Chapter 9

Cellular Respiration: Harvesting Chemical Energy

Key Concepts

9.1 Catabolic pathways yield energy by oxidizing organic fuels

9.2 Glycolysis harvests chemical energy by oxidizing glucose to pyruvate

9.3 The citric acid cycle completes the energy-yielding oxidation of organic molecules

9.4 During oxidative phosphorylation, chemiosmosis couples electron transport to ATP synthesis

9.5 Fermentation enables some cells to produce ATP without the use of oxygen

9.6 Glycolysis and the citric acid cycle connect to many other metabolic pathways

Framework

The catabolic pathways of glycolysis and cellular respiration release the chemical energy in glucose and other fuels and store it in ATP. Glycolysis, occurring in the cytosol, produces ATP, pyruvate, and NADH; the latter two may then enter the mitochondria for respiration. A mitochondrion consists of a matrix in which the enzymes of the citric acid cycle are localized, a highly folded inner membrane in which enzymes and the molecules of the electron transport chain are embedded, and an intermembrane space between the two membranes to temporarily house H^+ that has been pumped across the inner membrane during the redox reactions of the electron transport chain. ATP is produced by oxidative phosphorylation, a chemiosmotic mechanism in which a proton motive force drives protons through ATP synthases located in the membrane.

Chapter Review

Photosynthesis stores the energy of sunlight in organic compounds. Through catabolic pathways, a cell breaks down these complex molecules to simpler ones, generating ATP for cellular work. Energy leaves an ecosystem as heat.

9.1 Catabolic pathways yield energy by oxidizing organic fuels

Catabolic Pathways and Production of ATP **Fermentation,** which occurs without oxygen, is the partial degradation of sugars to release energy. **Cellular respiration** uses oxygen in the breakdown of glucose (or other energy-rich organic compounds) to yield carbon dioxide and water and release energy as ATP and heat. This exergonic process has a free energy change of −686 kcal/mol of glucose.

■ INTERACTIVE QUESTION 9.1

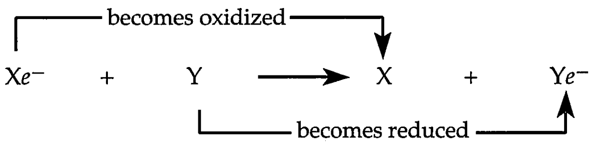
Fill in this summary equation for cellular respiration.

________ $+ 6\,O_2 \rightarrow$ ________ $+ 6\,H_2O +$ ________

Redox Reactions: Oxidation and Reduction Oxidation-reduction or **redox reactions** involve the partial or complete transfer of one or more electrons from one reactant to another. **Oxidation** is the loss of electrons from one substance; **reduction** is the addition of electrons to another substance. The substance that loses electrons becomes oxidized and acts as a **reducing agent** (electron donor) to the substance that gains electrons. By gaining electrons, a substance acts as an **oxidizing agent** (electron acceptor) and becomes reduced.

■ INTERACTIVE QUESTION 9.2

Fill in the appropriate terms in this equation.



X is the reducing agent; it becomes a. __________.

Y is the b. __________; it becomes c. __________.

Oxygen strongly attracts electrons and is one of the most powerful oxidizing agents. As electrons shift toward a more electronegative atom, they give up potential energy. Thus, chemical energy is released in a redox reaction that relocates electrons closer to oxygen.

Organic molecules with an abundance of hydrogen are rich in "hilltop" electrons that release their potential energy when they "fall" closer to oxygen.

■ INTERACTIVE QUESTION 9.3

a. In the conversion of glucose and oxygen to carbon dioxide and water, which molecule is reduced?

b. Which molecule is oxidized?

c. What happens to the energy that is released in this redox reaction?

At certain steps in the oxidation of glucose, two hydrogen atoms are removed by enzymes called dehydrogenases, and the two electrons and one proton are passed to a coenzyme, **NAD^+** (nicotinamide adenine dinucleotide), reducing it to NADH.

