Abbreviated Solutions to Problems

Fuller solutions to all chapter problems are published in the *Absolute Ultimate Study Guide to Accompany Principles of Biochemistry*. For all numerical problems, answers are expressed with the correct number of significant figures.

Chapter 1

1. **(a)** Diameter of magnified cell = 500 mm **(b)** 2.7×10^{12} actin molecules **(c)** 36,000 mitochondria **(d)** 3.9×10^{10} glucose molecules **(e)** 50 glucose molecules per hexokinase molecule

2. **(a)** 1×10^{-12} g = 1 pg **(b)** 10% **(c)** 5%

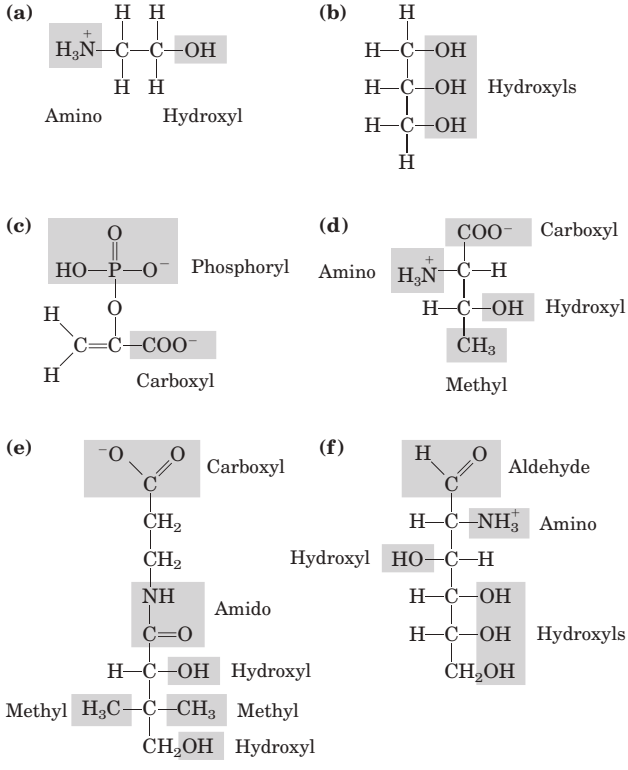
3. **(a)** 1.6 mm; 800 times longer than the cell; DNA must be tightly coiled. **(b)** 4,000 proteins

4. **(a)** Metabolic rate is limited by diffusion, which is limited by surface area. **(b)** 12 μm^{-1} for the bacterium; 0.04 μm^{-1} for the amoeba; surface-to-volume ratio 300 times higher in the bacterium.

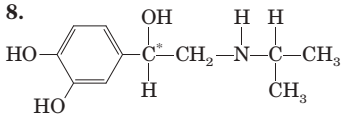
5. 2×10^6 s (about 23 days)

6. The vitamin molecules from the two sources are identical; the body cannot distinguish the source; only associated impurities might vary with the source.

7.



8.



The two enantiomers have different interactions with a chiral biological "receptor" (a protein).

9. **(a)** Only the amino acids have amino groups; separation could be based on the charge or binding affinity of these groups. Fatty acids are less soluble in water than amino acids, and the two types of molecules also differ in size and shape—either of these property differences could be the basis for separation. **(b)** Glucose is a smaller molecule than a nucleotide; separation could be based on size. The nitrogenous base and/or the phosphate group also endows nucleotides with characteristics (solubility, charge) that could be used for separation from glucose.

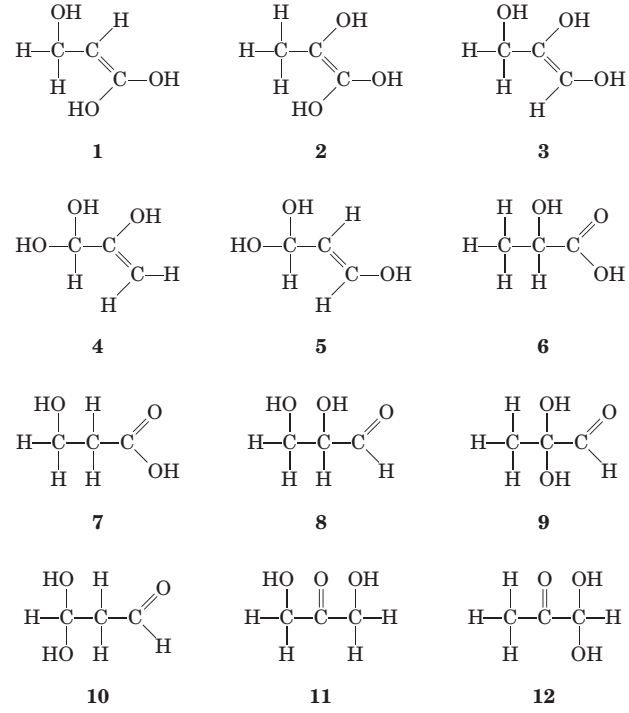
10. It is improbable that silicon could serve as the central organizing element for life, especially in an O_2-containing atmosphere such as that of Earth. Long chains of silicon atoms are not readily synthesized; the polymeric macromolecules necessary for more complex functions would not readily form. Oxygen disrupts bonds between silicon atoms, and silicon–oxygen bonds are extremely stable and difficult to break, preventing the breaking and making of bonds that is essential to life processes.

11. Only one enantiomer of the drug was physiologically active. Dexedrine consisted of the single enantiomer; Benzedrine consisted of a racemic mixture.

12. **(a)** 3 Phosphoric acid groups; α-D-ribose; guanine **(b)** Choline; phosphoric acid; glycerol; oleic acid; palmitic acid **(c)** Tyrosine; 2 glycines; phenylalanine; methionine

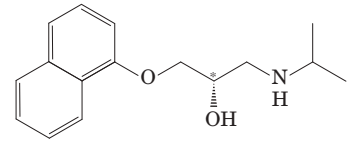
13. **(a)** CH_2O; $C_3H_6O_3$

(b)

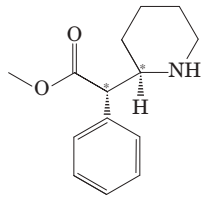


(c) X contains a chiral center; eliminates all but **6** and **8.** **(d)** X contains an acidic functional group; eliminates **8**; structure **6** is consistent with all data. **(e)** Structure **6**; we cannot distinguish between the two possible enantiomers.

14. The compound shown is (*R*)-propranolol; the carbon bearing the hydroxyl group is the chiral carbon. (*S*)-Propranolol has the structure:



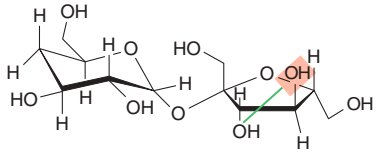
15. The compound shown is (*S*,*S*)-methylphenidate. (*R*,*R*)-methylphenidate has the structure:



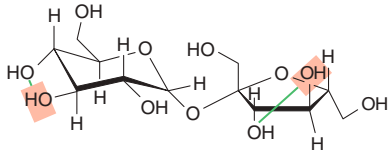
The chiral carbons are indicated with asterisks.

16. **(a)** A more negative $\Delta G°$ corresponds to a larger K_{eq} for the binding reaction, so the equilibrium is shifted more toward products and tighter binding—and thus greater sweetness and higher MRS. **(b)** Animal-based sweetness assays are time-consuming. A computer program to predict sweetness, even if not always completely accurate, would allow chemists to design effective sweeteners much faster. Candidate molecules could then be tested in the conventional assay. **(c)** The range 0.25 to 0.4 nm corresponds to about 1.5 to 2.5 single-bond lengths. The figure below can be used to construct an approximate ruler; any atoms in the light red rectangle are between 0.25 and 0.4 nm from the origin of the ruler.

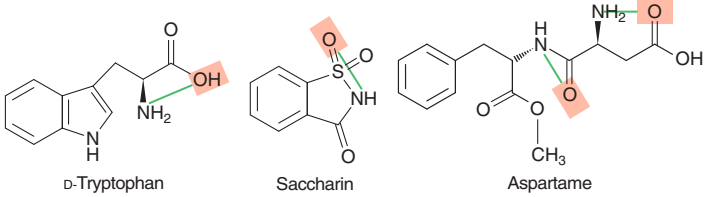
There are many possible AH-B groups in the molecules; a few are shown here.



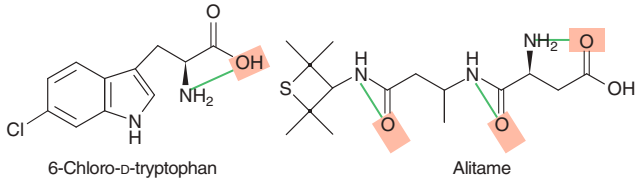
Deoxysucrose



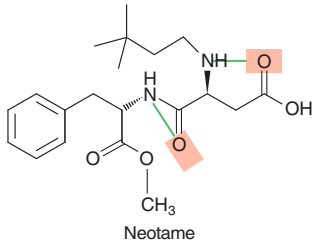
Sucrose



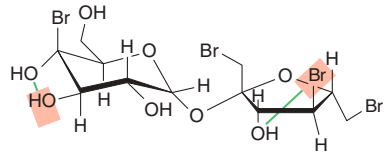
D-Tryptophan Saccharin Aspartame



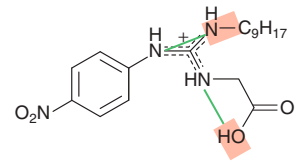
6-Chloro-D-tryptophan Alitame



Neotame



Tetrabromosucrose



Sucronic acid

(d) First, each molecule has multiple AH-B groups, so it is difficult to know which is the important one. Second, because the AH-B motif is very simple, many nonsweet molecules will have this group. **(e)** Sucrose and deoxysucrose. Deoxysucrose lacks one of the AH-B groups present in sucrose and has a slightly lower MRS than sucrose—as is expected if the AH-B groups are important for sweetness. **(f)** There are many such examples; here are a few: (1) D-Tryptophan and 6-chloro-D-tryptophan have the same AH-B group but very different MRS values. (2) Aspartame and neotame have the same AH-B groups but very different MRS values. (3) Neotame has two AH-B groups and alitame has three, yet neotame is more than five times sweeter than alitame. (4) Bromine is less electronegative than oxygen and thus is expected to weaken an AH-B group, yet tetrabromosucrose is much sweeter than sucrose. **(g)** Given enough "tweaking" of parameters, any model can be made to fit a defined dataset. Because the objective was to create a model to predict $\Delta G°$ for molecules not tested in vivo, the researchers needed to show that the model worked well for molecules it had not been trained on. The degree of inaccuracy with the test set could give researchers an idea of how the model would behave for novel molecules. **(h)** MRS is related to K_{eq}, which is related exponentially to $\Delta G°$, so adding a constant amount to $\Delta G°$ multiplies the MRS by a constant amount. Based on the values given with the structures, a change in $\Delta G°$ of 1.3 kcal/mol corresponds to a 10-fold change in MRS.

Chapter 2

1. Ethanol is polar; ethane is not. The ethanol —OH group can hydrogen-bond with water.

2. **(a)** 4.76 **(b)** 9.19 **(c)** 4.0 **(d)** 4.82

3. **(a)** 1.51×10^{-4} M **(b)** 3.02×10^{-7} M **(c)** 7.76×10^{-12} M

4. 1.1

5. **(a)** $HCl \rightleftharpoons H^+ + Cl^-$ **(b)** 3.3 **(c)** $NaOH \rightleftharpoons Na^+ + OH^-$ **(d)** 9.8

6. 1.1

7. 1.7×10^{-9} mol of acetylcholine

8. 0.1 M HCl

9. **(a)** greater **(b)** higher **(c)** lower

10. 3.3 mL

11. **(a)** $RCOO^-$ **(b)** RNH_2 **(c)** $H_2PO_4^-$ **(d)** HCO_3^-

12. **(a)** 5.06 **(b)** 4.28 **(c)** 5.46 **(d)** 4.76 **(e)** 3.76

13. **(a)** 0.1 M HCl **(b)** 0.1 M NaOH **(c)** 0.1 M NaOH

14. **(d)** Bicarbonate, a weak base, titrates —OH to $—O^-$, making the compound more polar and more water-soluble.

15. Stomach; the neutral form of aspirin present at the lower pH is less polar and passes through the membrane more easily.

16. 9

17. 7.4

18. **(a)** pH 8.6 to 10.6 **(b)** 4/5 **(c)** 10 mL **(d)** $pH = pK_a - 2$

19. 8.9

20. 2.4

21. 6.9

22. 1.4

23. $NaH_2PO_4 \cdot H_2O$, 5.8 g/L; Na_2HPO_4, 8.2 g/L

24. $[A^-]/[HA] = 0.10$

25. Mix 150 mL of 0.10 M sodium acetate and 850 mL of 0.10 M acetic acid.

26. Acetic acid; its pK_a is closest to the desired pH.

27. **(a)** 4.6 **(b)** 0.1 pH unit **(c)** 4 pH units

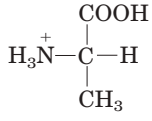
28. 4.3

29. 0.13 M acetate and 0.07 M acetic acid

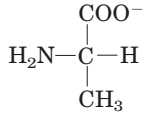
30. 1.7

31. 7

32. **(a)**



Fully protonated



Fully deprotonated

(b) fully protonated **(c)** zwitterion **(d)** zwitterion **(e)** fully deprotonated

33. **(a)** Blood pH is controlled by the carbon dioxide–bicarbonate buffer system, $CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-$. During *hypoventilation*, [CO_2] increases in the lungs and arterial blood, driving the equilibrium to the right, raising [H^+] and lowering pH. **(b)** During *hyperventilation*, [CO_2] decreases in the lungs and arterial blood, reducing [H^+] and increasing pH above the normal 7.4 value. **(c)** Lactate is a moderately strong acid, completely dissociating under physiological conditions and thus lowering the pH of blood and muscle tissue. Hyperventilation removes H^+, raising the pH of blood and tissues in anticipation of the acid buildup.

34. 7.4

35. Dissolving more CO_2 in the blood increases [H^+] in blood and extracellular fluids, lowering pH: $CO_2(d) + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$

36. **(a)** Use the substance in its surfactant form to emulsify the spilled oil, collect the emulsified oil, then switch to the nonsurfactant form. The oil and water will separate and the oil can be collected for further use. **(b)** The equilibrium lies strongly to the right. The stronger acid (lower pK_a), H_2CO_3, donates a proton to the conjugate base of the weaker acid (higher pK_a), amidine. **(c)** The strength of a surfactant depends on the hydrophilicity of its head groups: the more hydrophilic, the more powerful the surfactant. The amidinium form of s-surf is much more hydrophilic than the amidine form, so it is a more powerful surfactant. **(d)** *Point A:* amidinium; the CO_2 has had plenty of time to react with the amidine to produce the amidinium form. *Point B:* amidine; Ar has removed CO_2 from the solution, leaving the amidine form. **(e)** The conductivity rises as uncharged amidine reacts with CO_2 to produce the charged amidinium form. **(f)** The conductivity falls as Ar removes CO_2, shifting the equilibrium to the uncharged amidine form. **(g)** Treat s-surf with CO_2 to produce the surfactant amidinium form and use this to emulsify the spill. Treat the emulsion with Ar to remove the CO_2 and produce the nonsurfactant amidine form. The oil will separate from the water and can be recovered.

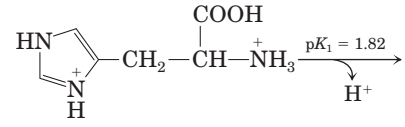
Chapter 3

1. L; determine the absolute configuration at the α carbon and compare it with D- and L-glyceraldehyde.

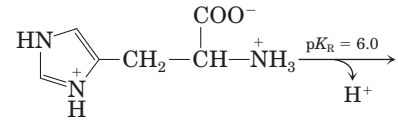
2. **(a)** I **(b)** II **(c)** IV **(d)** II **(e)** IV **(f)** II and IV **(g)** III **(h)** III **(i)** V **(j)** III **(k)** V **(l)** II **(m)** III **(n)** V **(o)** I, III, and V

3. **(a)** pI > pK_a of the α-carboxyl group and pI < pK_a of the α-amino group, so both groups are charged (ionized). **(b)** 1 in 2.19×10^7. The pI of alanine is 6.01. From Table 3–1 and the Henderson-Hasselbalch equation, 1/4,680 carboxyl groups and 1/4,680 amino groups are uncharged. The fraction of alanine molecules with both groups uncharged is the product of these fractions.

