule that cannot pass through the nuclear envelope. Transcription uses DNA as a template to create a small single strand of RNA that can leave the nucleus (**FIG. 4.19**). The synthesis of RNA from the double-stranded DNA template requires an enzyme known as **RNA polymerase,** plus magnesium or manganese ions and energy in the form of high-energy phosphate bonds:

DNA template + nucleotides A, U, C, G
↓ *RNA polymerase, Mg^{2+} or Mn^{2+}, and energy*
DNA template + mRNA

A **promoter** region that precedes the gene must be activated before transcription can begin. Regulatory-protein **transcription factors** bind to DNA and activate the promoter. The active promoter tells the RNA polymerase where to bind to the DNA (Fig. 4.19 1). The polymerase moves along the DNA molecule and "unwinds" the double strand by breaking the hydrogen bonds between paired bases 2. One strand of DNA, called the *template strand,* serves as the guide for RNA synthesis 3. The promoter region is not transcribed into RNA.

During transcription, each base in the DNA template strand pairs with the complementary RNA base (G-C, C-G, T-A, A-U). This pairing of complementary bases is similar to the process by which a double strand of DNA forms [see Appendix C for a review of DNA synthesis]. For example, a DNA segment containing the base sequence AGTAC is transcribed into the RNA sequence UCAUG.

As the RNA bases bind to the DNA template strand, they also bond with one another to create a single strand of RNA. During transcription, bases are linked at an average rate of 40 per second. In humans, the largest RNAs may contain as many as 5000 bases, and their transcription may take more than a minute—a long time for a cellular process. When RNA polymerase reaches the stop codon, it stops adding bases to the growing RNA strand and releases the strand (Fig. 4.19 4).

Overview of Protein Synthesis

The major steps required to convert the genetic code of DNA into a functional protein.