Energy from respiration is slowly released in a series of small steps as electrons are passed from NADH down an **electron transport chain,** a group of carrier molecules located in the inner mitochondrial membrane, to a stable location close to a highly electronegative oxygen atom.

■ INTERACTIVE QUESTION 9.4

a. NAD^+ is called an __________.

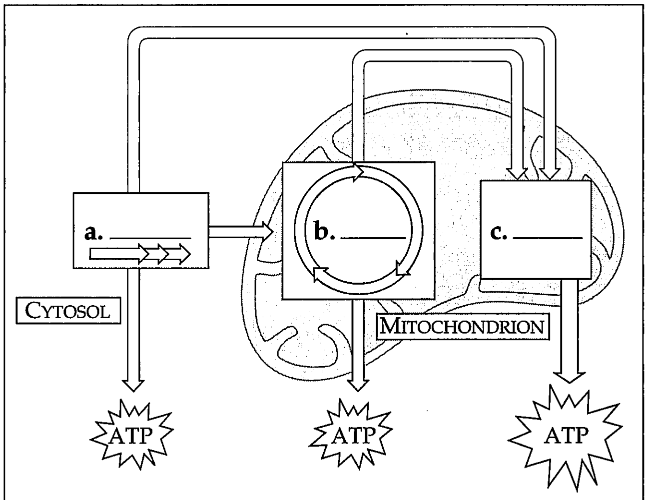
b. Its reduced form is __________.

The Stages of Cellular Respiration: A Preview **Glycolysis,** occurring in the cytosol, breaks glucose into two molecules of pyruvate. The **citric acid cycle,** located in the mitochondrial matrix, converts a derivative of pyruvate into carbon dioxide. In some of the steps of glycolysis and the citric acid cycle, dehydrogenase enzymes transfer electrons to NAD^+. NADH passes electrons to the electron transport chain, from which they eventually combine with hydrogen ions and oxygen to form water. The energy released through this chain of redox reactions is used to synthesize ATP by **oxidative phosphorylation,** a process that includes electron transport and chemiosmosis.

Up to 38 molecules of ATP may be generated for each molecule of glucose oxidized to carbon dioxide. About 10% of this ATP is produced by **substrate-level phosphorylation,** in which an enzyme transfers a phosphate group from a substrate to ADP.

■ INTERACTIVE QUESTION 9.5

Fill in the three stages of respiration (a–c). Indicate whether ATP is produced by substrate-level or oxidative phosphorylation (d–f). Label the arrows indicating electrons carried by NA.



d. __________ e. __________ f. __________

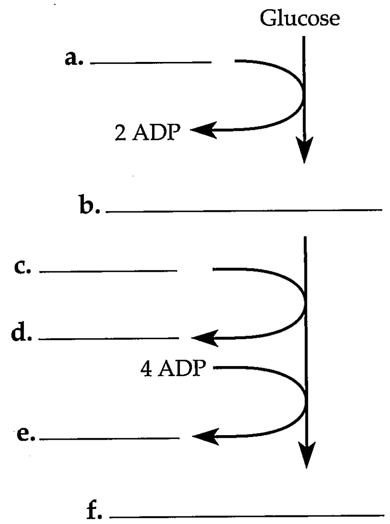
9.2 Glycolysis harvests chemical energy by oxidizing glucose to pyruvate

Glycolysis, a ten-step process occurring in the cytosol, has an energy-investment phase and an energy-payoff phase. Two molecules of ATP are consumed as glucose is split into two three-carbon sugars (glyceraldehyde-3-phosphate). The conversion of these molecules to pyruvate produces two NADH and four ATP by substrate-level phosphorylation. For each molecule of glucose, glycolysis yields a net gain of two ATP and two NADH.

Enzymes catalyze each step in glycolysis. Kinases transfer phosphate groups; a dehydrogenase oxidizes glyceraldehyde-3-phosphate and reduces NAD^+; and other enzymes rearrange atoms in substrate molecules.

■ INTERACTIVE QUESTION 9.6

Fill in the blanks in this summary diagram of glycolysis.