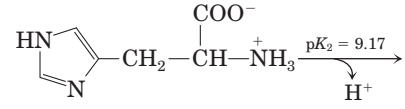
4. **(a)–(c)**



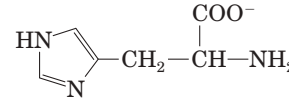
1



2



3

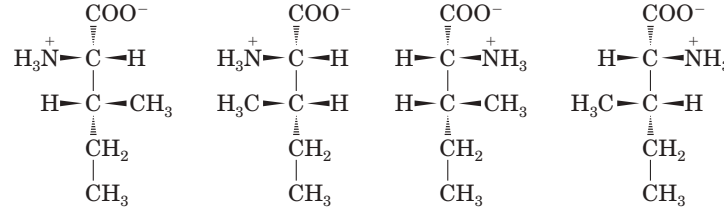


4

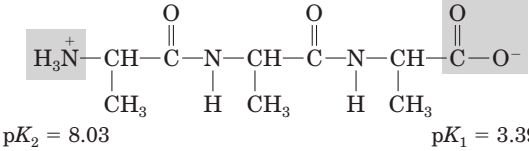
pH	Structure	Net charge	Migrates toward
1	**1**	+2	Cathode
4	**2**	+1	Cathode
8	**3**	0	Does not migrate
12	**4**	−1	Anode

5. **(a)** Asp **(b)** Met **(c)** Glu **(d)** Gly **(e)** Ser

6. **(a)** 2 **(b)** 4 **(c)**



7. **(a)** Structure at pH 7:



pK_2 = 8.03 pK_1 = 3.39

(b) Electrostatic interaction between the carboxylate anion and the protonated amino group of the alanine zwitterion favorably affects the ionization of the carboxyl group. This favorable electrostatic interaction decreases as the length of the poly(Ala) increases, resulting in an increase in pK_1. **(c)** Ionization of the protonated amino group destroys the favorable electrostatic interaction noted in (b). With increasing distance between the charged groups, removal of the proton from the amino group in poly(Ala) becomes easier and thus pK_2 is lower. The intramolecular effects of the amide (peptide bond) linkages keep pK_a values lower than they would be for an alkyl-substituted amine.

8. 75,000

9. **(a)** 32,000. The elements of water are lost when a peptide bond forms, so the molecular weight of a Trp residue is not the same as the molecular weight of free tryptophan. **(b)** 2

10. The protein has four subunits, with molecular masses of 160, 90, 90, and 60 kDa. The two 90 kDa subunits (possibly identical) are linked by one or more disulfide bonds.

11. **(a)** at pH 3, +2; at pH 8, 0; at pH 11, −1 **(b)** pI = 7.8

12. pI ≈ 1; carboxylate groups; Asp and Glu

13. Lys, His, Arg; negatively charged phosphate groups in DNA interact with positively charged side groups in histones.

14. **(a)** $(Glu)_{20}$ **(b)** $(Lys–Ala)_3$ **(c)** $(Asn–Ser–His)_5$ **(d)** $(Asn–Ser–His)_5$

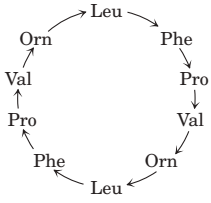
15. **(a)** Specific activity after step 1 is 200 units/mg; step 2, 600 units/mg; step 3, 250 units/mg; step 4, 4,000 units/mg; step 5, 15,000 units/mg; step 6, 15,000 units/mg **(b)** Step 4 **(c)** Step 3 **(d)** Yes. Specific activity did not increase in step 6; SDS polyacrylamide gel electrophoresis

16. **(a)** [NaCl] = 0.5 mM **(b)** [NaCl] = 0.05 mM.

17. C elutes first, B second, A last.

18. Tyr–Gly–Gly–Phe–Leu

19.



The arrows correspond to the orientation of the peptide bonds, —CO → NH—.

20. 88%, 97%. The percentage (x) of correct amino acid residues released in cycle n is x_n/x. All residues released in the first cycle are correct, even though the efficiency of cleavage is not perfect.

21. **(a)** Y (1), F (7), and R (9) **(b)** Positions 4 and 9; K (Lys) is more common at 4, R (Arg) is invariant at 9 **(c)** Positions 5 and 10; E (Glu) is more common at both positions **(d)** Position 2; S (Ser)

22. **(a)** peptide 2 **(b)** peptide 1 **(c)** peptide 2 **(d)** peptide 3

23. **(a)** Any linear polypeptide chain has only two kinds of free amino groups: a single α-amino group at the amino terminus, and an ε-amino group on each Lys residue present. These amino groups react with FDNB to form a DNP–amino acid derivative. Insulin gave two different α-amino-DNP derivatives, suggesting that it has two amino termini and thus two polypeptide chains—one with an amino-terminal Gly and the other with an amino-terminal Phe. Because the DNP-lysine product is ε-DNP-lysine, the Lys is not at an amino terminus. **(b)** Yes. The A chain has amino-terminal Gly; the B chain has amino-terminal Phe; and (nonterminal) residue 29 in the B chain is Lys. **(c)** Phe–Val–Asp–Glu–. Peptide B1 shows that the amino-terminal residue is Phe. Peptide B2 also includes Val, but since no DNP-Val is formed, Val is not at the amino terminus; it must be on the carboxyl side of Phe. Thus the sequence of B2 is DNP-Phe–Val. Similarly, the sequence of B3 must be DNP-Phe–Val–Asp, and the sequence of the A chain must begin Phe–Val–Asp–Glu–. **(d)** No. The known amino-terminal sequence of the A chain is Phe–Val–Asn–Gln–. The Asn and Gln appear in Sanger's analysis as Asp and Glu because the vigorous hydrolysis in step 7 hydrolyzed the amide bonds in Asn and Gln (as well as the peptide bonds), forming Asp and Glu. Sanger et al. could not distinguish Asp from Asn or Glu from Gln at this stage in their analysis. **(e)** The sequence exactly matches that in Fig. 3–24. Each peptide in the table gives specific information about which Asx residues are Asn or Asp and which Glx residues are Glu or Gln.

Ac1: residues 20–21. This is the only Cys–Asx sequence in the A chain; there is ~1 amido group in this peptide, so it must be Cys–Asn:

N–Gly–Ile–Val–Glx–Glx–Cys–Cys–Ala–Ser–Val–
1 5 10

Cys–Ser–Leu–Tyr–Glx–Leu–Glx–Asx–Tyr–Cys–**Asn**–*C*
15 20

Ap15: residues 14–15–16. This is the only Tyr–Glx–Leu in the A chain; there is ~1 amido group, so the peptide must be Tyr–Gln–Leu:

N–Gly–Ile–Val–Glx–Glx–Cys–Cys–Ala–Ser–Val–
1 5 10

Cys–Ser–Leu–Tyr–**Gln**–Leu–Glx–Asx–Tyr–Cys–Asn–*C*
15 20

Ap14: residues 14–15–16–17. It has ~1 amido group, and we already know that residue 15 is Gln, so residue 17 must be Glu:

N–Gly–Ile–Val–Glx–Glx–Cys–Cys–Ala–Ser–Val–
1 5 10

Cys–Ser–Leu–Tyr–Gln–Leu–**Glu**–Asx–Tyr–Cys–Asn–*C*
15 20

Ap3: residues 18–19–20–21. It has ~2 amido groups, and we know that residue 21 is Asn, so residue 18 must be Asn:

N–Gly–Ile–Val–Glx–Glx–Cys–Cys–Ala–Ser–Val–
1 5 10

Cys–Ser–Leu–Tyr–Gln–Leu–Glu–**Asn**–Tyr–Cys–Asn–*C*
15 20

Ap1: residues 17–18–19–20–21, which is consistent with residues 18 and 21 being Asn.

Ap5pa1: residues 1–2–3–4. It has ~0 amido group, so residue 4 must be Glu:

N–Gly–Ile–Val–**Glu**–Glx–Cys–Cys–Ala–Ser–Val–
1 5 10

Cys–Ser–Leu–Tyr–Gln–Leu–Glu–Asn–Tyr–Cys–Asn–*C*
15 20

Ap5: residues 1 through 13. It has ~1 amido group, and we know that residue 4 is Glu, so residue 5 must be Gln:

N–Gly–Ile–Val–Glu–**Gln**–Cys–Cys–Ala–Ser–Val–
1 5 10

Cys–Ser–Leu–Tyr–Gln–Leu–Glu–Asn–Tyr–Cys–Asn–*C*
15 20

Chapter 4

1. **(a)** Shorter bonds have a higher bond order (are multiple rather than single) and are stronger. The peptide C—N bond is stronger than a single bond and is midway between a single and a double bond in character. **(b)** Rotation about the peptide bond is difficult at physiological temperatures because of its partial double-bond character.

2. **(a)** The principal structural units in the wool fiber polypeptide (α-keratin) are successive turns of the α helix, at 5.4 Å intervals; coiled coils produce the 5.2 Å spacing. Steaming and stretching the fiber yields an extended polypeptide chain with the β conformation, with a distance between adjacent R groups of about 7.0 Å. As the polypeptide reassumes an α-helical structure, the fiber shortens. **(b)** Processed wool shrinks when polypeptide chains are converted from an extended β conformation to the native α-helical conformation in the presence of moist heat. The structure of silk—β sheets, with their small, closely packed amino acid side chains—is more stable than that of wool.

3. ~42 peptide bonds per second

4. At pH > 6, the carboxyl groups of poly(Glu) are deprotonated; repulsion among negatively charged carboxylate groups leads to unfolding. Similarly, at pH 7, the amino groups of poly(Lys) are protonated; repulsion among these positively charged groups also leads to unfolding.

5. **(a)** Disulfide bonds are covalent bonds, which are much stronger than the noncovalent interactions that stabilize most proteins. They cross-link protein chains, increasing their stiffness, mechanical strength, and hardness. **(b)** Cystine residues (disulfide bonds) prevent the complete unfolding of the protein.

6. ϕ = (f) and ψ = (e).

7. **(a)** Bends are most likely at residues 7 and 19; Pro residues in the cis configuration accommodate turns well. **(b)** The Cys residues at positions 13 and 24 can form disulfide bonds. **(c)** External surface: polar and charged residues (Asp, Gln, Lys); interior: nonpolar and aliphatic residues (Ala, Ile); Thr, though polar, has a hydropathy index near zero and thus can be found either on the external surface or in the interior of the protein.

8. 30 amino acid residues; 0.87

9. Myoglobin is all three. The folded structure, the "globin fold," is a motif found in all globins. The polypeptide folds into a single domain, which for this protein represents the entire three-dimensional structure.

10. Protein (a), a β barrel, is described by Ramachandran plot (c), which shows most of the allowable conformations in the upper left quadrant where the bond angles characteristic of the β conformation are concentrated; (b), a series of α helices, is described by plot (d), where most of the allowable conformations are in the lower left quadrant.

11. The bacterial enzyme is a collagenase; it destroys the connective tissue barrier of the host, allowing the bacterium to invade the tissues. Bacteria do not contain collagen.

12. **(a)** The number of moles of DNP-valine formed per mole of protein equals the number of amino termini and thus the number of polypeptide chains. **(b)** 4 **(c)** Different chains would probably run as discrete bands on an SDS polyacrylamide gel.

13. (a); it has more amino acid residues that favor α-helical structure (see Table 4–1).

14. **(a)** Aromatic residues seem to play an important role in stabilizing amyloid fibrils. Thus, molecules with aromatic substituents may inhibit amyloid formation by interfering with the stacking or association of the aromatic side chains. **(b)** Amyloid is formed in the pancreas in association with type 2 diabetes, as it is in the brain in Alzheimer disease. Although the amyloid fibrils in the two diseases involve different proteins, the fundamental structure of the amyloid is similar and similarly stabilized in both, and so they are potential targets for similar drugs designed to disrupt this structure.

15. **(a)** NFκB transcription factor, also called RelA transforming factor. **(b)** No. You will obtain similar results, but with additional related proteins listed. **(c)** The protein has two subunits. There are multiple variants of the subunits, with the best characterized being 50, 52, or 65 kDa. These pair with each other to form a variety of homodimers and heterodimers. The structures of a number of different variants can be found in the PDB. **(d)** The NFκB transcription factor is a dimeric protein that binds specific DNA sequences, enhancing transcription of nearby genes. One such gene is the immunoglobulin κ light chain, from which the transcription factor gets its name.

16. **(a)** Aba is a suitable replacement because Aba and Cys have side chains of approximately the same size and are similarly hydrophobic. However, Aba cannot form disulfide bonds, so it will not be a suitable replacement if these are required. **(b)** There are many important differences between the synthesized protein and HIV protease produced by a human cell, any of which could result in an inactive synthetic enzyme: (1) Although Aba and Cys have similar size and hydrophobicity, Aba may not be similar enough for the protein to fold properly. (2) HIV protease may require disulfide bonds for proper functioning. (3) Many proteins synthesized by ribosomes fold as they are produced; the protein in this study folded only after the chain was complete. (4) Proteins synthesized by ribosomes may interact with the ribosomes as they fold; this is not possible for the protein in the study. (5) Cytosol is a more complex solution than the buffer used in the study; some proteins may require specific, unknown proteins for proper folding. (6) Proteins synthesized in cells often require chaperones for proper folding; these are not present in the study buffer. (7) In cells, HIV protease is synthesized as part of a larger chain that is then proteolytically processed; the protein in the study was synthesized as a single molecule. **(c)** Because the enzyme *is* functional with Aba substituted for Cys, disulfide bonds do not play an important role in the structure of HIV protease. **(d)** *Model 1:* It would fold like the L-protease. *Argument for:* The covalent structure is the same (except for chirality), so it should fold like the L-protease. *Argument against:* Chirality is not a trivial detail; three-dimensional shape is a key feature of biological molecules. The synthetic enzyme will not fold like the L-protease. *Model 2:* It would fold to the mirror image of the L-protease. *For:* Because the individual components are mirror images of those in the biological protein, it will fold in the mirror-image shape. *Against:* The interactions involved in protein folding are very complex, so the synthetic protein will most likely fold in another form. *Model 3:* It would fold to something else. *For:* The interactions involved in protein folding are very complex, so the synthetic protein will most likely fold in another form. *Against:* Because the individual components are mirror images of those in the biological protein, it will fold in the mirror-image shape. **(e)** *Model 1.* The enzyme is active, but with the enantiomeric form of the biological substrate, and it is inhibited by the enantiomeric form of the biological inhibitor. This is consistent with the D-protease being the mirror image of the L-protease. **(f)** Evans blue is achiral; it binds to both forms of the enzyme. **(g)** No. Because proteases contain only L-amino acids and recognize only L-peptides, chymotrypsin would not digest the D-protease. **(h)** Not necessarily. Depending on the individual enzyme, any of the problems listed in (b) could result in an inactive enzyme.

Chapter 5

1. Protein B has a higher affinity for ligand X; it will be half-saturated at a much lower concentration of X than will protein A. Protein A has $K_a = 10^6\ M^{-1}$; protein B has $K_a = 10^9\ M^{-1}$.

2. **(a), (b),** and **(c)** all have $n_H < 1.0$. Apparent negative cooperativity in ligand binding can be caused by the presence of two or more types of ligand-binding sites with different affinities for the ligand on the same or different proteins in the same solution. Apparent negative cooperativity is also commonly observed in heterogeneous protein preparations. There are few well-documented cases of true negative cooperativity.

3. **(a)** decreases **(b)** increases **(c)** decreases **(d)** increases

4. $k_d = 8.9 \times 10^{-5}\ s^{-1}$.

5. **(a)** 0.5 nM (shortcut: the K_d is equivalent to the ligand concentration where $\theta = 0.5$). **(b)** Protein 2 has the highest affinity, as it has the lowest K_d.

6. The cooperative behavior of hemoglobin arises from subunit interactions.

7. **(a)** The observation that hemoglobin A (HbA; maternal) is about 60% saturated when the pO_2 is 4 kPa, whereas hemoglobin F (HbF; fetal) is more than 90% saturated under the same physiological conditions, indicates that HbF has a higher O_2 affinity than HbA. **(b)** The higher O_2 affinity of HbF ensures that oxygen will flow from maternal blood to fetal blood in the placenta. Fetal blood approaches full saturation where the O_2 affinity of HbA is low. **(c)** The observation that the O_2-saturation curve of HbA undergoes a larger shift on BPG binding than that of HbF suggests that HbA binds BPG more tightly than does HbF. Differential binding of BPG to the two hemoglobins may determine the difference in their O_2 affinities.

8. **(a)** Hb Memphis **(b)** HbS, Hb Milwaukee, Hb Providence, possibly Hb Cowtown **(c)** Hb Providence

9. More tightly. An inability to form tetramers would limit the cooperativity of these variants, and the binding curve would become more hyperbolic. Also, the BPG-binding site would be

disrupted. Oxygen binding would probably be tighter, because the default state in the absence of bound BPG is the tight-binding R state.

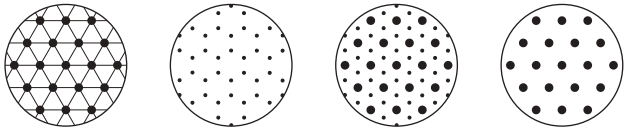
10. **(a)** 1×10^{-8} M **(b)** 5×10^{-8} M **(c)** 8×10^{-8} M **(d)** 2×10^{-7} M. Note that a rearrangement of Eqn 5–8 gives $[L] = \theta K_d/(1 - \theta)$.