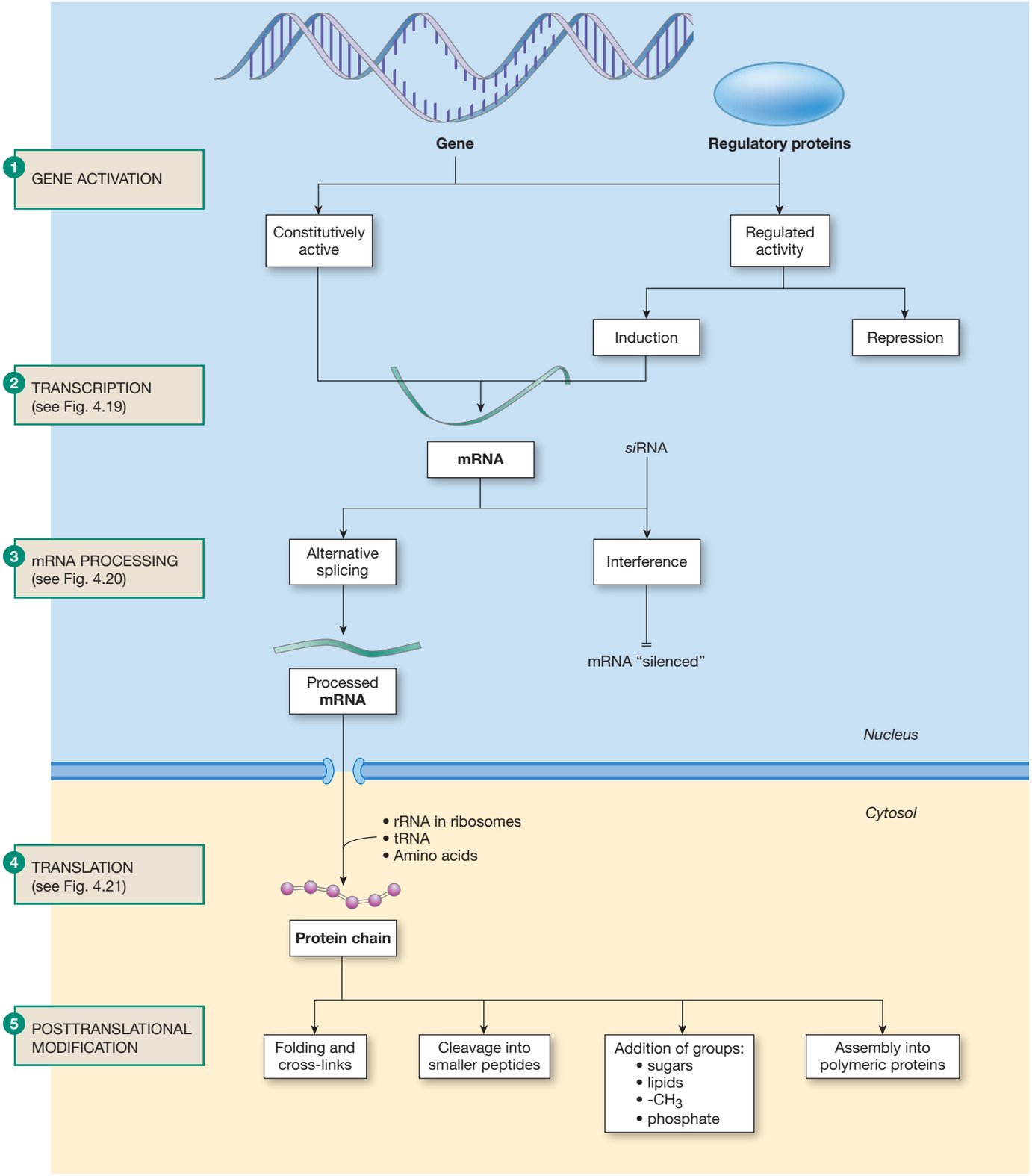
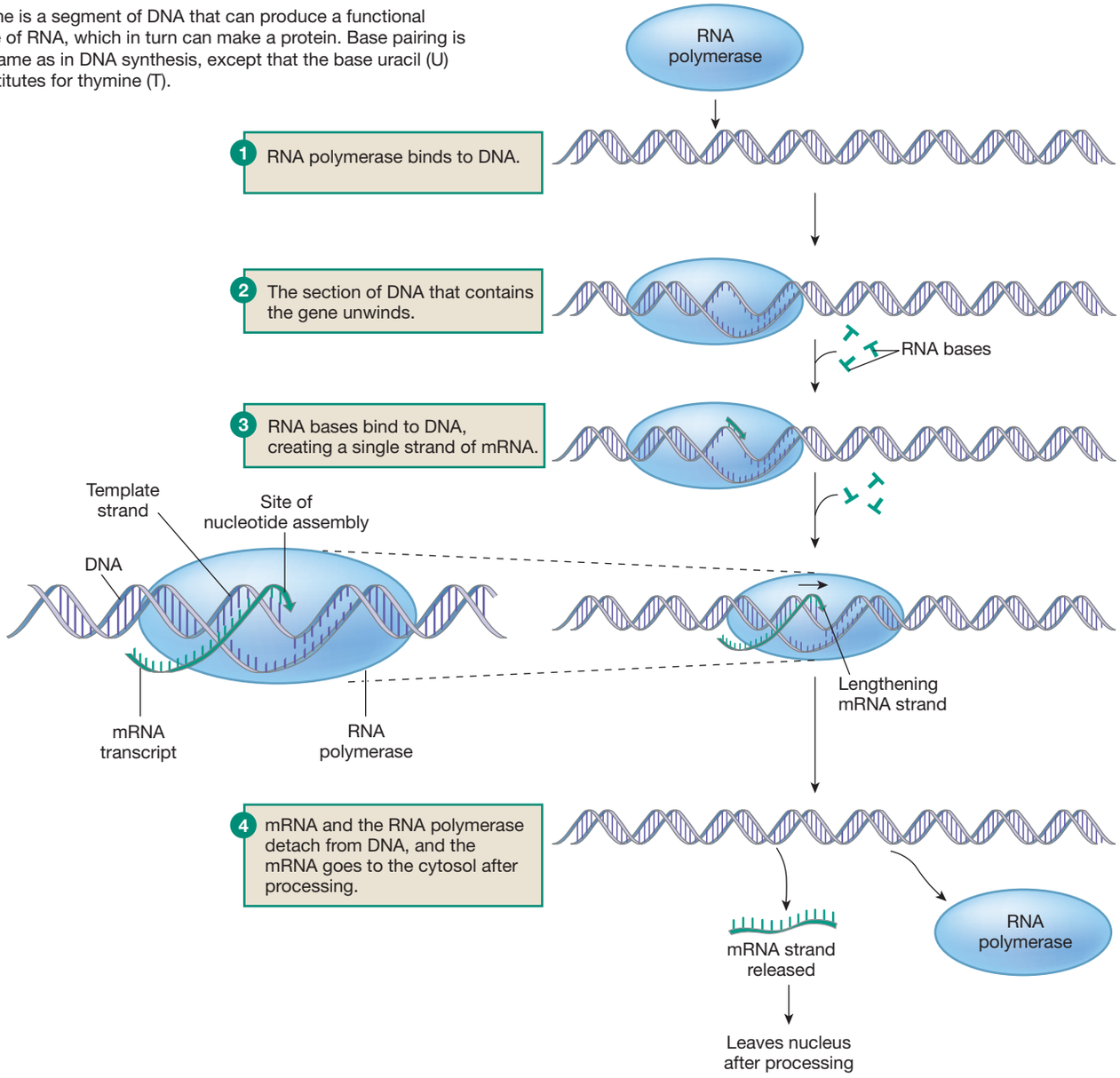


FIG. 4.19 Transcription

A gene is a segment of DNA that can produce a functional piece of RNA, which in turn can make a protein. Base pairing is the same as in DNA synthesis, except that the base uracil (U) substitutes for thymine (T).