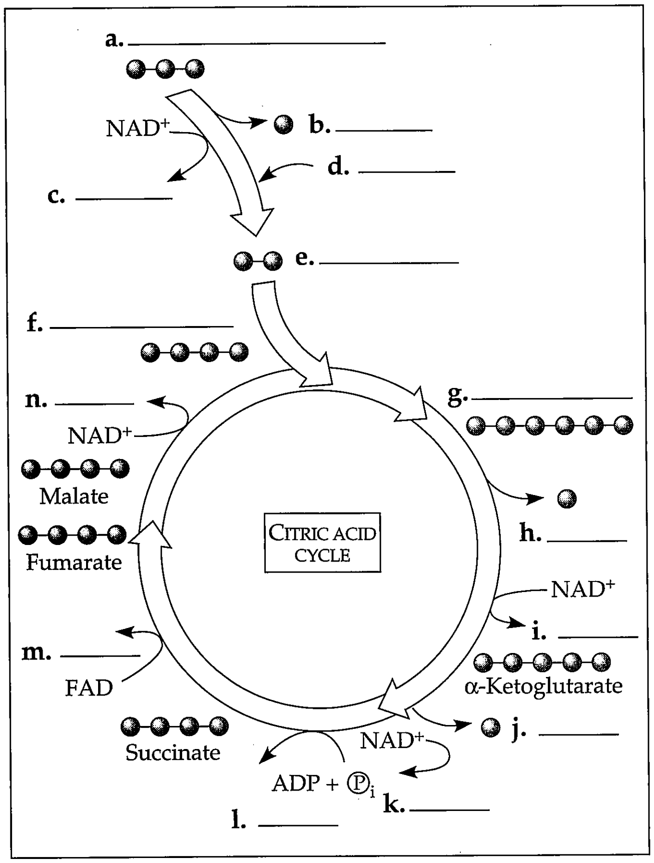
9.3 The citric acid cycle completes the energy-yielding oxidation of organic molecules

Pyruvate is actively transported into the mitochondrion. Before the citric acid cycle begins, a series of steps occurs within a multienzyme complex. A carboxyl group is removed from the three-carbon pyruvate and released as CO_2; the remaining two-carbon group is oxidized to form acetate with the accompanying reduction of NAD^+ to NADH; and coenzyme A is attached to the acetate by an unstable bond, forming **acetyl CoA.**

In the citric acid cycle (also called the Krebs cycle), the acetyl group of acetyl CoA is added to oxaloacetate to form citrate, which is progressively decomposed back to oxaloacetate. For each turn of the citric acid cycle, two carbons enter in the reduced form from acetyl CoA; two carbons exit completely oxidized as CO_2; three NADH and one $FADH_2$ are formed; and one ATP is made by substrate-level phosphorylation. There are two turns of the citric acid cycle for each glucose molecule oxidized.

■ INTERACTIVE QUESTION 9.7

Fill in the blanks in this summary figure of the citric acid cycle. Balls represent carbon atoms.



9.4 During oxidative phosphorylation, chemiosmosis couples electron transport to ATP synthesis

Pathway of Electron Transport Thousands of electron transport chains are embedded in the cristae (infoldings) of the inner mitochondrial membrane. Most components of the electron transport chain are proteins, with tightly bound, nonprotein *prosthetic groups*. The electron carriers shift between reduced and oxidized states as they accept and donate electrons. The components are organized into four complexes. The transfer of electrons goes from NADH to a flavoprotein to an iron-sulfur protein (Complex I) to a mobile hydrophobic molecule, ubiquinone (Q). Next electrons pass down a series of molecules called **cytochromes (cyt),** proteins with an iron-containing heme group. The last cytochrome, cyt a_3, passes electrons to oxygen, which picks up a pair of H^+ and forms water.

$FADH_2$ adds its electrons to the chain at a lower energy level (at Complex II); thus, one-third less energy is provided for ATP synthesis by $FADH_2$ as compared to NADH.