11. The epitope is likely to be a structure that is buried when G-actin polymerizes to F-actin.

12. Many pathogens, including HIV, have mechanisms by which they can repeatedly alter the surface proteins to which immune system components initially bind. Thus the host organism regularly faces new antigens and requires time to mount an immune response to each one. As the immune system responds to one variant, new variants are created.

13. Binding of ATP to myosin triggers dissociation of myosin from the actin thin filament. In the absence of ATP, actin and myosin bind tightly to each other.

14.

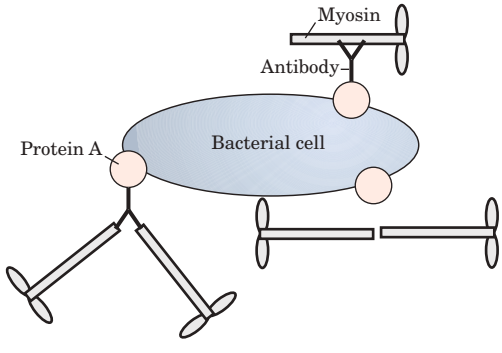


(a) **(b)** **(c)** **(d)**

15. **(a)** Chain L is the light chain and chain H is the heavy chain of the Fab fragment of this antibody molecule. Chain Y is lysozyme. **(b)** β structures are predominant in the variable and constant regions of the fragment. **(c)** Fab heavy-chain fragment, 218 amino acid residues; light-chain fragment, 214; lysozyme, 129. Less than 15% of the lysozyme molecule is in contact with the Fab fragment. **(d)** In the H chain, residues that seem to be in contact with lysozyme include Gly^{31}, Tyr^{32}, Arg^{99}, Asp^{100}, and Tyr^{101}. In the L chain the residues that seem to be in contact with lysozyme include Tyr^{32}, Tyr^{49}, Tyr^{50}, and Trp^{92}. In lysozyme, residues Asn^{19}, Gly^{22}, Tyr^{23}, Ser^{24}, Lys^{116}, Gly^{117}, Thr^{118}, Asp^{119}, Gln^{121}, and Arg^{125} seem to be situated at the antigen-antibody interface. Not all these residues are adjacent in the primary structure. Folding of the polypeptide chain into higher levels of structure brings the nonconsecutive residues together to form the antigen-binding site.

16. **(a)** The protein with a K_d of 5 μM will have the highest affinity for ligand L. When the K_d is 10 μM, doubling [L] from 0.2 to 0.4 μM (values well below the K_d) will nearly double θ (the actual increase factor is 1.96). This is a property of the hyperbolic curve; at low ligand concentrations, θ is an almost linear function of [L]. On the other hand, doubling [L] from 40 to 80 μM (well above the K_d, where the binding curve is approaching its asymptotic limit) will increase θ by a factor of only 1.1. The increase factors are identical for the curves generated from Eqn 5–11. **(b)** $\theta = 0.998$. **(c)** A variety of answers will be obtained, depending on the values entered for the different parameters.

17. **(a)**



The drawing is not to scale; any given cell would have many more myosin molecules on its surface. **(b)** ATP is needed to provide the chemical energy to drive the motion (see Chapter 13). **(c)** An antibody that bound to the myosin tail, the actin-binding site, would block actin binding and prevent movement. An antibody that bound to actin would also prevent actin-myosin interaction and thus movement. **(d)** There are two possible explanations: (1) Trypsin cleaves only at Lys and Arg residues (see Table 3–6) so would not cleave at many sites in the protein. (2) Not all Arg or Lys residues are equally accessible to trypsin; the most-exposed sites would be cleaved first. **(e)** The S1 model. The hinge model predicts that bead-antibody-HMM complexes (with the hinge) would move, but bead-antibody-SHMM complexes (no hinge) would not. The S1 model predicts that because both complexes include S1, both would move. The finding that the beads move with SHMM (no hinge) is consistent only with the S1 model. **(f)** With fewer myosin molecules bound, the beads could temporarily fall off the actin as a myosin let go of it. The beads would then move more slowly, as time is required for a second myosin to bind. At higher myosin density, as one myosin lets go, another quickly binds, leading to faster motion. **(g)** Above a certain density, what limits the rate of movement is the intrinsic speed with which myosin molecules move the beads. The myosin molecules are moving at a maximum rate and adding more will not increase speed. **(h)** Because the force is produced in the S1 head, damaging the S1 head would probably inactivate the resulting molecule, and SHMM would be incapable of producing movement. **(i)** The S1 head must be held together by noncovalent interactions that are strong enough to retain the active shape of the molecule.

Chapter 6

1. The activity of the enzyme that converts sugar to starch is destroyed by heat denaturation.

2. 2.4×10^{-6} M

3. 9.5×10^{8} years

4. The enzyme-substrate complex is more stable than the enzyme alone.

5. **(a)** 190 Å **(b)** Three-dimensional folding of the enzyme brings the amino acid residues into proximity.

6. The reaction rate can be measured by following the decrease in absorption by NADH (at 340 nm) as the reaction proceeds. Determine the K_m value; using substrate concentrations well above the K_m, measure initial rate (rate of NADH disappearance with time, measured spectrophotometrically) at several known enzyme concentrations, and make a plot of initial rate versus concentration of enzyme. The plot should be linear, with a slope that provides a measure of LDH concentration.

7. (b), (e), (g)

8. **(a)** 1.7×10^{-3} M **(b)** 0.33; 0.67; 0.91 **(c)** The upper curve corresponds to enzyme B ($[X] > K_m$ for this enzyme); the lower curve, enzyme A.

9. **(a)** 400 s^{-1} **(b)** 10 μM **(c)** $\alpha = 2$, $\alpha' = 3$ **(d)** Mixed inhibitor

10. **(a)** 24 nM **(b)** 4 μM (V_0 is exactly half V_{max}, so $[A] = K_m$) **(c)** 40 μM (V_0 is exactly half V_{max}, so $[A] = 10$ times K_m in the presence of inhibitor) **(d)** No. $k_{cat}/K_m = (0.33\ s^{-1})/(4 \times 10^{-6}\ M) = 8.25 \times 10^{4}\ M^{-1}\ s^{-1}$, well below the diffusion-controlled limit.

11. $V_{max} \approx 140$ μM/min; $K_m \approx 1 \times 10^{-5}$ M

12. **(a)** $V_{max} = 51.5$ mM/min; $K_m = 0.59$ mM **(b)** Competitive inhibition

13. $K_m = 2.2$ mM; $V_{max} = 0.50$ μmol/min

14. Curve A

15. $k_{cat} = 2.0 \times 10^{7}\ min^{-1}$

16. The basic assumptions of the Michaelis-Menten equation still hold. The reaction is at steady state, and the rate is determined by $V_0 = k_2$ [ES]. The equations needed to solve for [ES] are

$$[E_t] = [E] + [ES] + [EI] \quad \text{and} \quad [EI] = \frac{[E][I]}{K_I}$$

[E] can be obtained by rearranging Eqn 6–19. The rest follows the pattern of the Michaelis-Menten equation derivation in the text.

17. Minimum $M_r = 29{,}000$

18. Activity of the prostate enzyme equals total phosphatase activity in a blood sample minus phosphatase activity in the presence of enough tartrate to completely inhibit the prostate enzyme.

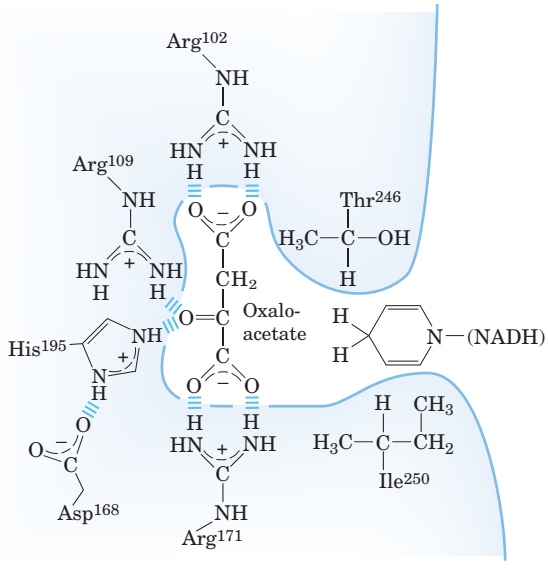
19. The inhibition is mixed. Because K_m seems not to change appreciably, this could be the special case of mixed inhibition called noncompetitive.

20. The [S] at which $V_0 = V_{max}/2\alpha'$ is obtained when all terms except V_{max} on the right side of Eqn 6–30—that is, $[S]/(\alpha K_m + \alpha'[S])$—equal $\frac{1}{2}\alpha'$. Begin with $[S]/(\alpha K_m + \alpha'[S]) = \frac{1}{2}\alpha'$ and solve for [S].

21. The optimum activity occurs when Glu^{35} is protonated and Asp^{52} is unprotonated.

22. **(a)** Increase factor = 1.96; $V_0 = 50\ \mu M\ s^{-1}$; increase factor = 1.048. **(b)** When $\alpha = 2.0$, the curve is shifted to the right as the K_m is increased by a factor of 2. When $\alpha' = 3.0$, the asymptote of the curve (the V_{max}) declines by a factor of 3. When $\alpha = 2.0$ and $\alpha' = 3.0$, the curve briefly rises above the curve where both α and $\alpha' = 1.0$, due to a decline in K_m. However, the asymptote is lower, because V_{max} declines by a factor of 3. **(c)** When $\alpha = 2.0$, the x intercept moves to the right. When $\alpha = 2.0$ and $\alpha' = 3.0$, the x intercept moves to the left.

23. **(a)** In the wild-type enzyme, the substrate is held in place by a hydrogen bond and an ion-dipole interaction between the charged side chain of Arg^{109} and the polar carbonyl of pyruvate. During catalysis, the charged Arg^{109} side chain also stabilizes the polarized carbonyl transition state. In the mutant, the binding is reduced to just a hydrogen bond, substrate binding is weaker, and ionic stabilization of the transition state is lost, reducing catalytic activity. **(b)** Because Lys and Arg are roughly the same size and have a similar positive charge, they probably have very similar properties. Furthermore, because pyruvate binds to Arg^{171} by (presumably) an ionic interaction, an Arg to Lys mutation would probably have little effect on substrate binding. **(c)** The "forked" arrangement aligns two positively charged groups of Arg residues with the negatively charged oxygens of pyruvate and facilitates two combined hydrogen-bond and ion-dipole interactions. When Lys is present, only one such combined hydrogen-bond and ion-dipole interaction is possible, thus reducing the strength of the interaction. The positioning of the substrate is less precise. **(d)** Ile^{250} interacts hydrophobically with the ring of NADH. This type of interaction is not possible with the hydrophilic side chain of Gln. **(e)** The structure is shown below. **(f)** The mutant enzyme rejects pyruvate because pyruvate's hydrophobic methyl group will not interact with the highly hydrophilic guanidinium group of Arg^{102}. The mutant binds oxaloacetate because of the strong ionic interaction between the Arg^{102} side chain and the carboxyl of oxaloacetate. **(g)** The protein must be flexible enough to accommodate the added bulk of the side chain and the larger substrate.



Chapter 7

1. With reduction of the carbonyl oxygen to a hydroxyl group, the chemistry at C-1 and C-3 is the same; the glycerol molecule is not chiral.

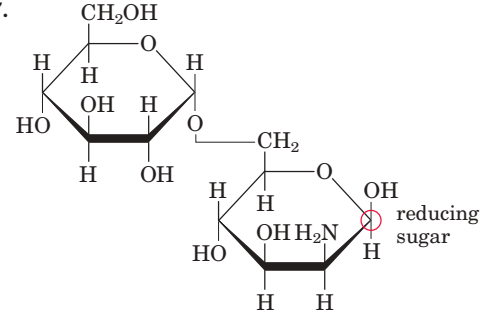
2. Epimers differ by the configuration about only *one* carbon.
(a) D-altrose (C-2), D-glucose (C-3), D-gulose (C-4)
(b) D-idose (C-2), D-galactose (C-3), D-allose (C-4)
(c) D-arabinose (C-2), D-xylose (C-3)

3. Osazone formation destroys the configuration around C-2 of aldoses, so aldoses differing only at the C-2 configuration give the same derivative, with the same melting point.

4. To convert α-D-glucose to β-D-glucose, the bond between C-1 and the hydroxyl on C-5 (as in Fig. 7–6). To convert D-glucose to D-mannose, either the —H or the —OH on C-2. Conversion between chair conformations does not require bond breakage; this is the critical distinction between configuration and conformation.

5. No; glucose and galactose differ at C-4.

6. **(a)** Both are polymers of D-glucose, but they differ in the glycosidic linkage: (β1→4) for cellulose, (α1→4) for glycogen. **(b)** Both are hexoses, but glucose is an aldohexose, fructose a ketohexose. **(c)** Both are disaccharides, but maltose has two (α1→4)-linked D-glucose units; sucrose has (α1↔2β)-linked D-glucose and D-fructose.

7.


8. A hemiacetal is formed when an aldose or ketose condenses with an alcohol; a glycoside is formed when a hemiacetal condenses with an alcohol (see Fig. 7–5).

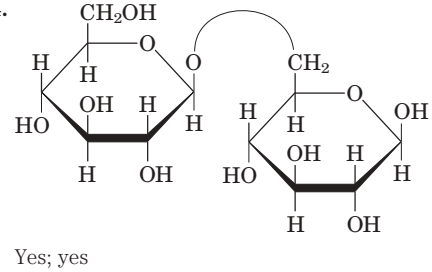
9. Fructose cyclizes to either the pyranose or the furanose structure. Increasing the temperature shifts the equilibrium in the direction of the furanose, the less sweet form.

10. The rate of mutarotation is sufficiently high that, as the enzyme consumes β-D-glucose, more α-D-glucose is converted to the β form and, eventually, all the glucose is oxidized. Glucose oxidase is specific for glucose and does not detect other reducing sugars (such as galactose) that react with Fehling's reagent.

11. **(a)** Measure the change in optical rotation with time. **(b)** The optical rotation of the mixture is negative (inverted) relative to that of the sucrose solution. **(c)** −2.0°

12. Prepare a slurry of sucrose and water for the core; add a small amount of sucrase (invertase); immediately coat with chocolate.

13. Sucrose has no free anomeric carbon to undergo mutarotation.

14.


Yes; yes

15. *N*-Acetyl-β-D-glucosamine is a reducing sugar; its C-1 can be oxidized (see p. 252). D-Gluconate is not a reducing sugar; its C-1 is already at the oxidation state of a carboxylic acid. GlcN(α1↔1α)Glc is not a reducing sugar; the anomeric carbons of both monosaccharides are involved in the glycosidic bond.

16. Humans lack cellulase in the gut and cannot break down cellulose.

17. Native cellulose consists of glucose units linked by (β1→4) glycosidic bonds, which force the polymer chain into an extended conformation. Parallel series of these extended chains form intermolecular hydrogen bonds, aggregating into long, tough, insoluble fibers. Glycogen consists of glucose units linked by (α1→4) glycosidic bonds, which cause bends in the chain and prevent formation of long fibers. In addition, glycogen is highly branched and, because many of its hydroxyl groups are exposed to water, is highly hydrated and disperses in water.

Cellulose is a structural material in plants, consistent with its side-by-side aggregation into insoluble fibers. Glycogen is a storage fuel in animals. Highly hydrated glycogen granules with their many nonreducing ends are rapidly hydrolyzed by glycogen phosphorylase to release glucose 1-phosphate.

18. Cellulose is several times longer; it assumes an extended conformation, whereas amylose has a helical structure.

19. 6,000 residues/s

20. 11 s

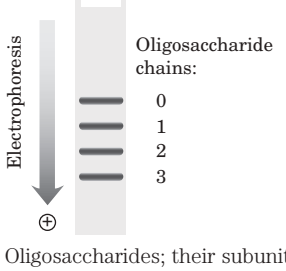
21. The ball-and-stick model of the disaccharide in Fig. 7–18b shows no steric interactions, but a space-filling model, showing atoms with their real relative sizes, would show several strong steric hindrances in the −170°, −170° conformer that are not present in the 30°, −40° conformer.

22. The negative charges on chondroitin sulfate repel each other and force the molecule into an extended conformation. The polar molecule attracts many water molecules, increasing the molecular volume. In the dehydrated solid, each negative charge is counterbalanced by a positive ion, and the molecule condenses.

23. Positively charged amino acid residues would bind the highly negatively charged groups on heparin. In fact, Lys residues of antithrombin III interact with heparin.

24. 8 possible sequences, 144 possible linkages, and 64 stereochemical possibilities, for a total of 73,728 permutations!

25.



26. Oligosaccharides; their subunits can be combined in more ways than the amino acid subunits of oligopeptides. Each hydroxyl group can participate in glycosidic bonds, and the configuration of each glycosidic bond can be either α or β. The polymer can be linear or branched.