CONCEPT CHECK

20. Use the genetic code in Figure 4.17 to write the DNA codons that correspond to the three mRNA stop codons.

21. What does the name RNA polymerase tell you about the function of this enzyme?

Alternative Splicing Creates Multiple Proteins from One DNA Sequence

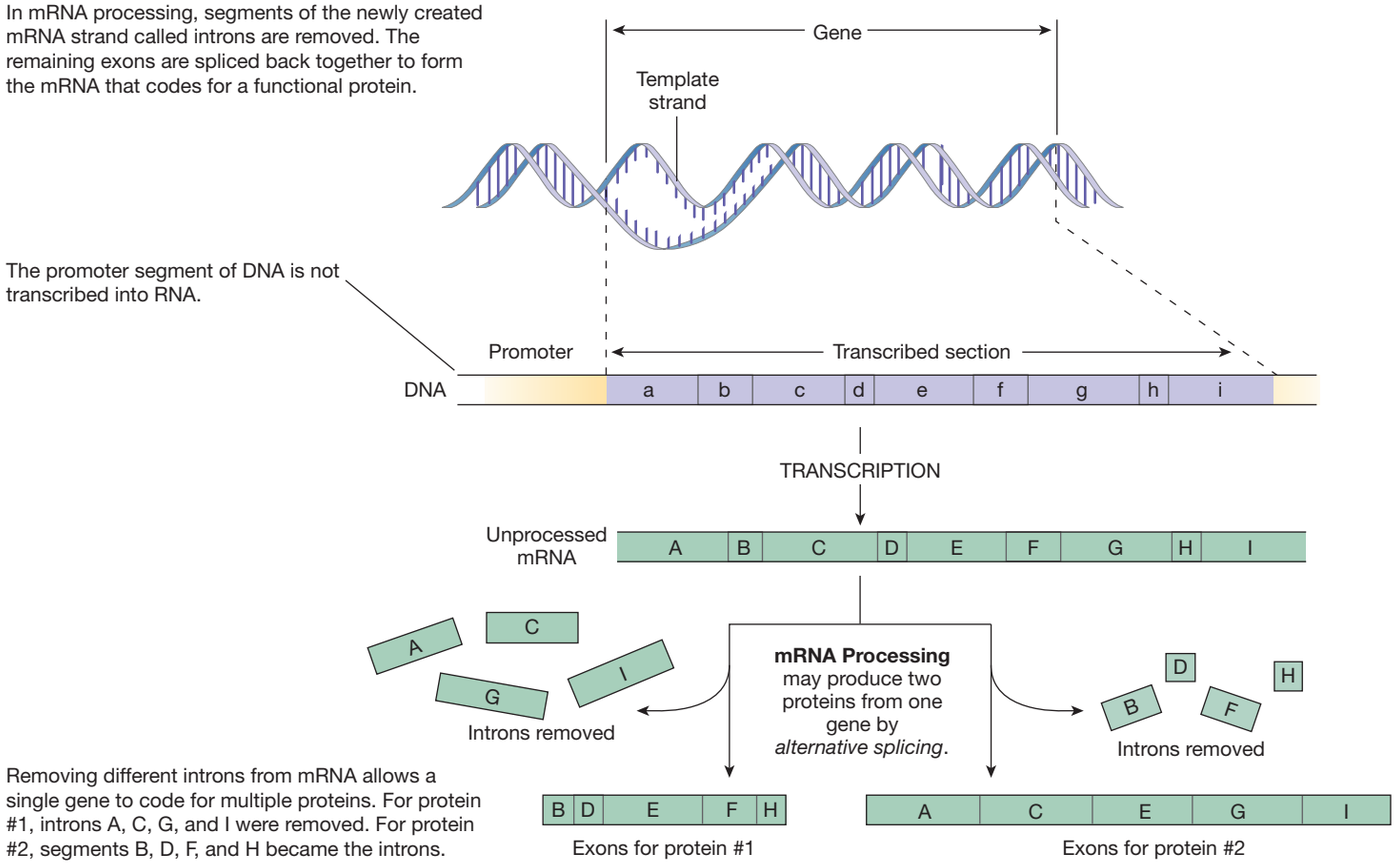
The next step in the process of protein synthesis is **mRNA processing,** which takes two forms (Fig. 4.18 3). In *RNA interference*, newly synthesized mRNA is inactivated or destroyed before it can be translated into proteins (see the Emerging Concepts box). In **alternative splicing**, enzymes clip segments out of the middle or off the ends of the mRNA strand. Other enzymes then splice the remaining pieces of the strand back together.

Alternative splicing is necessary because a gene contains both segments that encode proteins (**exons**) and noncoding segments called **introns** (FIG. 4.20). That means the mRNA initially made from the gene's DNA contains noncoding segments that must be removed before the mRNA leaves the nucleus. The result of alternative splicing is a smaller piece of mRNA that now contains only the coding sequence for a specific protein.

One advantage of alternative splicing is that it allows a single base sequence on DNA to code for more than one protein. The

FIG. 4.20 mRNA processing

In mRNA processing, segments of the newly created mRNA strand called introns are removed. The remaining exons are spliced back together to form the mRNA that codes for a functional protein.



Removing different introns from mRNA allows a single gene to code for multiple proteins. For protein #1, introns A, C, G, and I were removed. For protein #2, segments B, D, F, and H became the introns.

designation of segments as coding or noncoding is not fixed for a given gene. Segments of mRNA that are removed one time can be left in the next time, producing a finished mRNA with a different sequence. The closely related forms of a single enzyme known as *isozymes* are probably made by alternative splicing of a single gene.

After mRNA has been processed, it exits the nucleus through nuclear pores and goes to ribosomes in the cytosol. There mRNA directs the construction of protein.