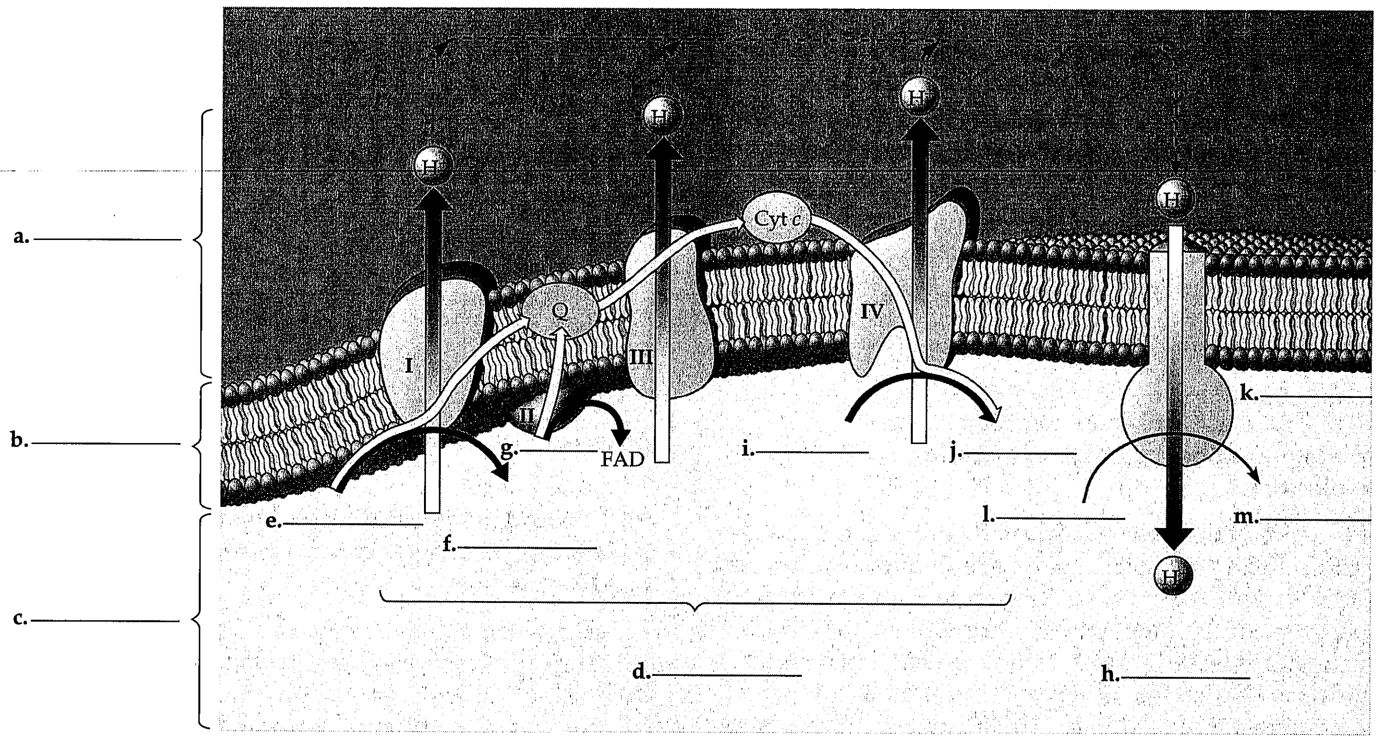
Chemiosmosis: The Energy-Coupling Mechanism **ATP synthase,** a protein complex embedded in the inner membrane, uses the energy of a proton (H^+) gradient to make ATP, an example of the process called **chemiosmosis.** The electron transport chain creates the proton gradient. When some members of the chain pass electrons, they also accept and release protons, which are pumped into the intermembrane space at three points. The resulting proton gradient stores potential energy, referred to as the **proton-motive force.**

The flow of H^+ ions down their gradient through the rotor and stator part of the ATP synthase complex causes the rotor and attached rod to rotate, activating catalytic sites on the knob portion where ADP and inorganic phosphate join to make ATP.