27. **(a)** Branch-point residues yield 2,3-di-*O*-methylglucose; the unbranched residues yield 2,3,6-tri-*O*-methylglucose. **(b)** 3.75%

28. Chains of (1→6)-linked D-glucose residues with occasional (1→3)-linked branches, with about one branch every 20 residues

29. **(a)** The tests involve trying to dissolve only part of the sample in a variety of solvents, then analyzing both dissolved and undissolved materials to see whether their compositions differ. **(b)** For a pure substance, all molecules are the same and any dissolved fraction will have the same composition as any undissolved fraction. An impure substance is a mixture of more than one compound. When treated with a particular solvent, more of one component may dissolve, leaving more of the other component(s) behind. As a result, the dissolved and undissolved fractions have different compositions. **(c)** A quantitative assay allows researchers to be sure that none of the activity has been lost through degradation. When determining the structure of a molecule, it is important that the sample under analysis consist only of intact (undegraded) molecules. If the sample is contaminated with degraded material, this will give confusing and perhaps uninterpretable structural results. A qualitative assay would detect the presence of activity, even if it had become significantly degraded. **(d)** Results 1 and 2. Result 1 is consistent with the known structure, because type B antigen has three molecules of galactose; types A and O each have only two. Result 2 is also consistent, because type A has two amino sugars (*N*-acetylgalactosamine and *N*-acetylglucosamine); types B and O have only one (*N*-acetylglucosamine). Result 3 is *not* consistent with the known structure: for type A, the glucosamine: galactosamine ratio is 1:1; for type B, it is 1:0. **(e)** The samples were probably impure and/or partly degraded. The first two results were correct possibly because the method was only roughly quantitative and thus not as sensitive to inaccuracies in measurement. The third result is more quantitative and thus more likely to differ from predicted values because of impure or degraded samples. **(f)** An exoglycosidase. If it were an endoglycosidase, one of the products of its action on O antigen would include galactose, *N*-acetylglucosamine, or *N*-acetylgalactosamine, and at least one of those sugars would be able to inhibit the degradation. Given that the enzyme is not inhibited by any of these sugars, it must be an exoglycosidase, removing only the terminal sugar from the chain. The terminal sugar of O antigen is fucose, so fucose is the only sugar that could inhibit the degradation of O antigen. **(g)** The exoglycosidase removes *N*-acetylgalactosamine from A antigen and galactose from B antigen. Because fucose is not a product of either reaction, it will not prevent removal of these sugars, and the resulting substances will no longer be active as A or B antigen. However, the products should be active as O antigen, because degradation stops at fucose. **(h)** All the results are consistent with Fig. 10–15. (1) D-Fucose and L-galactose, which would protect against degradation, are not present in any of the antigens. (2) The terminal sugar of A antigen is *N*-acetylgalactosamine, and this sugar alone protects this antigen from degradation. (3) The terminal sugar of B antigen is galactose, which is the only sugar capable of protecting this antigen.

Chapter 8

1. N-3 and N-7

2. (5′)GCGCAATATTTTGAGAAATATTGCGC(3′); it contains a palindrome. The individual strands can form hairpin structures; the two strands can form a cruciform.

3. 9.4×10^{-4} g

4. **(a)** 40° **(b)** 0°

5. The RNA helix is in the A conformation; the DNA helix is generally in the B conformation.

6. In eukaryotic DNA, about 5% of C residues are methylated. 5-Methylcytosine can spontaneously deaminate to form thymine; the resulting G–T pair is one of the most common mismatches in eukaryotic cells.

7. Higher

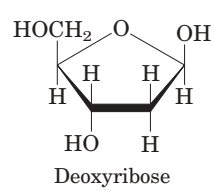
8. Without the base, the ribose ring can be opened to generate the noncyclic aldehyde form. This, and the loss of base-stacking interactions, could contribute significant flexibility to the DNA backbone.

9. CGCGCGTGCGCGCGCG

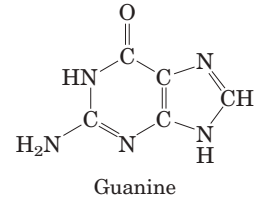
10. Base stacking in nucleic acids tends to reduce the absorption of UV light. Denaturation involves loss of base stacking, and UV absorption increases.

11. 0.35 mg/mL

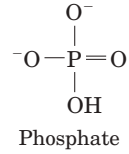
12.



Deoxyribose



Guanine

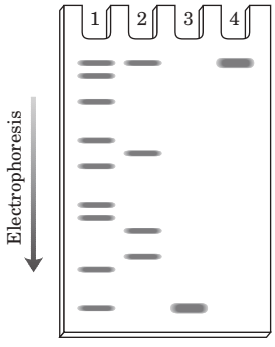


Phosphate

Solubilities: phosphate > deoxyribose > guanine. The highly polar phosphate groups and sugar moieties are on the outside of the double helix, exposed to water; the hydrophobic bases are in the interior of the helix.

13. If dCTP is omitted, when the first G residue is encountered in the template, ddCTP will be added, and polymerization will halt. Only one band will be seen in the sequencing gel.

14.



15. (5′)P—GCGCCAUUGC(3′)—OH
(5′)P—GCGCCAUUG(3′)—OH
(5′)P—GCGCCAUU(3′)—OH
(5′)P—GCGCCAU(3′)—OH
(5′)P—GCGCCA(3′)—OH
(5′)P—GCGCC(3′)—OH
(5′)P—GCGC(3′)—OH
(5′)P—GCG(3′)—OH
(5′)P—GC(3′)—OH
and the nucleoside 5′-phosphates

16. **(a)** Water is a participant in most biological reactions, including those that cause mutations. The low water content in endospores reduces the activity of mutation-causing enzymes and slows the rate of nonenzymatic depurination reactions, which are hydrolysis reactions. **(b)** UV light induces formation of cyclobutane pyrimidine dimers. Because *B. subtilis* is a soil organism, spores can be lofted to the top of the soil or into the air, where they may be subject to prolonged UV exposure.

17. DMT is a blocking group that prevents reaction of the incoming base with itself.

18. **(a)** Right-handed. The base at one 5′ end is adenine; at the other 5′ end, cytidine. **(b)** Left-handed **(c)** If you cannot see the structures in stereo, see additional tips in the expanded solutions manual, or use a search engine to find tips online.

19. **(a)** It would not be easy! The data for different samples from the same organism show significant variation, and the recovery is never 100%. The numbers for C and T show much more consistency than those for A and G, so for C and T it is much easier to make the case that samples from the same organism have the same composition. But even with the less consistent values for A and G, (1) the range of values for different tissues does overlap substantially; (2) the difference between different preparations of the same tissue is about the same as the difference between samples from different tissues; and (3) in samples for which recovery is high, the numbers are more consistent. **(b)** This technique would not be sensitive enough to detect a difference between normal and cancerous cells. Cancer is caused by mutations, but these changes in DNA—a few base pairs out of several billion—would be too small to detect with these techniques. **(c)** The ratios of A:G and T:C vary widely among different species. For example, in the bacterium *Serratia marcescens*, both ratios are 0.4, meaning that the DNA contains mostly G and C. In *Haemophilus influenzae*, by contrast, the ratios are 1.74 and 1.54, meaning that the DNA is mostly A and T. **(d)** Conclusion 4 has three requirements. A = T: The table shows an A:T ratio very close to 1 in all cases. Certainly, the variation in this ratio is substantially less than the variation in the A:G and T:C ratios. G = C: Again, the G:C ratio is very close to 1, and the other ratios vary widely. (A + G) = (T + C): This is the purine:pyrimidine ratio, which also is very close to 1. **(e)** The different "core" fractions represent different regions of the wheat germ DNA. If the DNA were a monotonous repeating sequence, the base composition of all regions would be the same. Because different core regions have different sequences, the DNA sequence must be more complex.

Chapter 9

1. **(a)** (5′) – – – G(3′) and (5′)AATTC – – – (3′)
(3′) – – – CTTAA(5′) (3′)G – – – (5′)
(b) (5′) – – – GAATT(3′) and (5′)AATTC – – – (3′)
(3′) – – – CTTAA(5′) (3′)TTAAG – – – (5′)
(c) (5′) – – – GAATTAATTC – – – (3′)
(3′) – – – CTTAATTAAG – – – (5′)
(d) (5′) – – – G(3′) and (5′)C – – – (3′)
(3′) – – – C(5′) (3′)G – – – (5′)
(e) (5′) – – – GAATTC – – – (3′)
(3′) – – – CTTAAG – – – (5′)
(f) (5′) – – – CAG(3′) and (5′)CTG – – – (3′)
(3′) – – – GTC(5′) (3′)GAC – – – (5′)
(g) (5′) – – – CAGAATTC – – – (3′)
(3′) – – – GTCTTAAG – – – (5′)
(h) Method 1: Cut the DNA with *Eco*RI as in (a). At this point, one could treat the DNA as in (b) or (d), then ligate a synthetic DNA fragment with the *Bam*HI recognition sequence between the two resulting blunt ends. Method 2 (more efficient): Synthesize a DNA fragment with the structure

(5′)AATTGGATCC(3′)
(3′)CCTAGGTTAA(5′)

This would ligate efficiently to the sticky ends generated by *Eco*RI cleavage, would introduce a *Bam*HI site, but would not regenerate the *Eco*RI site. **(i)** The four fragments (with N = any nucleotide), in order of discussion in the problem, are

(5′)AATTCNNNNCTGCA(3′)
(3′)GNNNNG(5′)
(5′)AATTCNNNNGTGCA(3′)
(3′)GNNNNC(5′)
(5′)AATTGNNNNCTGCA(3′)
(3′)CNNNNG(5′)
(5′)AATTGNNNNGTGCA(3′)
(3′)CNNNNC(5′)

2. λ phage DNA can be packaged into infectious phage particles only if it is between 40,000 and 53,000 bp in length. Since bacteriophage vectors generally include about 30,000 bp (in two pieces), they will not be packaged into phage particles unless they contain a sufficient length of inserted DNA (10,000 to 23,000 bp).

3. **(a)** Plasmids in which the original pBR322 was regenerated without insertion of a foreign DNA fragment; these would retain resistance to ampicillin. Also, two or more molecules of pBR322 might be ligated together with or without insertion of foreign DNA. **(b)** The clones in lanes 1 and 2 each have one DNA fragment inserted in different orientations. The clone in lane 3 has two DNA fragments, ligated such that the *Eco*RI proximal ends are joined.

4. (5′)GAAAGTCCGCGTTATAGGCATG(3′)
(3′)ACGTCTTTCAGGCGCAATATCCGTACTTAA(5′)

5. Your test would require DNA primers, a heat-stable DNA polymerase, deoxynucleoside triphosphates, and a PCR machine (thermal cycler). The primers would be designed to amplify a DNA segment encompassing the CAG repeat. The DNA strand shown is the coding strand, oriented 5′→3′ left to right. The primer targeted to DNA to the left of the repeat would be identical to any 25-nucleotide sequence shown in the region to the left of the CAG repeat. The primer on the right

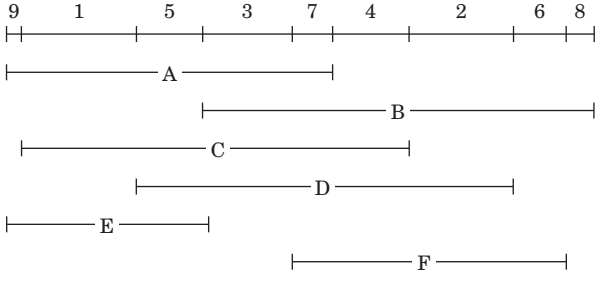
side must be *complementary* and *antiparallel* to a 25-nucleotide sequence to the right of the CAG repeat. Using the primers, DNA including the CAG repeat would be amplified by PCR, and its size would be determined by comparison to size markers after electrophoresis. The length of the DNA would reflect the length of the CAG repeat, providing a simple test for the disease.

6. Design PCR primers that are complementary to the DNA in the deleted segment but that would direct DNA synthesis away from each other. No PCR product will be generated unless the ends of the deleted segment are joined to create a circle.

7. The plant expressing firefly luciferase must take up luciferin, the substrate of luciferase, before it can "glow" (albeit weakly). The plant expressing green fluorescent protein glows without requiring any other compound.

8. Primer 1: CCTCGAGTCAATCGATGCTG
Primer 2: CGCGCACATCAGACGAACCA
Recall that all DNA sequences are always written in the 5′ to 3′ direction, left to right; that the two strands of a DNA molecule are antiparallel; and that both PCR primers must target the end sequences so that their 3′ ends are oriented toward the segment to be amplified. In a lab, writing a sequence in the wrong orientation on an order form when ordering a synthetic oligonucleotide primer can be a very expensive mistake.

9.



10. The production of labeled antibodies is difficult and expensive. The labeling of every antibody to every protein target would be impractical. By labeling one antibody preparation for binding to all antibodies of a particular class, the same labeled antibody preparation can be used in many different immunofluorescence experiments.

11. Express the protein in yeast strain 1 as a fusion protein with one of the domains of Gal4p—say, the DNA-binding domain. Using yeast strain 2, make a library in which essentially every protein of the fungus is expressed as a fusion protein with the interaction domain of Gal4p. Mate strain 1 with the strain 2 library, and look for colonies that are colored due to expression of the reporter gene. These colonies will generally arise from mated cells containing a fusion protein that interacts with your target protein.

12. Cover spot 4, add solution containing activated T, irradiate, wash.

1. A–T 2. G–T 3. A–T 4. G–C

Cover spots 2 and 4, add solution containing activated G, irradiate, wash.

1. A–T–G 2. G–T 3. A–T–G 4. G–C

Cover spot 3, add solution containing activated C, irradiate, wash.

1. A–T–G–C 2. G–T–C 3. A–T–G 4. G–C–C

Cover spots 1, 3, and 4, add solution containing activated C, irradiate, wash.

1. A–T–G–C 2. G–T–C–C 3. A–T–G 4. G–C–C

Cover spots 1 and 2, add solution containing activated G, irradiate, wash.

1. A–T–G–C 2. G–T–C–C 3. A–T–G–C 4. G–C–C–C

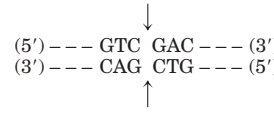
13. The primers can be used to probe libraries containing long genomic clones to identify contig ends that lie close to each other. If the contigs flanking the gap are close enough, the primers can be used in PCR to directly amplify the intervening DNA separating the contigs, which can then be cloned and sequenced.

14. ATSAAG**W**DEWEGGK**V**LIHL**DG**KLQNRGALLELDIGAV

15. The same disease condition can be caused by defects in two or more genes, which are on different chromosomes.

16. **(a)** DNA solutions are highly viscous because the very long molecules are tangled in solution. Shorter molecules tend to tangle less and form a less viscous solution, so decreased viscosity corresponds to shortening of the polymers—as caused by nuclease activity. **(b)** An endonuclease. An exonuclease removes single nucleotides from the 5′ or 3′ end and would produce TCA-soluble ^{32}P-labeled nucleotides. An endonuclease cuts DNA into oligonucleotide fragments and produces little or no TCA-soluble ^{32}P-labeled material. **(c)** The 5′ end. If the phosphate were left on the 3′ end, the kinase would incorporate significant ^{32}P as it added phosphate to the 5′ end; treatment with the phosphatase would have no effect on this. In this case, samples A and B would incorporate significant amounts of ^{32}P. When the phosphate is left on the 5′ end, the kinase does not incorporate any ^{32}P: it cannot add a phosphate if one is already present. Treatment with the phosphatase removes 5′ phosphate, and the kinase then incorporates significant amounts of ^{32}P. Sample A will have little or no ^{32}P, and B will show substantial ^{32}P incorporation—as was observed.
(d) Random breaks would produce a distribution of fragments of random size. The production of specific fragments indicates that the enzyme is site-specific. **(e)** Cleavage at the site of recognition. This produces a specific sequence at the 5′ end of the fragments. If cleavage occurred near but not within the recognition site, the sequence at the 5′ end of the fragments would be random. **(f)** The results are consistent with two recognition sequences, as shown below, cleaved where shown by the arrows,

which gives the (5′)pApApC and (3′)TpTp fragments, and



which gives the (5′)pGpApC and (3′)CpTp fragments

Chapter 10

1. The term "lipid" does not specify a particular chemical structure. Compounds are categorized as lipids based on their greater solubility in organic solvents than in water.

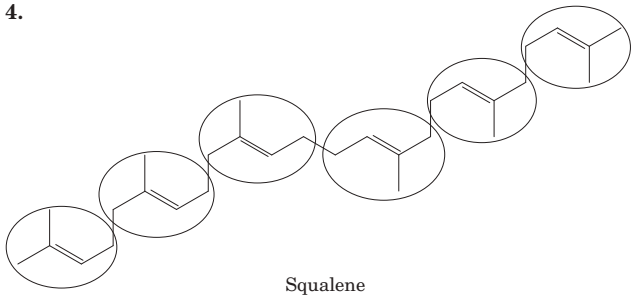
2. **(a)** The number of cis double bonds. Each cis double bond causes a bend in the hydrocarbon chain, lowering the melting temperature. **(b)** Six different triacylglycerols can be constructed, in order of increasing melting points:

$$OOO < OOP = OPO < PPO = POP < PPP$$

where O = oleic and P = palmitic acid. The greater the content of saturated fatty acid, the higher is the melting point.
(c) Branched-chain fatty acids increase the fluidity of membranes because they decrease the extent of membrane lipid packing.