CONCEPT CHECK **22.** Explain in one or two sentences the relationship of mRNA, nitrogenous bases, introns, exons, mRNA processing, and proteins.

mRNA Translation Links Amino Acids

Protein synthesis requires cooperation and coordination among all three types of RNA: mRNA, rRNA, and tRNA. Upon arrival in the cytosol, processed mRNA binds to ribosomes, which are small particles of protein and several types of rRNA [p. 35]. Each ribosome has two subunits, one large and one small, that come together when protein synthesis begins (**FIG. 4.21** 3). The small ribosomal subunit binds the mRNA, then adds the large subunit so that the mRNA is sandwiched in the middle. Now the ribosome-mRNA complex is ready to begin translation.

During translation, the mRNA codons are matched to the proper amino acid. This matching is done with the assistance of a tRNA molecule (Fig. 4.21 4). One region of each tRNA contains a three-base sequence called an **anticodon** that is complementary to an mRNA codon. A different region of the tRNA molecule binds to a specific amino acid.

As translation begins, the anticodons of tRNAs carrying amino acids attach to the complementary codons of ribosomal mRNA. For example, a tRNA with anticodon sequence UUU carries the amino acid lysine. The UUU anticodon pairs with an AAA codon, one of two codons for lysine, on mRNA. The pairing between mRNA and tRNA puts newly arrived amino acids into the correct orientation to link to the growing peptide chain.

Dehydration synthesis links amino acids by creating a *peptide bond* between the amino group ($-NH_2$) of the newly arrived amino acid and the carboxyl end (-COOH) of the peptide chain [p. 32]. Once this happens, mRNA releases the "empty" tRNA. The tRNA can then attach to another amino acid molecule with the aid of a cytosolic enzyme and ATP.

EMERGING CONCEPTS

Purple Petunias and RNAi

Who could have guessed that research to develop a deep purple petunia would lead the way to one of the most exciting new areas of molecular biology research? **RNA interference (RNAi)** was first observed in 1990, when botanists who introduced purple pigment genes into petunias ended up with plants that were white or striped with white instead of the deeper purple color they expected. This observation did not attract attention until 1998, when scientists doing research in animal biology and medicine had similar problems in experiments on a nematode worm. Now RNAi is one of the newest tools in biotechnology research.

In very simple terms, RNA "silencing" of mRNA is a naturally occurring event accomplished through the production or introduction of short RNA molecules. These short RNAs bind to mRNA and keep it from being translated. They may even target the mRNA for destruction.

RNAi is a naturally occurring RNA processing mechanism that may have evolved as a means of blocking the replication of RNA viruses. Now researchers are using it to selectively block the production of single proteins within a cell. The scientists' ultimate goal is to create technologies that can be used for the diagnosis and treatment of disease.

When the last amino acid has been joined to the newly synthesized peptide chain, the termination stage has been reached (Fig. 4.21 5). The mRNA, the peptide, and the ribosomal subunits separate. The ribosomes are ready for a new round of protein synthesis, but the mRNA is broken down by enzymes known as *ribonucleases*. Some forms of mRNA are broken down quite rapidly, while others may linger in the cytosol and be translated many times.

Protein Sorting Directs Proteins to Their Destination

One of the amazing aspects of protein synthesis is the way specific proteins go from the ribosomes directly to where they are needed in the cell, a process called *protein sorting*. Many newly made proteins carry a *sorting signal,* an address label that tells the cell where the protein should go. Some proteins that are synthesized on cytosolic ribosomes do not have sorting signals. Without a "delivery tag," they remain in the cytosol when they are released from the ribosome [Fig. 3.7, p. 73].

The sorting signal is a special segment of amino acids known as a **signal sequence.** The signal sequence tag directs the protein to the proper organelle, such as the mitochondria or peroxisomes, and allows it to be transported through the organelle membrane. Peptides synthesized on ribosomes attached to the rough endoplasmic reticulum have a signal sequence directs them through the membrane of the rough ER and into the lumen of this organelle. Once a protein enters the ER lumen, enzymes remove the signal sequence.

Proteins Undergo Posttranslational Modification

The amino acid sequence that comes off a ribosome is the primary structure of a newly synthesized protein [p. 32], but not the final form. The newly made protein can now form different types of covalent and noncovalent bonds, a process known as **posttranslational modification.** Cleavage of the amino acid chain, attachment of molecules or groups, and cross-linkages are three general types of posttranslational modification. More than 100 different types of posttranslational modification have been described so far.

In some common forms of posttranslational modification, the amino acid chain can:

1. fold into various three-dimensional shapes. Protein folding creates the tertiary structure of the protein.
2. create cross-links between different regions of its amino acid chain
3. be cleaved (split) into fragments
4. add other molecules or groups
5. assemble with other amino acid chains into a polymeric (many-part) protein. Assembly of proteins into polymers creates the quaternary structure of the protein.

Protein Folding Peptides released from ribosomes are free to take on their final three-dimensional shape. Each peptide first forms its secondary structure, which may be an α-helix or a β-strand [p. 32]. The molecule then folds into its final shape when hydrogen bonds, covalent bonds, and ionic bonds form between amino acids in the chain. Studies show that some protein folding takes place spontaneously, but it is often facilitated by helper proteins called *molecular chaperones*.