In mitochondria, exergonic redox reactions produce the H^+ gradient that drives the production of ATP. Chloroplasts use light energy to create the proton-motive force used to make ATP by chemiosmosis. Prokaryotes use H^+ gradients generated across their plasma membranes to transport molecules, make ATP, and rotate flagella.

■ INTERACTIVE QUESTION 9.8

Label this diagram of oxidative phosphorylation in a mitochondrial membrane.



An Accounting of ATP Production by Cellular Respiration About 36 or 38 ATPs may be produced per glucose molecule oxidized. This number is only an estimate for three reasons: The 3 ATPs/NADH and 2 ATPs/$FADH_2$ are rounded off numbers; the electrons from the NADH produced by glycolysis may be passed across the inner mitochondrial membrane to NAD^+ or FAD, depending on the type of shuttle used in the cell; and the proton-motive force generated by the electron transport chain is also used to power other work in the mitochondrion.

The efficiency of respiration in its energy conversions is approximately 40%. The rest of the energy is released as heat.

■ INTERACTIVE QUESTION 9.9

Fill in the tally for maximum ATP yield from the oxidation of one molecule of glucose to six molecules of carbon dioxide.

Process	# ATP
Initial phosphorylation of glucose:	a. ______
Substrate-level phosphorylation: in glycolysis	b. ______
in c. ______________________	2
Oxidative phosphorylation:*	d. ______
Maximum Total	e. ______

*approximately 3 ATP for each of the **f.** ______ NADH from pyruvate → acetyl CoA and the **g.** ______ NADH from citric acid cycle; **h.** ______ ATP for each of the **i.** ______ $FADH_2$ from citric acid cycle; 2 or 3 ATP of the **j.** ______ NADH from glycolysis, depending on whether the shuttle passes electrons across the membrane to NAD^+ or FAD.

9.5 Fermentation enables some cells to produce ATP without the use of oxygen

Types of Fermentation Glycolysis oxidizes glucose to produce a net of 2 ATP per glucose molecule, under both **aerobic** and **anaerobic** conditions. Without oxygen, glycolysis is part of fermentation—the anaerobic catabolism of organic nutrients to generate ATP by substrate-level phosphorylation and the reactions that regenerate NAD^+, the oxidizing agent for glycolysis.

In **alcohol fermentation,** pyruvate is converted into acetaldehyde, and CO_2 is released. Acetaldehyde is then reduced by NADH to form ethanol (ethyl alcohol), and NAD^+ is regenerated. In **lactic acid fermentation,** pyruvate is reduced directly by NADH to form lactate and recycle NAD^+. Muscle cells make ATP by lactic acid fermentation when energy demand is high and oxygen supply is low.

Fermentation and Cellular Respiration Compared Both fermentation and respiration use glycolysis with NAD^+ as the oxidizing agent to convert glucose and other organic fuels to pyruvate. To oxidize NADH back to NAD^+, fermentation uses pyruvate or acetaldehyde as the final electron acceptor, whereas respiration uses oxygen, via the electron transport chain.

Facultative anaerobes, such as yeasts and many bacteria, can make ATP by fermentation or respiration, depending upon the availability of oxygen.

Evolutionary Significance of Glycolysis Glycolysis is common to fermentation and respiration. This most widespread of all metabolic processes probably evolved in ancient prokaryotes before oxygen was available. The cytosolic location of glycolysis is also evidence of its antiquity.

■ INTERACTIVE QUESTION 9.10

How much more ATP can be generated by respiration than by fermentation? Explain why.

9.6 Glycolysis and the citric acid cycle connect to many other metabolic pathways

The Versatility of Catabolism Fats, proteins, and carbohydrates can all be used by cellular respiration to make ATP. Proteins are digested into amino acids, which are then deaminated (amino group removed) and can enter into respiration at several sites. The digestion of fats yields glycerol, which is converted to an intermediate of glycolysis, and fatty acids, which are broken down by **beta oxidation** to two-carbon fragments that enter the citric acid cycle as acetyl CoA.