3. Lecithin, an amphipathic compound, is an emulsifying agent, facilitating the solubilization of butter.

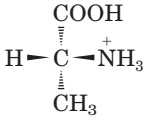
4.



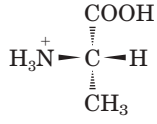
Squalene

5. Spearmint is (*R*)-carvone; caraway is (*S*)-carvone.

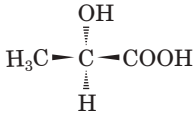
6.



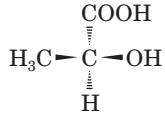
(*R*)-2-Aminopropanoic acid



(*S*)-2-Aminopropanoic acid



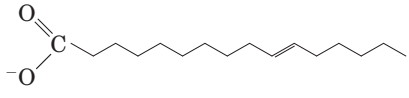
(*R*)-2-Hydroxypropanoic acid



(*S*)-2-Hydroxypropanoic acid

7. *Hydrophobic units:* (a) 2 fatty acids; (b), (c), and (d) 1 fatty acid and the hydrocarbon chain of sphingosine; (e) steroid nucleus and acyl side chain. *Hydrophilic units:* (a) phosphoethanolamine; (b) phosphocholine; (c) D-galactose; (d) several sugar molecules; (e) alcohol group (OH)

8.

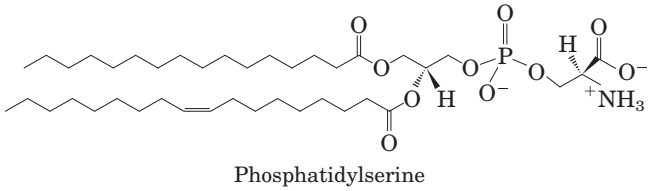


9. It reduces double bonds, which increases the melting point of lipids containing the fatty acids.

10. The triacylglycerols of animal fats (grease) are hydrolyzed by NaOH (saponified) to form soaps, which are much more soluble in water than are triacylglycerols.

11. It could only be a sphingolipid (sphingomyelin).

12.



Phosphatidylserine

13. Long, saturated acyl chains, nearly solid at air temperature, form a hydrophobic layer in which a polar compound such as H_2O cannot dissolve or diffuse.

14. **(a)** The free —OH group on C-2 and the phosphocholine head group on C-3 are hydrophilic; the fatty acid on C-1 of lysolecithin is hydrophobic. **(b)** Certain steroids such as prednisone inhibit the action of phospholipase A_2, inhibiting the release of arachidonic acid from C-2. Arachidonic acid is converted to a variety of eicosanoids, some of which cause inflammation and pain. **(c)** Phospholipase A_2 releases arachidonic acid, a precursor of other eicosanoids with vital protective functions in the body; it also breaks down dietary glycerophospholipids.

15. The part of the membrane lipid that determines blood type is the oligosaccharide in the head group of the membrane sphingolipids (see Fig. 10–15). This same oligosaccharide is attached to certain membrane glycoproteins, which also serve as points of recognition by the antibodies that distinguish blood groups.

16. Diacylglycerol is hydrophobic and remains in the membrane. Inositol 1,4,5-trisphosphate is highly polar, very soluble in water, and more readily diffusible in the cytosol. Both are second messengers.

17. Water-soluble vitamins are more rapidly excreted in the urine and are not stored effectively. Fat-soluble vitamins have very low solubility in water and are stored in body lipids.

18. **(a)** Glycerol and the sodium salts of palmitic and stearic acids. **(b)** D-Glycerol 3-phosphocholine and the sodium salts of palmitic and oleic acids.

19. Solubilities in water: monoacylglycerol > diacylglycerol > triacylglycerol.

20. First eluted to last eluted: cholesteryl palmitate and triacylglycerol; cholesterol and *n*-tetradecanol; phosphatidylcholine and phosphatidylethanolamine; sphingomyelin; phosphatidylserine and palmitate.

21. **(a)** Subject acid hydrolysates of each compound to chromatography (GLC or silica gel TLC) and compare the result with known standards. *Sphingomyelin hydrolysate:* sphingosine, fatty acids, phosphocholine, choline, and phosphate; *cerebroside hydrolysate:* sphingosine, fatty acids, sugars, but no phosphate. **(b)** Strong alkaline hydrolysis of sphingomyelin yields sphingosine; phosphatidylcholine yields glycerol. Detect hydrolysate components on thin-layer chromatograms by comparing with standards or by their differential reaction with FDNB (only sphingosine reacts to form a colored product). Treatment with phospholipase A_1 or A_2 releases free fatty acids from phosphatidylcholine, but not from sphingomyelin.

22. Phosphatidylethanolamine and phosphatidylserine.

23. **(a)** GM1 and globoside. Both glucose and galactose are hexoses, so "hexose" in the molar ratio refers to glucose + galactose. The ratios for the four gangliosides are: GM1, 1:3:1:1; GM2, 1:2:1:1; GM3, 1:2:0:1; globoside, 1:3:1:0. **(b)** Yes. The ratio matches GM2, the ganglioside expected to build up in Tay-Sachs disease (see Box 10–1, Fig. 1). **(c)** This analysis is similar to that used by Sanger to determine the amino acid sequence of insulin. The analysis of each fragment reveals only its *composition*, not its *sequence*, but because each fragment is formed by sequential removal of one sugar, we can draw conclusions about sequence. The structure of the normal asialoganglioside is ceramide–glucose–galactose–galactosamine–galactose, consistent with Box 10–1 (excluding Neu5Ac, removed before hydrolysis). **(d)** The Tay-Sachs asialoganglioside is ceramide–glucose–galactose–galactosamine, consistent with Box 10–1. **(e)** The structure of the normal asialoganglioside, GM1, is: *ceramide–glucose* (2 —OH involved in glycosidic links; 1 —OH involved in ring structure; 3 —OH (2,3,6) free for methylation)–*galactose* (2 —OH in links; 1 —OH in ring; 3 —OH (2,4,6) free for methylation)–*galactosamine* (2 —OH in links; 1 —OH in ring; 1 —NH_2 instead of an —OH; 2 —OH (4,6) free for methylation)–*galactose* (1 —OH in link; 1 —OH in ring; 4 —OH (2,3,4,6) free for methylation). **(f)** Two key pieces of information are missing: What are the linkages between the sugars? Where is Neu5Ac attached?

Chapter 11

1. The area per molecule would be calculated from the known amount (number of molecules) of lipid used and the area occupied by a monolayer when it begins to resist compression (when the required force increases dramatically, as shown in the plot of force vs. area).

2. The data support a bilayer of lipid in the dog erythrocytes: a single cell, with surface area 98 μm^2, has a lipid monolayer area of 200 μm^2. In the case of sheep and human erythrocytes, the data suggest a monolayer, not a bilayer. In fact, significant

experimental errors occurred in these early experiments; recent, more accurate measurements support a bilayer in all cases.

3. 63 SDS molecules per micelle

4. **(a)** Lipids that form bilayers are amphipathic molecules: they contain a hydrophilic and a hydrophobic region. To minimize the hydrophobic area exposed to the water surface, these lipids form two-dimensional sheets, with the hydrophilic regions exposed to water and the hydrophobic regions buried in the interior of the sheet. Furthermore, to avoid exposing the hydrophobic edges of the sheet to water, lipid bilayers close on themselves. **(b)** These sheets form the closed membrane surfaces that envelop cells and compartments within cells (organelles).

5. 2 nm. Two palmitates placed end to end span about 4 nm, approximately the thickness of a typical bilayer.

6. Decrease. Movement of individual lipids in bilayers occurs much faster at 37°C, when the lipids are in the "fluid" phase, than at 10°C, when they are in the "solid" phase.

7. 35 kJ/mol, neglecting the effects of transmembrane electrical potential; 0.60 mol.

8. 13 kJ/mol.

9. Most of the O_2 consumed by a tissue is for oxidative phosphorylation, the source of most of the ATP. Therefore, about two-thirds of the ATP synthesized by the kidney is used for pumping K^+ and Na^+.

10. No. The symporter may carry more than one equivalent of Na^+ for each mole of glucose transported.

11. Salt extraction indicates a peripheral location, and inaccessibility to protease in intact cells indicates an internal location. X seems to be a peripheral protein on the cytosolic face of the membrane.

12. The hydrophobic interactions among membrane lipids are noncovalent and reversible, allowing membranes to spontaneously reseal.

13. The temperature of body tissues at the extremities is lower than that of tissues closer to the center of the body. If lipid is to remain fluid at this lower temperature, it must contain a higher proportion of unsaturated fatty acids; unsaturated fatty acids lower the melting point of lipid mixtures.

14. The energetic cost of moving the highly polar, sometimes charged, head group through the hydrophobic interior of the bilayer is prohibitive.

15. At pH 7, tryptophan bears a positive and a negative charge, but indole is uncharged. The movement of the less polar indole through the hydrophobic core of the bilayer is energetically more favorable.

16. 3×10^{-2} s

17. Treat a suspension of cells with unlabeled NEM in the presence of excess lactose, remove the lactose, then add radiolabeled NEM. Use SDS-PAGE to determine the M_r of the radiolabeled band (the transporter).

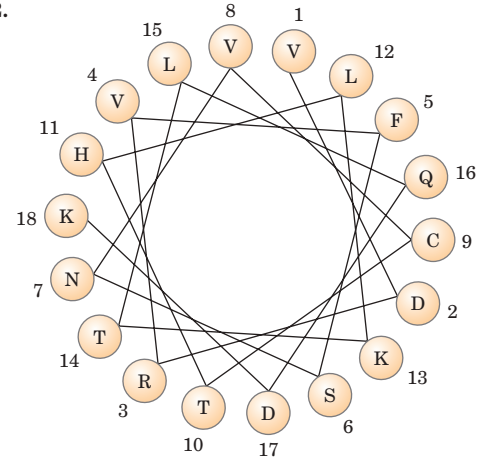
18. Construct a hydropathy plot; hydrophobic regions of 20 or more residues suggest transmembrane segments. Determine whether the protein in intact erythrocytes reacts with a membrane-impermeant reagent specific for primary amines; if so, the transporter is of type I.

19. The leucine transporter is specific for the L isomer, but the binding site can accommodate either L-leucine or L-valine. Reduction of V_{max} in the absence of Na^+ indicates that leucine (or valine) is transported by symport with Na^+.

20. V_{max} reduced; K_t unaffected.

21. ~1%; estimated by calculating the surface area of the cell and of 10,000 transporter molecules (using the dimensions of hemoglobin (5.5 nm diameter, p. 163) as a model globular protein).

22.



The amino acids with the greatest hydropathy index (V, L, F, and C) are clustered on one side of the helix. This amphipathic helix is likely to dip into the lipid bilayer along its hydrophobic surface while exposing the other surface to the aqueous phase. Alternatively, a group of helices may cluster with their polar surfaces in contact with one another and their hydrophobic surfaces facing the lipid bilayer.

23. ~22. To estimate the fraction of membrane surface covered by phospholipids, you would need to know (or estimate) the average cross-sectional area of a phospholipid molecule in a bilayer (e.g., from an experiment such as that diagrammed in problem 1 in this chapter) and the average cross-sectional area of a 50 kDa protein.

24. **(a)** The rise-per-residue for an α helix (Chapter 4) is about 1.5 Å = 0.15 nm. To span a 4 nm bilayer, an α helix must contain about 27 residues; thus for seven spans, about 190 residues are required. A protein of M_r 64,000 has about 580 residues. **(b)** A hydropathy plot is used to locate transmembrane regions. **(c)** Because about half of this portion of the epinephrine receptor consists of charged residues, it probably represents an intracellular loop that connects two adjacent membrane-spanning regions of the protein. **(d)** Because this helix is composed mostly of hydrophobic residues, this portion of the receptor is probably one of the membrane-spanning regions of the protein.

25. **(a)** *Model A:* supported. The two dark lines are either the protein layers or the phospholipid heads, and the clear space is either the bilayer or the hydrophobic core, respectively. *Model B:* not supported. This model requires a more-or-less uniformly stained band surrounding the cell. *Model C:* supported, with one reservation. The two dark lines are the phospholipid heads; the clear zone is the tails. This assumes that the membrane proteins are not visible, because they do not stain with osmium or do not happen to be in the sections viewed. **(b)** *Model A:* supported. A "naked" bilayer (4.5 nm) + two layers of protein (2 nm) sums to 6.5 nm, which is within the observed range of thickness. *Model B:* neither. This model makes no predictions about membrane thickness. *Model C:* unclear. The result is hard to reconcile with this model, which predicts a membrane as thick as, or slightly thicker than (due to the projecting ends of embedded proteins), a "naked" bilayer. The model is supported only if the smallest values for membrane thickness are correct or if a substantial amount of protein projects from the bilayer. **(c)** *Model A:* unclear. The result is hard to reconcile with this model. If the proteins are bound to the membrane by ionic interactions, the model predicts that the proteins contain a high proportion of charged amino acids, in contrast to what was observed. Also, because the protein layer must be very thin (see (b)), there would not be much room for a hydrophobic protein core, so hydrophobic residues would be exposed to the solvent. *Model B:* supported. The proteins have a mixture of hydrophobic residues (interacting with lipids) and charged residues (interacting with

water). *Model C:* supported. The proteins have a mixture of hydrophobic residues (anchoring in the membrane) and charged residues (interacting with water). **(d)** *Model A:* unclear. The result is hard to reconcile with this model, which predicts a ratio of exactly 2.0; this would be hard to achieve under physiologically relevant pressures. *Model B:* neither. This model makes no predictions about amount of lipid in the membrane. *Model C:* supported. Some membrane surface area is taken up with proteins, so the ratio would be less than 2.0, as was observed under more physiologically relevant conditions. **(e)** *Model A:* unclear. The model predicts proteins in extended conformations rather than globular, so supported only if one assumes that proteins layered on the surfaces include helical segments. *Model B:* supported. The model predicts mostly globular proteins (containing some helical segments). *Model C:* supported. The model predicts mostly globular proteins. **(f)** *Model A:* unclear. The phosphorylamine head groups are protected by the protein layer, but only if the proteins completely cover the surface will the phospholipids be completely protected from phospholipase. *Model B:* supported. Most head groups are accessible to phospholipase. *Model C:* supported. All head groups are accessible to phospholipase. **(g)** *Model A:* not supported. Proteins are entirely accessible to trypsin digestion and virtually all will undergo multiple cleavage, with no protected hydrophobic segments. *Model B:* not supported. Virtually all proteins are in the bilayer and inaccessible to trypsin. *Model C:* supported. Segments of protein that penetrate or span the bilayer are protected from trypsin; those exposed at the surfaces will be cleaved. The trypsin-resistant portions have a high proportion of hydrophobic residues.

Chapter 12

1. X is cAMP; its production is stimulated by epinephrine. **(a)** Centrifugation sediments adenylyl cyclase (which catalyzes cAMP formation) in the particulate fraction. **(b)** Added cAMP stimulates glycogen phosphorylase. **(c)** cAMP is heat stable; it can be prepared by treating ATP with barium hydroxide.

2. Unlike cAMP, dibutyryl cAMP passes readily through the plasma membrane.

3. **(a)** It increases [cAMP]. **(b)** cAMP regulates Na^+ permeability. **(c)** Replace lost body fluids and electrolytes.

4. **(a)** The mutation makes R unable to bind and inhibit C, so C is constantly active. **(b)** The mutation prevents cAMP binding to R, leaving C inhibited by bound R.

5. Albuterol raises [cAMP], leading to relaxation and dilation of the bronchi and bronchioles. Because β-adrenergic receptors control many other processes, this drug would have undesirable side effects. To minimize them, find an agonist specific for the subtype of β-adrenergic receptors found in the bronchial smooth muscle.

6. Hormone degradation; hydrolysis of GTP bound to a G protein; degradation, metabolism, or sequestration of second messenger; receptor desensitization; removal of receptor from the cell surface.

7. Fuse CFP to β-arrestin and YFP to the cytoplasmic domain of the β-adrenergic receptor, or vice versa. In either case, illuminate at 433 nm and observe at both 476 and 527 nm. If the interaction occurs, emitted light intensity will decrease at 476 nm and increase at 527 nm on addition of epinephrine to cells expressing the fusion proteins. If the interaction does not occur, the wavelength of emitted light will remain at 476 nm. Some reasons why this might fail: The fusion proteins (1) are inactive or otherwise unable to interact, (2) are not translocated to their normal subcellular location, or (3) are not stable to proteolytic breakdown.

8. Vasopressin acts by elevating cytosolic $[Ca^{2+}]$ to 10^{-6} M, activating protein kinase C. EGTA injection blocks vasopressin action but should not affect the response to glucagon, which uses cAMP, *not* Ca^{2+}, as second messenger.