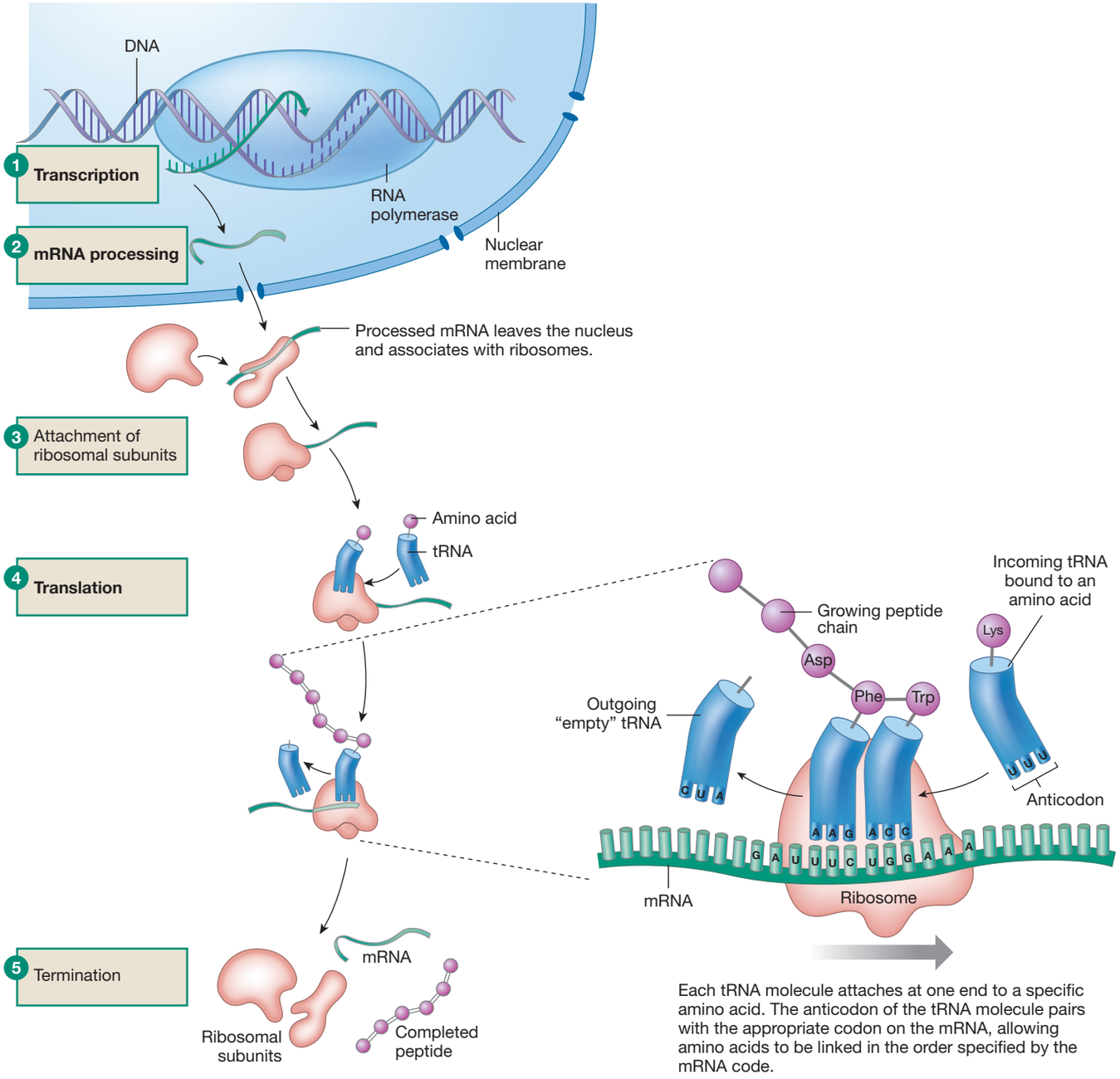
The three-dimensional shape of proteins is often essential for proper function. Misfolded proteins, along with other proteins the cell wishes to destroy, are tagged with a protein called *ubiquitin* and sent to *proteasomes,* cylindrical cytoplasmic enzyme complexes that break down proteins.

Cross-Linkage Some protein folding is held in place by relatively weak hydrogen bonds and ionic bonds. However, other proteins form strong covalent bonds between different parts of the amino acid chain. These bonds are often disulfide bonds (S–S) between two cysteine amino acids, which contain sulfur atoms. For example, the three chains of the digestive enzyme chymotrypsin are held together by disulfide bonds.

Cleavage Some biologically active proteins, such as enzymes and hormones, are synthesized initially as inactive molecules that

FIG. 4.21 Translation

Translation matches the codons of RNA with amino acids to create a protein.



Each tRNA molecule attaches at one end to a specific amino acid. The anticodon of the tRNA molecule pairs with the appropriate codon on the mRNA, allowing amino acids to be linked in the order specified by the mRNA code.

must have segments removed before they become active. The enzyme chymotrypsin must have two small peptide fragments removed before it can catalyze a reaction [Fig. 2.12a, p. 50]. Post-translational processing also activates some peptide hormones.

Addition of Other Molecules or Groups Proteins can be modified by the addition of sugars (glycosylation) to create glycoproteins, or by combination with lipids to make lipoproteins [p. 29]. The two most common chemical groups added to proteins are phosphate groups, PO_4^{2-} and methyl groups, $-CH_3$. (Addition of a methyl group is called *methylation*.)