Biosynthesis (Anabolic Pathways) The organic molecules of food also provide carbon skeletons for biosynthesis. Some monomers, such as amino acids, can be directly incorporated into the cell's macromolecules. Intermediates of glycolysis and the citric acid cycle serve as precursors for anabolic pathways. The molecules of carbohydrates, fats, and proteins can all be interconverted to provide for a cell's needs.

Regulation of Cellular Respiration Via Feedback Mechanisms Through feedback inhibition, the end product of a pathway inhibits an enzyme early in the pathway, thus preventing a cell from producing an excess of a particular substance. The supply of ATP in the cell regulates respiration. The allosteric enzyme that catalyzes the third step of glycolysis, phosphofructokinase, is inhibited by ATP and activated by AMP (derived from ADP). Phosphofructokinase is also inhibited by citrate released from the mitochondria into the cytosol, thus synchronizing the rates of glycolysis and the citric acid cycle. Other enzymes located at key intersections help to maintain metabolic balance.

Word Roots

aero- = air (*aerobic:* chemical reaction using oxygen)
an- = not (*anaerobic:* chemical reaction not using oxygen)
chemi- = chemical (*chemiosmosis:* the production of ATP using the energy of hydrogen ion gradients across membranes to phosphorylate ADP)
glyco- = sweet; **-lysis** = split (*glycolysis:* the splitting of glucose into pyruvate)

Structure Your Knowledge

1. This chapter describes how the catabolic pathways of glycolysis and respiration release chemical energy and store it in ATP. One of the best ways to learn the three main components of cellular respiration is to explain them to someone. Find two study partners and have each person be responsible for learning and explaining the important concepts and steps of either glycolysis, the citric acid cycle, or oxidative phosphorylation (electron transport and chemiosmosis). You may want to involve a fourth person to teach fermentation, or learn that together as a group. Use diagrams and sketches to help you explain your process to your partners.
2. Fill in the table below to summarize the major inputs and outputs of glycolysis, the citric acid cycle, oxidative phosphorylation, and fermentation. Base inputs and outputs on one glucose molecule.
3. Create a concept map to organize your understanding of oxidative phosphorylation.

Process	Main Function	Inputs Outputs
Glycolysis		
~~Pyruvate to acetyl CoA~~		
Citric acid cycle		
Oxidative phosphorylation (Electron transport and chemiosmosis)		
Fermentation		

Test Your Knowledge

MULTIPLE CHOICE: *Choose the one best answer.*

1. When electrons move closer to a more electronegative atom,
   a. energy is released.
   b. energy is consumed.
   c. a proton gradient is established.
   d. water is produced.
   e. ATP is synthesized.
2. In the reaction $C_6H_{12}O_6 + 6\,O_2 \rightarrow 6\,CO_2 + 6\,H_2O$,
   a. oxygen becomes reduced.
   b. glucose becomes reduced.
   c. oxygen becomes oxidized.
   d. water is a reducing agent.
   e. oxygen is a reducing agent.
3. A substrate that is phosphorylated
   a. has lost a phosphate group.
   b. has been formed by the reaction $ADP + Ⓟ_i \rightarrow ATP$.
   c. has an increased reactivity; it is primed to do work.
   d. has been oxidized.
   e. will pass its electrons to the electron transport chain.
4. Which of the following is *not* true of oxidative phosphorylation?
   a. It produces approximately three ATP for every NADH that is oxidized.
   b. It involves the redox reactions of the electron transport chain.
   c. It involves an ATP synthase located in the inner mitochondrial membrane.
   d. It uses oxygen as the initial electron donor.
   e. It is an example of chemiosmosis.

5. Substrate-level phosphorylation
   a. involves the shifting of a phosphate group from ATP to a substrate.
   b. can use NADH or $FADH_2$.
   c. takes place only in the cytosol.
   d. accounts for 10% of the ATP formed by fermentation.
   e. is the energy source for facultative anaerobes under anaerobic conditions.