9. Amplification results as one molecule of a catalyst activates many molecules of another catalyst, in an amplification cascade involving, in order, insulin receptor, IRS-1, Raf, MEK, ERK; ERK activates a transcription factor, which stimulates mRNA production.

10. A mutation in *ras* that inactivates the Ras GTPase activity creates a protein that, once activated by the binding of GTP, continues to give, through Raf, the insulin-response signal.

11. *Shared properties of Ras and G_s:* Both bind either GDP or GTP; both are activated by GTP; both, when active, activate a downstream enzyme; both have intrinsic GTPase activity that shuts them off after a short period of activation. *Differences between Ras and G_s:* Ras is a small, monomeric protein; G_s is heterotrimeric. *Functional difference between G_s and G_i:* G_s activates adenylyl cyclase, G_i inhibits it.

12. *Kinase (factor in parentheses):* PKA (cAMP); PKG (cGMP); PKC (Ca^{2+}, DAG); Ca^{2+}/CaM kinase (Ca^{2+}, CaM); cyclin-dependent kinase (cyclin); protein Tyr kinase (ligand for the receptor, such as insulin); MAPK (Raf); Raf (Ras); glycogen phosphorylase kinase (PKA).

13. G_s remains in its activated form when the nonhydrolyzable analog is bound. The analog therefore prolongs the effect of epinephrine on the injected cell.

14. **(a)** Use the α-bungarotoxin–bound beads for affinity purification (see Fig. 3–17c) of AChR. Extract proteins from the electric organs and pass the mixture through the chromatography column; the AChR binds selectively to the beads. Elute the AChR with a solute that weakens its interaction with α-bungarotoxin. **(b)** Use binding of [^{125}I]α-bungarotoxin as a *quantitative assay* for AChR during purification by various techniques. At each step, assay AChR by measuring [^{125}I]α-bungarotoxin binding to the proteins in the sample. Optimize purification for the highest specific activity of AChR (counts/min of bound [^{125}I]α-bungarotoxin per mg of protein) in the final material.

15. **(a)** No. If V_m were set by permeability to (primarily) K^+, the Nernst equation would predict a V_m of -90 mV, not the observed -95 mV, so some other conductance must contribute to V_m. **(b)** Chloride ion is probably the determinant of V_m; the predicted E_{Cl^-} is -94 mV.

16. **(a)** V_m of the oocyte membrane changes from -60 mV to -10 mV—that is, the membrane is depolarized. **(b)** The effect of KCl depends on influx of Ca^{2+} from the extracellular medium.

17. Hyperpolarization results in the closing of voltage-dependent Ca^{2+} channels in the presynaptic region of the rod cell. The resulting decrease in $[Ca^{2+}]_{in}$ diminishes release of an inhibitory neurotransmitter that suppresses activity in the next neuron of the visual circuit. When this inhibition is removed in response to a light stimulus, the circuit becomes active and visual centers in the brain are excited.

18. **(a)** This would prevent influx of Na^+ and Ca^{2+} into the cells in response to light; the cone cells would fail to signal the brain that light had been received. Because rod cells are unaffected, the individuals would be able to see but would not have color vision. **(b)** This would prevent efflux of K^+, which would lead to depolarization of the β-cell membrane and constitutive release of insulin into the blood. **(c)** ATP is responsible for closing this channel, so the channels will remain open, preventing depolarization of the β-cell membrane and release of insulin.

19. Individuals with Oguchi disease might have a defect in rhodopsin kinase or in arrestin.

20. Rod cells would no longer show any change in membrane potential in response to light. This experiment has been done. Illumination did activate PDE, but the enzyme could not significantly reduce the 8-Br-cGMP level, which remained well above that needed to keep the gated ion channels open. Thus, light had no impact on membrane potential.

21. **(a)** On exposure to heat, TRPV1 channels open, causing an influx of Na^+ and Ca^{2+} into the sensory neuron. This depolarizes the neuron, triggering an action potential. When the action potential reaches the axon terminus, neurotransmitter is released, signaling the nervous system that heat has been sensed. **(b)** Capsaicin mimics the effects of heat by opening TRPV1 at low temperature, leading to the false sensation of heat. The extremely low EC_{50} indicates that even very small amounts of capsaicin will have dramatic sensory effects. **(c)** At low levels, menthol should open the TRPM8 channel, leading to a sensation of cool; at high levels, both TRPM8 and TRPV3 will open, leading to a mixed sensation of cool and heat, such as you may have experienced with very strong peppermints.

22. **(a)** These mutations might lead to permanent activation of the PGE_2 receptor, leading to unregulated cell division and tumor formation. **(b)** The viral gene might encode a constitutively active form of the receptor, causing a constant signal for cell division and thus tumor formation. **(c)** E1A protein might bind to pRb and prevent E2F from binding, so E2F is constantly active and cells divide uncontrollably. **(d)** Lung cells do not normally respond to PGE_2 because they do not express the PGE_2 receptor; mutations resulting in a constitutively active PGE_2 receptor do not affect lung cells.

23. A normal tumor suppressor gene encodes a protein that restrains cell division. A mutant form of the protein fails to suppress cell division, but if either of the two alleles encodes normal protein, normal function will continue. A normal oncogene encodes a regulator protein that triggers cell division, but only when an appropriate signal (growth factor) is present. The mutant version of the oncogene product constantly sends the signal to divide, whether or not growth factors are present.

24. In a child who develops multiple tumors in both eyes, every retinal cell had a defective copy of the *Rb* gene at birth. Early in the child's life, several cells independently underwent a second mutation that damaged the one good *Rb* allele, producing a tumor. A child who develops a single tumor had, at birth, two good copies of the *Rb* gene in every cell; mutation in both *Rb* alleles in one cell (extremely rare) caused a single tumor.

25. Two cells expressing the same surface receptor may have different complements of target proteins for protein phosphorylation.

26. **(a)** The cell-based model, which predicts different receptors present on different cells. **(b)** This experiment addresses the issue of the independence of different taste sensations. Even though the receptors for sweet and/or umami are missing, the animals' other taste sensations are normal; thus, pleasant and unpleasant taste sensations are independent. **(c)** Yes. Loss of either T1R1 or T1R3 subunits abolishes umami taste sensation. **(d)** Both models. With either model, removing one receptor would abolish that taste sensation. **(e)** Yes. Loss of either the T1R2 or T1R3 subunits almost completely abolishes the sweet taste sensation; complete elimination of sweet taste requires deletion of both subunits. **(f)** At very high sucrose concentrations, T1R2 and, to a lesser extent, T1R3 receptors, as homodimers, can detect sweet taste. **(g)** The results are consistent with either model of taste encoding, but do strengthen the researchers' conclusions. Ligand binding can be completely separated from taste sensation. If the ligand for the receptor in "sweet-tasting cells" binds a molecule, mice prefer that molecule as a sweet compound.

Chapter 13

1. Consider the developing chick as the system; the nutrients, egg shell, and outside world are the surroundings. Transformation of the single cell into a chick drastically reduces the entropy of the system. Initially, the parts of the egg outside the embryo (the surroundings) contain complex fuel molecules (a low-entropy condition). During incubation, some of these complex molecules are converted to large numbers of CO_2 and H_2O molecules (high entropy). This increase in the entropy of the surroundings is larger than the decrease in entropy of the chick (the system).

2. **(a)** −4.8 kJ/mol **(b)** 7.56 kJ/mol **(c)** −13.7 kJ/mol

3. **(a)** 262 **(b)** 608 **(c)** 0.30

4. $K'_{eq} = 21$; $\Delta G'^\circ = -7.6$ kJ/mol

5. −31 kJ/mol

6. **(a)** −1.68 kJ/mol **(b)** −4.4 kJ/mol **(c)** At a given temperature, the value of $\Delta G'^\circ$ for any reaction is fixed and is defined for standard conditions (here, both fructose 6-phosphate and glucose 6-phosphate at 1 M). In contrast, ΔG is a variable that can be calculated for any set of reactant and product concentrations.

7. $K'_{eq} \approx 1$; $\Delta G'^\circ \approx 0$

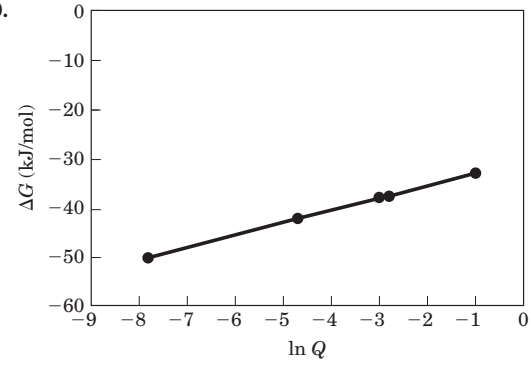
8. Less. The overall equation for ATP hydrolysis can be approximated as

$$ATP^{4-} + H_2O \rightarrow ADP^{3-} + HPO_4^{2-} + H^+$$

(This is only an approximation, because the ionized species shown here are the major, but not the only, forms present.) Under standard conditions (i.e., [ATP] = [ADP] = $[P_i]$ = 1 M), the concentration of water is 55 M and does not change during the reaction. Because H^+ ions are produced in the reaction, at a higher $[H^+]$ (pH 5.0) the equilibrium would be shifted to the left and less free energy would be released.

9. 10

10.



ΔG for ATP hydrolysis is lower when [ATP]/[ADP] is low (<<1) than when [ATP]/[ADP] is high. The energy available to the cell from a given [ATP] is lower when the [ATP]/[ADP] ratio falls and greater when it rises.

11. **(a)** 3.85×10^{-3} M^{-1}; [glucose 6-phosphate] = 8.9×10^{-8} M; no. **(b)** 14 M; because the maximum solubility of glucose is less than 1 M, this is not a reasonable step. **(c)** 837 ($\Delta G'^\circ = -16.7$ kJ/mol); [glucose] = 1.2×10^{-7} M; yes. **(d)** No. This would require such high $[P_i]$ that the phosphate salts of divalent cations would precipitate. **(e)** By directly transferring the phosphoryl group from ATP to glucose, the phosphoryl group transfer potential ("tendency" or "pressure") of ATP is utilized without generating high concentrations of intermediates. The essential part of this transfer is, of course, the enzymatic catalysis.

12. **(a)** −12.5 kJ/mol **(b)** −14.6 kJ/mol

13. **(a)** 3×10^{-4} **(b)** 68.7 **(c)** 7.4×10^4

14. −13 kJ/mol

15. 46.7 kJ/mol

16. Isomerization moves the carbonyl group from C-1 to C-2, setting up a carbon–carbon bond cleavage between C-3 and C-4. Without isomerization, bond cleavage would occur between C-2 and C-3, generating one two-carbon and one four-carbon compound.

17. The mechanism is the same as that of the alcohol dehydrogenase reaction (see Fig. 14–14).

18. The first step is the reverse of an aldol condensation (see the aldolase mechanism, Fig. 14–6); the second step is an aldol condensation (see Fig. 13–4).

19. **(a)** 46 kJ/mol **(b)** 46 kg; 68% **(c)** ATP is synthesized as it is needed, then broken down to ADP and P_i; its concentration is maintained in a steady state.

20. The ATP system is in a dynamic steady state; [ATP] remains constant because the rate of ATP consumption equals its rate of synthesis. ATP consumption involves release of the terminal (γ) phosphoryl group; synthesis of ATP from ADP involves replacement of this phosphoryl group. Hence the terminal phosphate undergoes rapid turnover. In contrast, the central (β) phosphate undergoes only relatively slow turnover.

21. **(a)** 1.7 kJ/mol **(b)** Inorganic pyrophosphatase catalyzes the hydrolysis of pyrophosphate and drives the net reaction toward the synthesis of acetyl-CoA.

22. 36 kJ/mol

23. **(a)** NAD^+/NADH **(b)** Pyruvate/lactate **(c)** Lactate formation **(d)** −26.1 kJ/mol **(e)** 3.63×10^4

24. **(a)** 1.14 V **(b)** −220 kJ/mol **(c)** ~4

25. **(a)** −0.35 V **(b)** −0.320 V **(c)** −0.29 V

26. In order of increasing tendency: (a), (d), (b), (c)

27. (c) and (d)

28. **(a)** The lowest-energy, highest-entropy state occurs when the dye concentration is the same in both cells. If a "fish trap" gap junction allowed unidirectional transport, more of the dye would end up in the oligodendrocyte and less in the astrocyte. This would be a higher-energy, lower-entropy state than the starting state, violating the second law of thermodynamics. The model proposed by Robinson et al. requires an impossible spontaneous decrease in entropy. In terms of energy, the model entails a spontaneous change from a lower-energy to a higher-energy state without an energy input—again, thermodynamically impossible. **(b)** Molecules, unlike fish, do not exhibit *directed behavior*; they move randomly by Brownian motion. Diffusion results in *net* movement of molecules from a region of higher concentration to a region of lower concentration simply because it is more likely that a molecule on the high-concentration side will enter the connecting channel. Look at this as a pathway with a rate-limiting step: the narrow end of the channel. The narrower end limits the rate at which molecules pass through because random motion of the molecules is less likely to move them through the smaller cross section. The wide end of the channel does *not* act like a funnel for molecules, although it may for fish, because molecules are not "crowded" by the sides of the narrowing funnel as fish would be. The narrow end limits the rate of movement equally in both directions. When the concentrations on both sides are equal, the rates of movement in both directions are equal and there will be no change in concentration. **(c)** Fish exhibit *nonrandom behavior*, adjusting their actions in response to the environment. Fish that enter the large opening of the channel tend to move forward because fish have behavior that tends to make them prefer forward movement, and they experience "crowding" as they move through the narrowing channel. It is easy for fish to enter the large opening, but they don't move out of the trap as readily because they are less likely to enter the small opening. **(d)** There are many possible explanations, some of which were proposed by the letter-writers who criticized the article. Here are two: (1) *The dye could bind to a molecule in the oligodendrocyte*. Binding effectively removes the dye from the bulk solvent, so it doesn't "count" as a solute for thermodynamic considerations yet remains visible in the fluorescence microscope. (2) *The dye could be sequestered in a subcellular organelle of the oligodendrocyte*, either actively pumped at the expense of ATP or drawn in by its attraction to other molecules in that organelle.

Chapter 14

1. Net equation: Glucose + 2ATP → 2 glyceraldehyde 3-phosphate + 2ADP + $2H^+$; $\Delta G'^\circ$ = 2.1 kJ/mol

2. Net equation: 2 Glyceraldehyde 3-phosphate + 4ADP + $2P_i$ → 2 lactate + $2NAD^+$; $\Delta G'^\circ$ = −114 kJ/mol

3. GLUT2 (and GLUT1) is found in liver and is always present in the plasma membrane of hepatocytes. GLUT3 is always present in the plasma membrane of certain brain cells. GLUT4 is normally sequestered in vesicles in cells of muscle and adipose tissue and enters the plasma membrane only in response to insulin. Thus, liver and brain can take up glucose from blood regardless of insulin level, but muscle and adipose tissue take up glucose only when insulin levels are elevated in response to high blood glucose.

4. $CH_3CHO + NADH + H^+ \rightleftharpoons CH_3CH_2OH + NAD^+$; $K'_{eq} = 1.45 \times 10^4$

5. −8.6 kJ/mol

6. **(a)** $^{14}CH_3CH_2OH$ **(b)** [3-^{14}C]glucose or [4-^{14}C]glucose

7. Fermentation releases energy, some conserved in the form of ATP but much of it dissipated as heat. Unless the fermenter contents are cooled, the temperature would become high enough to kill the microorganisms.

8. Soybeans and wheat contain starch, a polymer of glucose. The microorganisms break down starch to glucose, glucose to pyruvate via glycolysis, and—because the process is carried out in the absence of O_2 (i.e., it is a fermentation)—pyruvate to lactic acid and ethanol. If O_2 were present, pyruvate would be oxidized to acetyl-CoA, then to CO_2 and H_2O. Some of the acetyl-CoA, however, would also be hydrolyzed to acetic acid (vinegar) in the presence of oxygen.

9. C-1. This experiment demonstrates the reversibility of the aldolase reaction. The C-1 of glyceraldehyde 3-phosphate is equivalent to C-4 of fructose 1,6-bisphosphate (see Fig. 14–7). The starting glyceraldehyde 3-phosphate must have been labeled at C-1. The C-3 of dihydroxyacetone phosphate becomes labeled through the triose phosphate isomerase reaction, thus giving rise to fructose 1,6-bisphosphate labeled at C-3.

10. No. There would be no anaerobic production of ATP; aerobic ATP production would be diminished only slightly.

11. No. Lactate dehydrogenase is required to recycle NAD^+ from the NADH formed during the oxidation of glyceraldehyde 3-phosphate.

12. The transformation of glucose to lactate occurs when myocytes are low in oxygen, and it provides a means of generating ATP under O_2-deficient conditions. Because lactate can be oxidized to pyruvate, glucose is not wasted; pyruvate is oxidized by aerobic reactions when O_2 becomes plentiful. This metabolic flexibility gives the organism a greater capacity to adapt to its environment.