Assembly into Polymeric Proteins Many complex proteins have a quaternary structure with multiple subunits, in which protein chains assemble into dimers, trimers, or tetramers. One example is the enzyme lactate dehydrogenase (described on p. 99). Another example is the hemoglobin molecule, with four protein chains [Fig. 2.3, p. 32].

CONCEPT CHECK

23. What is the removal of a phosphate group called?
24. List three general types of posttranslational modification of proteins.
25. Is hemoglobin a monomer, dimer, trimer, or tetramer?

The many ways that proteins can be modified after synthesis add to the complexity of the human body. We must know not only the sequence of a protein but also how it is processed, where the protein occurs in or outside the cell, and what it does. Scientists working on the Human Genome Project initially predicted that our DNA would code for about 30,000 proteins, but they were not taking into account alternative splicing or posttranslational modifications. Scientists working on the Human Proteomics Initiative are now predicting that we will find more than a million different proteins. The magnitude of this project means that it will continue for many years into the future.

RUNNING PROBLEM CONCLUSION | Tay-Sachs Disease

In this running problem, you learned that Tay-Sachs disease is an incurable, recessive genetic disorder in which the enzyme that breaks down gangliosides in cells is missing. One in 27 Americans of Eastern European Jewish descent in the United States carries the gene for this disorder. Other high-risk populations include French Canadians, Louisiana "Cajuns," and Irish Americans. By one estimate, about one person in every 250 in the general American population is a carrier of the Tay-Sachs gene.

You have also learned that a blood test can detect the presence of genetic mutations that cause this deadly disease. Check your understanding of this running problem by comparing your answers to those in the summary table. To read more on Tay-Sachs disease, see the NIH reference page (*www.ninds.nih.gov/disorders/taysachs/taysachs.htm*) or the web site of the National Tay-Sachs & Allied Diseases Association (*www.ntsad.org*).

Question	Facts	Integration and Analysis
Q1: *What is another symptom of Tay-Sachs disease besides loss of muscle control and brain function?*	Hexosaminidase A breaks down gangliosides. In Tay-Sachs disease, this enzyme is absent, and gangliosides accumulate in cells, including light-sensitive cells of the eye, and cause them to function abnormally.	Damage to light-sensitive cells of the eye could cause vision problems and even blindness.
Q2: *How could you test whether Sarah and David are carriers of the Tay-Sachs gene?*	Carriers of the gene have lower-than-normal levels of hexosaminidase A.	Run tests to determine the average enzyme levels in known carriers of the disease (i.e., people who are parents of children with Tay-Sachs disease) and in people who have little likelihood of being carriers. Compare the enzyme levels of suspected carriers such as Sarah and David with the averages for the known carriers and noncarriers.
Q3: *Why might the genetic test for mutations in the Tay-Sachs gene be more accurate than the test that detects decreased amounts of hexosaminidase A?*	The genetic test detects three mutations in the gene. The enzyme test analyzes levels of the enzyme produced by the gene.	The genetic test is a direct way to test if a person is a carrier. The enzyme test is an indirect indicator. It is possible for factors other than a defective gene to alter a person's enzyme level. Can you think of some? (Answer in Appendix A, p. A-4.)
Q4: *Can you think of a situation in which the enzyme activity test might be more accurate than the genetic test?*	The genetic test looks for three mutations in the Tay-Sachs gene.	There are more than three mutations that can cause Tay-Sachs disease. If the person does not have one of the three mutations being tested, the result will appear to be normal.
Q5: *The Tay-Sachs gene is a recessive gene (t). What is the chance that any child of a carrier (Tt) and a noncarrier (TT) will be a carrier? What are the chances that a child of two carriers will have the disease or be a carrier?*	Mating of Tt × TT results in the following offspring: TT, Tt, TT, Tt. Mating of Tt × Tt results in the following offspring: TT, Tt, Tt, tt.	If only one parent is a carrier, each child has a 50% chance of being a carrier (Tt). If both parents are carriers, there is a 25% chance that a child will have Tay-Sachs disease and a 50% chance a child will be a carrier.

CHAPTER SUMMARY

The major theme of this chapter is *energy in biological systems* and how it is acquired, transferred, and used to do biological work. Energy is stored in large biomolecules such as fats and glycogen and is extracted from them through the processes of metabolism. Extracted energy is often stored temporarily in the high-energy phosphate bonds of ATP. Reactions and processes that require energy often use ATP as the energy source. This is a pattern you will see repeated as you learn more about the organ systems of the body.

Other themes in the chapter involve two kinds of *structure-function relationships:* molecular interactions and compartmentation. *Molecular interactions* are important in enzymes, where the ability of an enzyme to bind to its substrate influences the enzyme's activity or in protein synthesis, where nucleic acids direct the assembly of amino acids into larger molecules. *Compartmentation* of enzymes allows cells to direct energy flow by separating functions. Glycolysis takes place in the cytosol of the cell, but the citric acid cycle is isolated within mitochondria, requiring transport of substrates across the mitochondrial membrane. Modulation of enzyme activity and the separation of pathways into subcellular compartments are essential for organizing and separating metabolic processes.