6. The *major* reason that glycolysis is not as energy-productive as respiration is that
   a. NAD^+ is regenerated by alcohol or lactate production, without the high-energy electrons passing through the electron transport chain.
   b. it is the pathway common to fermentation and respiration.
   c. it does not take place in a specialized membrane-bound organelle.
   d. pyruvate is more reduced than CO_2; it still contains much of the energy from glucose.
   e. substrate-level phosphorylation is not as energy efficient as oxidative phosphorylation.

7. The net products of glycolysis are
   a. 2 ATP, 2 CO_2, 2 ethanol.
   b. 2 ATP, 2 NAD^+, 2 acetate.
   c. 2 ATP, 2 NADH, 2 pyruvate, 2 H_2O.
   d. 38 ATP, 6 CO_2, 6 H_2O.
   e. 4 ATP, 2 $FADH_2$, 2 pyruvate.

8. The electron carrier molecules Q and cytochrome *c*
   a. become reduced as they pass electrons on to the next molecule.
   b. contain heme prosthetic groups.
   c. shuttle protons to ATP synthase.
   d. transport H^+ into the mitochondrial matrix, establishing the proton-motive force.
   e. are mobile carriers that transfer electrons between the electron carrier complexes.

9. When pyruvate is converted to acetyl CoA,
   a. CO_2 and ATP are released.
   b. a multienzyme complex removes a carboxyl group, transfers electrons to NAD^+, and attaches a coenzyme.
   c. one turn of the citric acid cycle is completed.
   d. NAD^+ is regenerated so that glycolysis can continue to produce ATP by substrate-level phosphorylation.
   e. phosphofructokinase is activated and glycolysis continues.

10. How many molecules of CO_2 are generated for each molecule of acetyl CoA introduced into the citric acid cycle?
    a. 1　　c. 3　　e. 6
    b. 2　　d. 4

11. In the chemiosmotic mechanism,
    a. ATP production is linked to the proton gradient established by the electron transport chain.
    b. the difference in pH between the intermembrane space and the cytosol drives the formation of ATP.
    c. the flow of H^+ through ATP synthases from the matrix to the intermembrane space drives the phosphorylation of ADP.
    d. the energy released by the reduction and subsequent oxidation of components of the electron transport chain is transferred as a phosphate to ADP.
    e. the production of water in the matrix by the reduction of oxygen leads to a net flow of water out of a mitochondrion.

12. Which of the following reactions is *incorrectly* paired with its location?
    a. ATP synthesis—inner membrane of the mitochondrion (produced in matrix) and cytosol
    b. fermentation—cell cytosol
    c. glycolysis—cell cytosol
    d. substrate-level phosphorylation—cytosol and matrix
    e. citric acid cycle—cristae of mitochondrion

13. When glucose is oxidized to CO_2 and water, approximately 40% of its energy is transferred to
    a. heat.
    b. ATP.
    c. acetyl CoA.
    d. water.
    e. the citric acid cycle.

14. From an energetic viewpoint, what do muscle cells in oxygen deprivation gain from the reduction of pyruvate?
    a. ATP and lactate
    b. ATP and recycled NAD^+
    c. CO_2 and lactate
    d. ATP, alcohol, and NAD^+
    e. ATP, lactate, and CO_2

15. Glucose, made from six radioactively labeled carbon atoms, is fed to yeast cells in the absence of oxygen. How many molecules of radioactive alcohol (C_2H_5OH) are formed from each molecule of glucose?

a. 0 **c.** 2 **e.** 6
b. 1 **d.** 3

16. Which of the following produces the most ATP per gram?

a. glucose, because it is the starting place for glycolysis
b. glycogen or starch, because they are polymers of glucose
c. fats, because they are highly reduced compounds
d. proteins, because of the energy stored in their tertiary structure
e. amino acids, because they can be fed directly into the citric acid cycle

17. Fats and proteins can be used as fuel in the cell because they

a. can be converted to glucose by enzymes.
b. can be converted to intermediates of glycolysis or the citric acid cycle.
c. can pass through the mitochondrial membrane to enter the citric acid cycle.
d. contain unstable phosphate bonds.
e. contain more energy than glucose.