13. It rapidly removes the 1,3-bisphosphoglycerate in a favorable subsequent step, catalyzed by phosphoglycerate kinase.

14. **(a)** 3-Phosphoglycerate is the product. **(b)** In the presence of arsenate there is no net ATP synthesis under anaerobic conditions.

15. **(a)** Ethanol fermentation requires 2 mol of P_i per mole of glucose. **(b)** Ethanol is the reduced product formed during reoxidation of NADH to NAD^+, and CO_2 is the byproduct of the conversion of pyruvate to ethanol. Yes; pyruvate must be converted to ethanol, to produce a continuous supply of NAD^+ for the oxidation of glyceraldehyde 3-phosphate. Fructose 1,6-bisphosphate accumulates; it is formed as an intermediate in glycolysis. **(c)** Arsenate replaces P_i in the glyceraldehyde 3-phosphate dehydrogenase reaction to yield an acyl arsenate, which spontaneously hydrolyzes. This

prevents formation of ATP, but 3-phosphoglycerate continues through the pathway.

16. Dietary niacin is used to synthesize NAD^+. Oxidations carried out by NAD^+ are part of cyclic processes, with NAD^+ as electron carrier (reducing agent); one molecule of NAD^+ can oxidize many thousands of molecules of glucose, and thus the dietary requirement for the precursor vitamin (niacin) is relatively small.

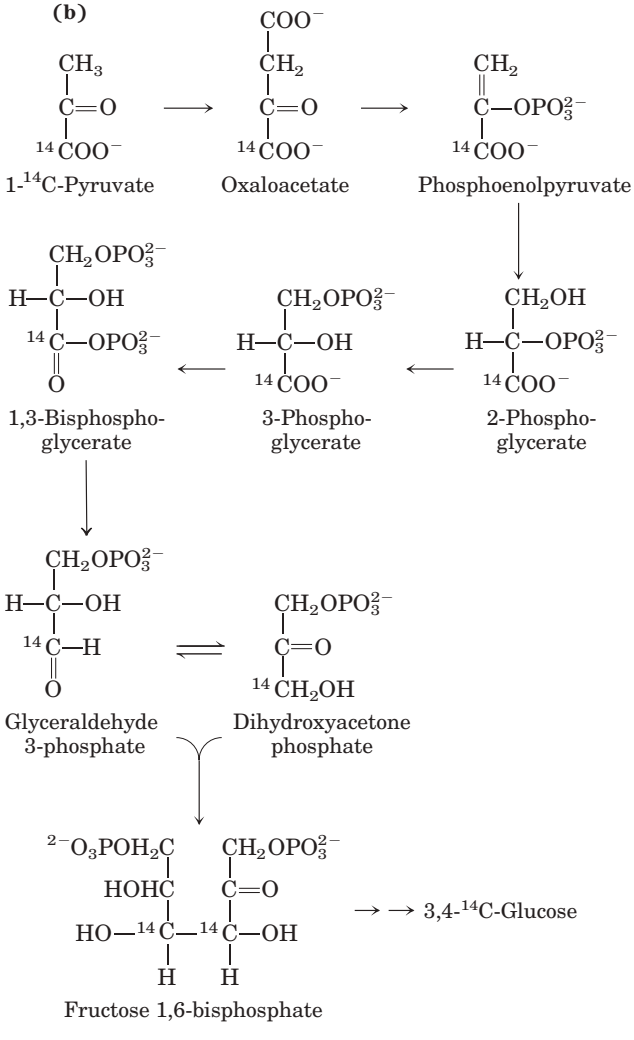
17. Dihydroxyacetone phosphate + NADH + H^+ → glycerol 3-phosphate + NAD^+ (catalyzed by a dehydrogenase)

18. *Galactokinase deficiency:* galactose (less toxic); *UDP-glucose: galactose 1-phosphate uridylyl deficiency:* galactose 1-phosphate (more toxic).

19. The proteins are degraded to amino acids and used for gluconeogenesis.

20. **(a)** In the pyruvate carboxylase reaction, $^{14}CO_2$ is added to pyruvate, but PEP carboxykinase removes the *same* CO_2 in the next step. Thus, ^{14}C is not (initially) incorporated into glucose.

(b)



21. 4 ATP equivalents per glucose molecule

22. Gluconeogenesis would be highly endergonic, and it would be impossible to separately regulate gluconeogenesis and glycolysis.

23. The cell "spends" 1 ATP and 1 GTP in converting pyruvate to PEP.

24. (a), (b), (d) are glucogenic; (c) (e) are not.

25. Consumption of alcohol forces competition for NAD^+ between ethanol metabolism and gluconeogenesis. The problem is compounded by strenuous exercise and lack of food, because at these times the level of blood glucose is already low.

26. **(a)** The rapid increase in glycolysis; the rise in pyruvate and NADH results in a rise in lactate. **(b)** Lactate is transformed to glucose via pyruvate; this is a slower process, because formation of pyruvate is limited by NAD^+ availability, the LDH equilibrium is in favor of lactate, and conversion of pyruvate to glucose is energy-requiring. **(c)** The equilibrium for the LDH reaction is in favor of lactate formation.

27. Lactate is transformed to glucose in the liver by gluconeogenesis (see Figs 14–16, 14–17). A defect in FBPase-1 would prevent entry of lactate into the gluconeogenic pathway in hepatocytes, causing lactate to accumulate in the blood.

28. Succinate is transformed to oxaloacetate, which passes into the cytosol and is converted to PEP by PEP carboxykinase. Two moles of PEP are then required to produce a mole of glucose by the route outlined in Fig. 14–17.

29. If the catabolic and anabolic pathways of glucose metabolism are operating simultaneously, futile cycling of ATP occurs, with extra O_2 consumption.

30. At the very least, accumulation of ribose 5-phosphate would tend to force this reaction in the reverse direction by mass action (see Eqn 13–4). It might also affect other metabolic reactions that involve ribose 5-phosphate as a substrate or product—such as the pathways of nucleotide synthesis.

31. **(a)** Ethanol tolerance is likely to involve many more genes, and thus the engineering would be a much more involved project. **(b)** L-Arabinose isomerase (the *araA* enzyme) converts an aldose to a ketose by moving the carbonyl of a nonphosphorylated sugar from C-1 to C-2. No analogous enzyme is discussed in this chapter; all the enzymes described here act on phosphorylated sugars. An enzyme that carries out a similar transformation with phosphorylated sugars is phosphohexose isomerase. L-Ribulokinase (*araB*) phosphorylates a sugar at C-5 by transferring the γ phosphate from ATP. Many such reactions are described in this chapter, including the hexokinase reaction. L-Ribulose 5-phosphate epimerase (*araD*) switches the —H and —OH groups on a chiral carbon of a sugar. No analogous reaction is described in the chapter, but it is described in Chapter 20 (see Fig. 20–13). **(c)** The three *ara* enzymes would convert arabinose to xylulose 5-phosphate by the following pathway: Arabinose $\xrightarrow{\text{L-arabinose isomerase}}$ L-ribulose $\xrightarrow{\text{L-ribulokinase}}$ L-ribulose 5-phosphate $\xrightarrow{\text{epimerase}}$ xylulose 5-phosphate. **(d)** The arabinose is converted to xylulose 5-phosphate as in (c), which enters the pathway in Fig. 14–23; the glucose 6-phosphate product is then fermented to ethanol and CO_2. **(e)** 6 molecules of arabinose + 6 molecules of ATP are converted to 6 molecules of xylulose 5-phosphate, which feed into the pathway in Fig. 14–23 to yield 5 molecules of glucose 6-phosphate, each of which is fermented to yield 3 ATP (they enter as glucose 6-phosphate, not glucose)—15 ATP in all. Overall, you would expect a yield of 15 ATP − 6 ATP = 9 ATP from the 6 arabinose molecules. The other products are 10 molecules of ethanol and 10 molecules of CO_2. **(f)** Given the lower ATP yield, for an amount of growth (i.e., of available ATP) equivalent to growth without the added genes, the engineered *Z. mobilis* must ferment more arabinose, and thus it produces more ethanol. **(g)** One way to allow the use of xylose would be to add the genes for two enzymes: an analog of the *araD* enzyme that converts xylose to ribose by switching the —H and —OH on C-3, and an analog of the *araB* enzyme that phosphorylates ribose at C-5. The resulting ribose 5-phosphate would feed into the existing pathway.

Chapter 15

1. **(a)** 0.0293 **(b)** 308 **(c)** No. Q is much lower than K'_{eq}, indicating that the PFK-1 reaction is far from equilibrium in cells; this reaction is slower than the subsequent reactions in glycolysis. Flux through the glycolytic pathway is largely determined by the activity of PFK-1.

2. **(a)** 1.4×10^{-9} M **(b)** The physiological concentration (0.023 mM) is 16,000 times the equilibrium concentration; this

reaction does not reach equilibrium in the cell. Many reactions in the cell are not at equilibrium.

3. In the absence of O_2, the ATP needs are met by anaerobic glucose metabolism (fermentation to lactate). Because aerobic oxidation of glucose produces far more ATP than does fermentation, less glucose is needed to produce the same amount of ATP.

4. **(a)** There are two binding sites for ATP: a catalytic site and a regulatory site. Binding of ATP to a regulatory site inhibits PFK-1, by reducing V_{max} or increasing K_m for ATP at the catalytic site. **(b)** Glycolytic flux is reduced when ATP is plentiful. **(c)** The graph indicates that increased [ADP] suppresses the inhibition by ATP. Because the adenine nucleotide pool is fairly constant, consumption of ATP leads to an increase in [ADP]. The data show that the activity of PFK-1 may be regulated by the [ATP]/[ADP] ratio.

5. The phosphate group of glucose 6-phosphate is completely ionized at pH 7, giving the molecule an overall negative charge. Because membranes are generally impermeable to electrically charged molecules, glucose 6-phosphate cannot pass from the bloodstream into cells and hence cannot enter the glycolytic pathway and generate ATP. (This is why glucose, once phosphorylated, cannot escape from the cell.)

6. **(a)** *In muscle:* Glycogen breakdown supplies energy (ATP) via glycolysis. Glycogen phosphorylase catalyzes the conversion of stored glycogen to glucose 1-phosphate, which is converted to glucose 6-phosphate, an intermediate in glycolysis. During strenuous activity, skeletal muscle requires large quantities of glucose 6-phosphate. *In the liver:* Glycogen breakdown maintains a steady level of blood glucose between meals (glucose 6-phosphate is converted to free glucose). **(b)** In actively working muscle, ATP flux requirements are very high and glucose 1-phosphate must be produced rapidly, requiring a high V_{max}.

7. **(a)** $[P_i]/[\text{glucose 1-phosphate}] = 3.3/1$ **(b), (c)** The value of this ratio in the cell (>100:1) indicates that [glucose 1-phosphate] is far below the equilibrium value. The rate at which glucose 1-phosphate is removed (through entry into glycolysis) is greater than its rate of production (by the glycogen phosphorylase reaction), so metabolite flow is from glycogen to glucose 1-phosphate. The glycogen phosphorylase reaction is probably the regulatory step in glycogen breakdown.

8. **(a)** increases **(b)** decreases **(c)** increases

9. *Resting:* [ATP] high; [AMP] low; [acetyl-CoA] and [citrate] intermediate. *Running:* [ATP] intermediate; [AMP] high; [acetyl-CoA] and [citrate] low. Glucose flux through glycolysis increases during the anaerobic sprint because (1) the ATP inhibition of glycogen phosphorylase and PFK-1 is partially relieved, (2) AMP stimulates both enzymes, and (3) lower citrate and acetyl-CoA levels relieve their inhibitory effects on PFK-1 and pyruvate kinase, respectively.

10. The migrating bird relies on the highly efficient aerobic oxidation of fats, rather than the anaerobic metabolism of glucose used by a sprinting rabbit. The bird reserves its muscle glycogen for short bursts of energy during emergencies.

11. *Case A:* (f), (3); *Case B:* (c), (3); *Case C:* (h), (4); *Case D:* (d), (6)

12. **(a)** (1) Adipose: fatty acid synthesis slower. (2) Muscle: glycolysis, fatty acid synthesis, and glycogen synthesis slower. (3) Liver: glycolysis faster; gluconeogenesis, glycogen synthesis, and fatty acid synthesis slower; pentose phosphate pathway unchanged. **(b)** (1) Adipose and (3) liver: fatty acid synthesis slower because lack of insulin results in inactive acetyl-CoA carboxylase, the first enzyme of fatty acid synthesis. Glycogen synthesis inhibited by cAMP-dependent phosphorylation (thus activation) of glycogen synthase. (2) Muscle: glycolysis slower because GLUT4 is inactive, so glucose uptake is inhibited. (3) Liver: glycolysis slower because the bifunctional PFK-2/FBPase-2 is converted to the form with active FBPase-2, decreasing [fructose 2,6-bisphosphate], which allosterically stimulates phosphofructokinase and inhibits FBPase-1; this also accounts for the stimulation of gluconeogenesis.

13. **(a)** elevated **(b)** elevated **(c)** elevated

14. **(a)** PKA cannot be activated in response to glucagon or epinephrine, and glycogen phosphorylase is not activated. **(b)** PP1 remains active, allowing it to dephosphorylate glycogen synthase (activating it) and glycogen phosphorylase (inhibiting it). **(c)** Phosphorylase remains phosphorylated (active), increasing the breakdown of glycogen. **(d)** Gluconeogenesis cannot be stimulated when blood glucose is low, leading to dangerously low blood glucose during periods of fasting.

15. The drop in blood glucose triggers release of glucagon by the pancreas. In the liver, glucagon activates glycogen phosphorylase by stimulating its cAMP-dependent phosphorylation and stimulates gluconeogenesis by lowering [fructose 2,6-bisphosphate], thus stimulating FBPase-1.

16. **(a)** Reduced capacity to mobilize glycogen; lowered blood glucose between meals **(b)** Reduced capacity to lower blood glucose after a carbohydrate meal; elevated blood glucose **(c)** Reduced fructose 2,6-bisphosphate (F26BP) in liver, stimulating glycolysis and inhibiting gluconeogenesis **(d)** Reduced F26BP, stimulating gluconeogenesis and inhibiting glycolysis **(e)** Increased uptake of fatty acids and glucose; increased oxidation of both **(f)** Increased conversion of pyruvate to acetyl-CoA; increased fatty acid synthesis.

17. **(a)** Given that each particle contains about 55,000 glucose residues, the equivalent free glucose concentration would be $55{,}000 \times 0.01\ \mu M = 550$ mM, or 0.55 M. This would present a serious osmotic challenge for the cell! (Body fluids have a substantially lower osmolarity.) **(b)** The lower the number of branches, the lower the number of free ends available for glycogen phosphorylase activity, and the slower the rate of glucose release. With no branches, there would be just one site for phosphorylase to act. **(c)** The outer tier of the particle would be too crowded with glucose residues for the enzyme to gain access to cleave bonds and release glucose. **(d)** The number of chains doubles in each succeeding tier: tier 1 has one chain (2^0), tier 2 has two (2^1), tier 3 has four (2^2), and so on. Thus, for t tiers, the number of chains in the outermost tier, C_A, is 2^{t-1}. **(e)** The total number of chains is $2^0 + 2^1 + 2^2 + \ldots 2^{t-1} = 2^t - 1$. Each chain contains g_c glucose molecules, so the total number of glucose molecules, G_T, is $g_c(2t - 1)$. **(f)** Glycogen phosphorylase can release all but four of the glucose residues in a chain of length g_c. Therefore, from each chain in the outer tier it can release $(g_c - 4)$ glucose molecules. Given that there are 2^{t-1} chains in the outer tier, the number of glucose molecules the enzyme can release, G_{PT}, is $(g_c - 4)(2^{t-1})$. **(g)** The volume of a sphere is $\frac{4}{3}\pi r^3$. In this case, r is the thickness of one tier times the number of tiers, or $(0.12g_c + 0.35)t$ nm. Thus $V_s = \frac{4}{3}\pi t^3\,(0.12g_c + 0.35)^3$ nm^3. **(h)** You can show algebraically that the value of g_c that maximizes f is independent of t. Choosing $t = 3$:

g_c	C_A	G_T	G_{PT}	V_s	f
5	4	35	4	11	5.8
6	4	42	8	19	9.7
7	4	49	12	24	12
8	4	56	16	28	14
9	4	63	20	32	15
10	4	70	24	34	16
11	4	77	28	36	16
12	4	84	32	38	17
13	4	91	36	40	17
14	4	98	40	41	17
15	4	100	44	42	16
16	4	110	48	43	16

The optimum value of g_c (i.e., at maximum *f*) is 13. In nature, g_c varies from 12 to 14, which corresponds to *f* values very close to the optimum. If you choose another value for *t*, the numbers will differ but the optimal g_c will still be 13.