Energy in Biological Systems

1. **Energy** is the capacity to do work. **Chemical work** enables cells and organisms to grow, reproduce, and carry out normal activities. **Transport work** enables cells to move molecules to create concentration gradients. **Mechanical work** is used for movement. (p. 94)
2. **Kinetic energy** is the energy of motion. **Potential energy** is stored energy. (p. 95; Fig. 4.2)

Chemical Reactions

3. A **chemical reaction** begins with one or more **reactants** and ends with one or more **products** (Tbl. 4.2). **Reaction rate** is measured as the change in concentration of products with time. (p. 96)
4. The energy stored in the chemical bonds of a molecule and available to perform work is the **free energy** of the molecule. (p. 96)
5. **Activation energy** is the initial input of energy required to begin a reaction. (p. 96; Fig. 4.3)
6. **Exergonic reactions** are energy-producing. **Endergonic reactions** are energy-utilizing. (p. 96; Fig. 4.3)
7. Metabolic pathways couple exergonic reactions to endergonic reactions. (p. 97; Fig. 4.4)
8. Energy for driving endergonic reactions is stored in ATP. (p. 97)
9. **Reversible reactions** can proceed in both directions. **Irreversible reactions** can go in one direction but not the other. The net free energy change of a reaction determines whether that reaction is reversible. (p. 98)

Enzymes

10. **Enzymes** are biological catalysts that speed up the rate of chemical reactions without themselves being changed. In reactions catalyzed by enzymes, the reactants are called **substrates.** (pp. 98, 99)
11. Like other proteins that bind ligands, enzymes exhibit saturation, specificity, and competition. Related isozymes may have different activities. (p. 99)
12. Some enzymes are produced as inactive precursors and must be activated. This may require the presence of a **cofactor.** Organic cofactors are called **coenzymes.** (p. 100)
13. Enzyme activity is altered by temperature, pH, and modulator molecules. (p. 100)
14. Enzymes work by lowering the activation energy of a reaction. (p. 100; Fig. 4.7)
15. Most reactions can be classified as **oxidation-reduction, hydrolysis-dehydration, addition-subtraction-exchange,** or **ligation** reactions. (pp. 101, 102; Tbl. 4.4)

Metabolism

16. All the chemical reactions in the body are known collectively as **metabolism. Catabolic reactions** release energy and break down large biomolecules. **Anabolic reactions** require a net input of energy and synthesize large biomolecules. (p. 102)
17. Cells regulate the flow of molecules through their metabolic pathways by (1) controlling enzyme concentrations, (2) producing allosteric and covalent modulators, (3) using different enzymes to catalyze reversible reactions, (4) isolating enzymes in intracellular organelles, or (5) maintaining an optimum ratio of ATP to ADP. (p. 103)
18. **Aerobic pathways** require oxygen and yield the most ATP. **Anaerobic pathways** can proceed without oxygen but produce ATP in much smaller quantities. (p. 105)

ATP Production

iP Muscular: Muscle Metabolism

19. Through **glycolysis,** one molecule of glucose is converted into two pyruvate molecules, and yields 2 ATP, 2 NADH, and 2 H^+. Glycolysis does not require the presence of oxygen. (p. 105; Fig. 4.12)
20. **Aerobic metabolism** of pyruvate through the **citric acid cycle** yields ATP, carbon dioxide, and high-energy electrons captured by NADH and $FADH_2$. (p. 108; Fig. 4.13)
21. **High-energy electrons** from NADH and $FADH_2$ give up their energy as they pass through the **electron transport system.** Their energy is trapped in the high-energy bonds of ATP. (p. 105; Fig. 4.14)
22. Maximum energy yield for aerobic metabolism of one glucose molecule is 30–32 ATP. (p. 105; Fig. 4.15)

23. In **anaerobic metabolism,** pyruvate is converted into lactate, with a net yield of 2 ATP for each glucose molecule. (p. 110; Fig. 4.15)
24. Protein synthesis is controlled by nuclear **genes** made of DNA. The code represented by the base sequence in a gene is transcribed into a complementary base code on **RNA. Alternative splicing** of mRNA in the nucleus allows one gene to code for multiple proteins. (pp. 112, 114; Figs. 4.18, 4.19, 4.20)
25. mRNA leaves the nucleus and goes to the cytosol where, with the assistance of **transfer RNA** and **ribosomal RNA,** it assembles amino acids into a designated sequence. This process is called **translation.** (p. 112; Fig. 4.21)
26. **Posttranslational modification** converts the newly synthesized protein to its finished form. (p. 116)

REVIEW QUESTIONS

In addition to working through these questions and checking your answers on p. A-5, review the Learning Outcomes at the beginning of this chapter.