18. Which is *not* true of the enzyme phosphofructokinase? It is

a. an allosteric enzyme.
b. inhibited by citrate.
c. the pacemaker of glycolysis and respiration.
d. inhibited by ADP.
e. an early enzyme in the glycolytic pathway.

19. Substrate-level phosphorylation accounts for approximately what percentage of ATP formation when glucose is oxidized to CO_2 and water?

a. 0% **c.** 10% **e.** 20%
b. 4% **d.** 15%

20. Cyanide is a poison that blocks the passage of electrons along the electron transport chain. Which of the following is a metabolic effect of this poison?

a. The pH of the intermembrane space is much lower than normal.
b. Electrons are passed directly to oxygen, causing cells to explode.
c. Alcohol would build up in the cells.
d. NADH supplies would be exhausted, and ATP synthesis would cease.
e. No proton gradient would be produced, and ATP synthesis would cease.

21. Which enzyme would use NAD^+ as a coenzyme?

a. phosphofructokinase
b. phosphoglucoisomerase
c. triose phosphate dehydrogenase
d. hexokinase
e. phosphoglyceromutase

22. List the order of the following compounds as you first encounter them during the process of cellular respiration.

1. glyceraldehyde-3-phosphate
2. pyruvate
3. glucose
4. acetyl CoA
5. fructose bisphosphate
6. CO_2

a. 5, 3, 1, 2, 6, 4
b. 3, 5, 1, 2, 6, 4
c. 3, 5, 2, 1, 4, 6
d. 6, 4, 1, 2, 3, 5
e. 5, 3, 2, 1, 6, 4

23. Which compound has the highest free energy (will produce the most ATP when oxidized)?

a. acetyl CoA
b. glucose
c. pyruvate
d. fructose bisphosphate
e. glyceraldehydes-3-phosphate

24. Why is glycolysis considered one of the first metabolic pathways to have evolved?

a. It relies on fermentation, which is characteristic of the archaea and bacteria.
b. It is found only in prokaryotes, whereas eukaryotes use their mitochondria to produce ATP.
c. It produces much less ATP than does the electron transport chain and chemiosmosis.
d. It relies totally on enzymes that are produced by free ribosomes, and bacteria have only free ribosomes and no bound ribosomes.
e. It is nearly universal, is located in the cytosol, and does not involve O_2.

25. The metabolic function of fermentation is to

a. oxidize NADH to NAD^+ so that glycolysis can continue in the absence of oxygen.
b. reduce NADH so that more ATP can be produced by the electron transport chain.
c. produce lactate during aerobic exercise.
d. oxidize pyruvate in order to release more energy.
e. make beer.

26. Which of the following conversions represents a reduction reaction?

a. pyruvate $\rightarrow$ acetyl CoA + CO_2
b. $C_6H_{12}O_6 \rightarrow 6\ CO_2$
c. NADH + $H^+ \rightarrow NAD^+ + 2\ H$
d. glucose $\rightarrow$ pyruvate
e. acetaldehyde (C_2H_4O) $\rightarrow$ ethanol (C_2H_6O)

27. The oxidation of a molecule of $FADH_2$ yields less ATP than a molecule of NADH yields because $FADH_2$

a. carries fewer electrons.
b. is formed in the cytosol and energy is lost when it shuttles its electrons across the mitochondrial membrane.
c. passes its electrons to a transport molecule later in the chain and at a lower energy level.
d. is the last molecule produced by the citric acid cycle, and little energy is left to be captured.
e. has a much lower energy conformation than does NADH.

28. What is the role of oxygen in cellular respiration?

a. It is reduced in glycolysis as glucose is oxidized.
b. It provides electrons to the electron transport chain.
c. It provides the activation energy needed for oxidation to occur.
d. It is the final electron acceptor for the electron transport chain.
e. It combines with the carbon removed during the citric acid cycle to form CO_2.