Level One Reviewing Facts and Terms

1. List the three basic forms of work and give a physiological example of each.
2. Explain the difference between potential energy and kinetic energy.
3. State the two laws of thermodynamics in your own words.
4. The sum of all chemical processes through which cells obtain and store energy is called _____.
5. In the reaction $CO_2 + H_2O \rightarrow H_2CO_3$, water and carbon dioxide are the reactants, and H_2CO_3 is the product. Because this reaction is catalyzed by an enzyme, it is also appropriate to call water and carbon dioxide _____. The speed at which this reaction occurs is called the reaction _____, often expressed as molarity/second.
6. _____ are protein molecules that speed up chemical reactions by (increasing or decreasing?) the activation energy of the reaction.
7. Match each definition in the left column with the correct term from the right column (you will not use all the terms):

1. reaction that can run either direction	(a) exergonic
2. reaction that releases energy	(b) endergonic
3. ability of an enzyme to catalyze one reaction but not another	(c) activation energy
4. boost of energy needed to get a reaction started	(d) reversible
	(e) irreversible
	(f) specificity
	(g) free energy
	(h) saturation

8. Since 1972, enzymes have been designated by adding the suffix _____ to their name.
9. Organic molecules that must be present in order for an enzyme to function are called _____. The precursors of these organic molecules come from _____ in our diet.
10. In an oxidation-reduction reaction, in which electrons are moved between molecules, the molecule that gains an electron is said to be _____, and the one that loses an electron is said to be _____.
11. The removal of H_2O from reacting molecules is called _____. Using H_2O to break down polymers, such as starch, is called _____.
12. The removal of an amino group $-NH_2$ from a molecule (such as an amino acid) is called _____. Transfer of an amino group from one molecule to the carbon skeleton of another molecule (to form a different amino acid) is called _____.
13. In metabolism, _____ reactions release energy and result in the breakdown of large biomolecules, and _____ reactions require a net input of energy and result in the synthesis of large biomolecules. In what units do we measure the energy of metabolism?
14. Metabolic regulation in which the last product of a metabolic pathway (the end product) accumulates and slows or stops reactions earlier in the pathway is called _____.
15. Explain how H^+ movement across the inner mitochondrial membrane results in ATP synthesis.
16. List two carrier molecules that deliver high-energy electrons to the electron transport system.

Level Two Reviewing Concepts

17. Create maps using the following terms.

Map 1: Metabolism

• acetyl CoA	• glycolysis
• ATP	• high-energy electrons
• citric acid cycle	• lactate
• CO_2	• mitochondria
• cytosol	• NADH
• electron transport system	• oxygen
• $FADH_2$	• pyruvate
• glucose	• water

Map 2: Protein synthesis

• alternative splicing	• ribosome
• base pairing	• RNA polymerase
• bases (A, C, G, T, U)	• RNA processing
• DNA	• start codon
• exon	• stop codon
• gene	• template strand
• intron	• transcription
• promoter	• transcription factors
• mRNA	• translation
• tRNA	

18. When bonds are broken during a chemical reaction, what are the three possible fates for the potential energy found in those bonds?

19. Match the metabolic processes with the letter of the biological theme that best describes the process:

a. Biological energy use b. Compartmentation c. Molecular interactions	1. Glycolysis takes place in the cytosol; oxidative phosphorylation takes place in mitochondria. 2. The electron transport system traps energy in a hydrogen ion concentration gradient. 3. Proteins are modified in the endoplasmic reticulum. 4. Metabolic reactions are often coupled to the reaction ATP → ADP + P_i. 5. Some proteins have S–S bonds between nonadjacent amino acids. 6. Enzymes catalyze biological reactions.

20. Explain why it is advantageous for a cell to store or secrete an enzyme in an inactive form.

21. Compare the following: (a) the energy yield from the aerobic breakdown of one glucose to CO_2 and H_2O, and (b) the energy yield from one glucose going through anaerobic glycolysis ending with lactate. What are the advantages of each pathway?

22. Briefly describe the processes of transcription and translation. Which organelles are involved in each process?

23. On what molecule does the anticodon appear? Explain the role of this molecule in protein synthesis.

24. Is the energy of ATP's phosphate bond an example of potential or kinetic energy?

25. If ATP releases energy to drive a chemical reaction, would you suspect the activation energy of that reaction to be large or small? Explain.

Level Three Problem Solving

26. Given the following strand of DNA: (1) Find the first start codon in the DNA sequence. *Hint:* The start codon in mRNA is AUG. (2) For the triplets that follow the start codon, list the sequence of corresponding mRNA bases. (3) Give the amino acids that correspond to those mRNA triplets. (See Fig. 4.17.)

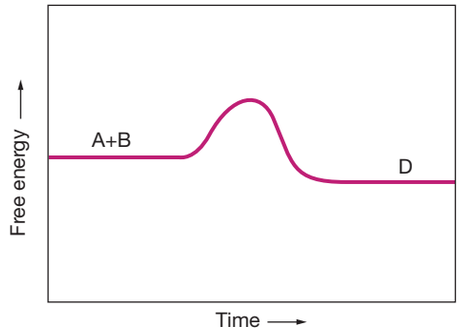
    DNA: C G C T A C A A G T C A C G T A C C G T A A C G A C T

    mRNA:

    Amino acids:

Level Four Quantitative Problems

27. The graph shows the free energy change for the reaction A + B → D. Is this an endergonic or exergonic reaction?



28. If the protein-coding portion of a piece of processed mRNA is 450 bases long, how many amino acids will be in the corresponding polypeptide? (*Hint:* The start codon is translated into an amino acid, but the stop codon is not.)

Answers to Concept Checks, Figure and Graph Questions, and end-of-chapter Review Questions can be found in Appendix A [A-1].