Chapter 16

1. (a)
❶ *Citrate synthase:*
Acetyl-CoA + oxaloacetate + H_2O → citrate + CoA
❷ *Aconitase:*
Citrate → isocitrate
❸ *Isocitrate dehydrogenase:*
Isocitrate + NAD^+ → α-ketoglutarate + CO_2 + NADH
❹ *α-Ketoglutarate dehydrogenase:*
α-Ketoglutarate + NAD^+ + CoA → succinyl-CoA + CO_2 + NADH
❺ *Succinyl-CoA synthetase:*
Succinyl-CoA + P_i + GDP → succinate + CoA + GTP
❻ *Succinate dehydrogenase:*
Succinate + FAD → fumarate + $FADH_2$
❼ *Fumarase:*
Fumarate + H_2O → malate
❽ *Malate dehydrogenase:*
Malate + NAD^+ → oxaloacetate + NADH + H^+

(b), (c) ❶ CoA, condensation; ❷ none, isomerization; ❸ NAD^+, oxidative decarboxylation; ❹ NAD^+, CoA, and thiamine pyrophosphate, oxidative decarboxylation; ❺ CoA, substrate-level phosphorylation; ❻ FAD, oxidation; ❼ none, hydration; ❽ NAD^+, oxidation

(d) Acetyl-CoA + $3NAD^+$ + FAD + GDP + P_i + $2H_2O$ → $2CO_2$ + CoA + 3NADH + $FADH_2$ + GTP + $2H^+$

2. Glucose + 4ADP + $4P_i$ + $10NAD^+$ + 2FAD → 4ATP + 10NADH + $2FADH_2$ + $6CO_2$

3. (a) Oxidation; methanol → formaldehyde + [H—H]

(b) Oxidation; formaldehyde → formate + [H—H]

(c) Reduction; CO_2 + [H—H] → formate + H^+

(d) Reduction; glycerate + H^+ + [H—H] → glyceraldehyde + H_2O

(e) Oxidation; glycerol → dihydroxyacetone + [H—H]

(f) Oxidation; $2H_2O$ + toluene → benzoate + H^+ + 3[H—H]

(g) Oxidation; succinate → fumarate + [H—H]

(h) Oxidation; pyruvate + H_2O → acetate + CO_2 + [H—H]

4. From the structural formulas, we see that the carbon-bound H/C ratio of hexanoic acid (11/6) is higher than that of glucose (7/6). Hexanoic acid is more reduced and yields more energy on complete combustion to CO_2 and H_2O.

5. (a) Oxidized; ethanol + NAD^+ → acetaldehyde + NADH + H^+

(b) Reduced; 1,3-bisphosphoglycerate + NADH + H^+ → glyceraldehyde 3-phosphate + NAD^+ + HPO_4^{2-}

(c) Unchanged; pyruvate + H^+ → acetaldehyde + CO_2

(d) Oxidized; pyruvate + NAD^+ → acetate + CO_2 + NADH + H^+

(e) Reduced; oxaloacetate + NADH + H^+ → malate + NAD^+

(f) Unchanged; acetoacetate + H^+ → acetone + CO_2

6. *TPP:* thiazolium ring adds to α carbon of pyruvate, then stabilizes the resulting carbanion by acting as an electron sink. *Lipoic acid:* oxidizes pyruvate to level of acetate (acetyl-CoA), and activates acetate as a thioester. *CoA-SH:* activates acetate as thioester. *FAD:* oxidizes lipoic acid. *NAD^+:* oxidizes FAD.

7. Lack of TPP inhibits pyruvate dehydrogenase; pyruvate accumulates.

8. Oxidative decarboxylation; NAD^+ or $NADP^+$; α-ketoglutarate dehydrogenase

9. Oxygen consumption is a measure of the activity of the first two stages of cellular respiration: glycolysis and the citric acid cycle. The addition of oxaloacetate or malate stimulates the citric acid cycle and thus stimulates respiration. The added oxaloacetate or malate serves a catalytic role, because it is regenerated in the latter part of the citric acid cycle.

10. (a) 5.6×10^{-6} **(b)** 1.1×10^{-8} M **(c)** 28 molecules

11. ADP (or GDP), P_i, CoA-SH, TPP, NAD^+; *not* lipoic acid, which is covalently attached to the isolated enzymes that use it

12. The flavin nucleotides, FMN and FAD, would not be synthesized. Because FAD is required in the citric acid cycle, flavin deficiency would strongly inhibit the cycle.

13. Oxaloacetate might be withdrawn for aspartate synthesis or for gluconeogenesis. Oxaloacetate is replenished by the anaplerotic reactions catalyzed by PEP carboxykinase, PEP carboxylase, malic enzyme, or pyruvate carboxylase (see Fig. 16–16).

14. The terminal phosphoryl group in GTP can be transferred to ADP in a reaction catalyzed by nucleoside diphosphate kinase, with an equilibrium constant of 1.0:

GTP + ADP → GDP + ATP

15. (a) $^-OOC—CH_2—CH_2—COO^-$ (succinate) **(b)** Malonate is a competitive inhibitor of succinate dehydrogenase. **(c)** A block in the citric acid cycle stops NADH formation, which stops electron transfer, which stops respiration. **(d)** A large excess of succinate (substrate) overcomes the competitive inhibition.

16. (a) Add uniformly labeled [^{14}C]glucose and check for the release of $^{14}CO_2$. **(b)** Equally distributed in C-2 and C-3 of oxaloacetate; an infinite number

17. Oxaloacetate equilibrates with succinate, in which C-1 and C-4 are equivalent. Oxaloacetate derived from succinate is labeled at C-1 and C-4, and the PEP derived from it has label at C-1, which gives rise to C-3 and C-4 of glucose.

18. (a) C-1 **(b)** C-3 **(c)** C-3 **(d)** C-2 (methyl group) **(e)** C-4 **(f)** C-4 **(g)** equally distributed in C-2 and C-3

19. Thiamine is required for the synthesis of TPP, a prosthetic group in the pyruvate dehydrogenase and α-ketoglutarate dehydrogenase complexes. A thiamine deficiency reduces the activity of these enzyme complexes and causes the observed accumulation of precursors.

20. No. For every two carbons that enter as acetate, two leave the cycle as CO_2; thus there is no net synthesis of oxaloacetate. Net synthesis of oxaloacetate occurs by the carboxylation of pyruvate, an anaplerotic reaction.

21. Yes, the citric acid cycle would be inhibited. Oxaloacetate is present at relatively low concentrations in mitochondria, and removing it for gluconeogenesis would tend to shift the equilibrium for the citrate synthase reaction toward oxaloacetate.

22. (a) Inhibition of aconitase **(b)** Fluorocitrate; competes with citrate; by a large excess of citrate **(c)** Citrate and fluorocitrate are inhibitors of PFK-1. **(d)** All catabolic processes necessary for ATP production are shut down.

23. *Glycolysis:*
Glucose + $2P_i$ + 2ADP + $2NAD^+$ → 2 pyruvate + 2ATP + 2NADH + $2H^+$ + $2H_2O$

Pyruvate carboxylase reaction:
2 Pyruvate + $2CO_2$ + 2ATP + $2H_2O$ → 2 oxaloacetate + 2ADP + $2P_i$ + $4H^+$

Malate dehydrogenase reaction:
2 Oxaloacetate + 2NADH + $2H^+$ → 2 L-malate + $2NAD^+$

This recycles nicotinamide coenzymes under anaerobic conditions. The overall reaction is

Glucose + $2CO_2$ → 2 L-malate + $4H^+$

This produces four H^+ per glucose, increasing the acidity and thus the tartness of the wine.

24. Net reaction: 2 Pyruvate + ATP + $2NAD^+$ + H_2O → α-ketoglutarate + CO_2 + ADP + P_i + 2NADH + $3H^+$

25. The cycle participates in catabolic and anabolic processes. For example, it generates ATP by substrate oxidation, but also provides precursors for amino acid synthesis (see Fig. 16–16).

26. **(a)** decreases **(b)** increases **(c)** decreases

27. **(a)** Citrate is produced through the action of citrate synthase on oxaloacetate and acetyl-CoA. Citrate synthase can be used for net synthesis of citrate when (1) there is a continuous influx of new oxaloacetate and acetyl-CoA and (2) isocitrate synthesis is restricted, as in a medium low in Fe^{3+}. Aconitase requires Fe^{3+}, so an Fe^{3+}-restricted medium restricts the synthesis of aconitase.

(b) Sucrose + H_2O → glucose + fructose

Glucose + $2P_i$ + 2ADP + $2NAD^+$ → 2 pyruvate + 2ATP + 2NADH + $2H^+$ + $2H_2O$

Fructose + $2P_i$ + 2ADP + $2NAD^+$ → 2 pyruvate + 2ATP + 2NADH + $2H^+$ + $2H_2O$

2 Pyruvate + $2NAD^+$ + 2CoA → 2 acetyl-CoA + 2NADH + $2H^+$ + $2CO_2$

2 Pyruvate + $2CO_2$ + 2ATP + $2H_2O$ → 2 oxaloacetate + 2ADP + $2P_i$ + $4H^+$

2 Acetyl-CoA + 2 oxaloacetate + $2H_2O$ → 2 citrate + 2CoA

The overall reaction is

Sucrose + H_2O + $2P_i$ + 2ADP + $6NAD^+$ → 2 citrate + 2ATP + 6NADH + $10H^+$

(c) The overall reaction consumes NAD^+. Because the cellular pool of this oxidized coenzyme is limited, it must be recycled by the electron-transfer chain with consumption of O_2. Consequently, the overall conversion of sucrose to citric acid is an aerobic process and requires molecular oxygen.

28. Succinyl-CoA is an intermediate of the citric acid cycle; its accumulation signals reduced flux through the cycle, calling for reduced entry of acetyl-CoA into the cycle. Citrate synthase, by regulating the primary oxidative pathway of the cell, regulates the supply of NADH and thus the flow of electrons from NADH to O_2.

29. Fatty acid catabolism increases [acetyl-CoA], which stimulates pyruvate carboxylase. The resulting increase in [oxaloacetate] stimulates acetyl-CoA consumption by the citric acid cycle, and [citrate] rises, inhibiting glycolysis at the level of PFK-1. In addition, increased [acetyl-CoA] inhibits the pyruvate dehydrogenase complex, slowing the utilization of pyruvate from glycolysis.

30. Oxygen is needed to recycle NAD^+ from the NADH produced by the oxidative reactions of the citric acid cycle. Reoxidation of NADH occurs during mitochondrial oxidative phosphorylation.

31. Increased [NADH]/[NAD^+] inhibits the citric acid cycle by mass action at the three NAD^+-reducing steps; high [NADH] shifts equilibrium toward NAD^+.

32. Toward citrate; ΔG for the citrate synthase reaction under these conditions is about −8 kJ/mol.

33. Steps 4 and 5 are essential in the reoxidation of the enzyme's reduced lipoamide cofactor.

34. The citric acid cycle is so central to metabolism that a serious defect in any cycle enzyme would probably be lethal to the embryo.

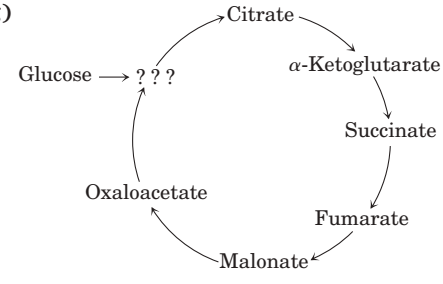
35. The first enzyme in each path is under reciprocal allosteric regulation. Inhibition of one path shunts isocitrate into the other path.

36. **(a)** The only reaction in muscle tissue that consumes significant amounts of oxygen is cellular respiration, so O_2 consumption is a good proxy for respiration. **(b)** Freshly prepared muscle tissue contains some residual glucose; O_2 consumption is due to oxidation of this glucose. **(c)** Yes. Because the amount of O_2 consumed increased when citrate or 1-phosphoglycerol was added, both can serve as substrate for cellular respiration in this system. **(d)** *Experiment I:* Citrate is causing much more O_2 consumption than would be expected from its complete oxidation. Each molecule of Citrate seems to be acting as though it were more than one molecule. The only possible explanation is that each molecule of citrate functions more than once in the reaction—which is how a catalyst operates. *Experiment II:* The key is to calculate the excess O_2 consumed by each sample compared with the control (sample 1).

Sample	Substrate(s) added	μL O_2 absorbed	Excess μL O_2 consumed
1	No extra	342	0
2	0.3 mL 0.2 M 1-phosphoglycerol	757	415
3	0.15 mL 0.02 M citrate	431	89
4	0.3 mL 0.2 M 1-phosphoglycerol + 0.15 mL 0.02 M citrate	1,385	1,043

If both citrate and 1-phosphoglycerol were simply substrates for the reaction, you would expect the excess O_2 consumption by sample 4 to be the sum of the individual excess consumptions by samples 2 and 3 (415 μL + 89 μL = 504 μL). However, the excess consumption when both substrates are present is roughly twice this amount (1,043 μL). Thus citrate increases the ability of the tissue to metabolize 1-phosphoglycerol. This behavior is typical of a catalyst. Both experiments (I and II) are required to make this case convincing. Based on experiment I only, citrate is somehow accelerating the reaction, but it is not clear whether it acts by helping substrate metabolism or by some other mechanism. Based on experiment II only, it is not clear which molecule is the catalyst, citrate or 1-phosphoglycerol. Together, the experiments show that citrate is acting as a "catalyst" for the oxidation of 1-phosphoglycerol. **(e)** Given that the pathway can consume citrate (see sample 3), if citrate is to act as a catalyst it must be regenerated. If the set of reactions first consumes then regenerates citrate, it must be a circular rather than a linear pathway. **(f)** When the pathway is blocked at α-ketoglutarate dehydrogenase, citrate is converted to α-ketoglutarate but the pathway goes no further. Oxygen is consumed by reoxidation of the NADH produced by isocitrate dehydrogenase.

(g)



This differs from Fig. 16–7 in that it does not include *cis*-aconitate and isocitrate (between citrate and α-ketoglutarate), or succinyl-CoA, or acetyl-CoA. **(h)** Establishing a quantitative conversion was essential to rule out a branched or other, more complex pathway.

Chapter 17

1. The fatty acid portion; the carbons in fatty acids are more reduced than those in glycerol.

2. **(a)** 4.0×10^5 kJ (9.6×10^4 kcal) **(b)** 48 days **(c)** 0.48 lb/day

3. The first step in fatty acid oxidation is analogous to the conversion of succinate to fumarate; the second step, to the conversion of fumarate to malate; the third step, to the conversion of malate to oxaloacetate.

4. 8 cycles; the last releases 2 acetyl-CoA.

5. **(a)** $R—COO^- + ATP \rightarrow$ acyl-AMP + PP_i

Acyl-AMP + CoA $\rightarrow$ acyl-CoA + AMP

(b) Irreversible hydrolysis of PP_i to $2P_i$ by cellular inorganic pyrophosphatase

6. *cis*-Δ^3-Dodecanoyl-CoA; it is converted to *cis*-Δ^2-dodecanoyl-CoA, then β-hydroxydodecanoyl-CoA.

7. 4 acetyl-CoA and 1 propionyl-CoA

8. Yes. Some of the tritium is removed from palmitate during the dehydrogenation reactions of β oxidation. The removed tritium appears as tritiated water.

9. Fatty acyl groups condensed with CoA in the cytosol are first transferred to carnitine, releasing CoA, then transported into the mitochondrion, where they are again condensed with CoA. The cytosolic and mitochondrial pools of CoA are thus kept separate, and no radioactive CoA from the cytosolic pool enters the mitochondrion.

10. **(a)** In the pigeon, β oxidation predominates; in the pheasant, anaerobic glycolysis of glycogen predominates. **(b)** Pigeon muscle would consume more O_2. **(c)** Fat contains more energy per gram than glycogen does. In addition, the anaerobic breakdown of glycogen is limited by the tissue's tolerance to lactate buildup. Thus the pigeon, operating on the oxidative catabolism of fats, is the long-distance flyer. **(d)** These enzymes are the regulatory enzymes of their respective pathways and thus limit ATP production rates.

11. Malonyl-CoA would no longer inhibit fatty acid entry into the mitochondrion and β oxidation, so there might be a futile cycle of simultaneous fatty acid synthesis in the cytosol and fatty acid breakdown in mitochondria.

12. **(a)** The carnitine-mediated entry of fatty acids into mitochondria is the rate-limiting step in fatty acid oxidation. Carnitine deficiency slows fatty acid oxidation; added carnitine increases the rate. **(b)** All increase the metabolic need for fatty acid oxidation. **(c)** Carnitine deficiency might result from a deficiency of lysine, its precursor, or from a defect in one of the enzymes in the biosynthesis of carnitine.

13. Oxidation of fats releases metabolic water; 1.4 L of water per kg of tripalmitoylglycerol (ignores the small contribution of glycerol to the mass).

14. The bacteria can be used to completely oxidize hydrocarbons to CO_2 and H_2O. However, contact between hydrocarbons and bacterial enzymes may be difficult to achieve. Bacterial nutrients such as nitrogen and phosphorus may be limiting and inhibit growth.

15. **(a)** M_r 136; phenylacetic acid **(b)** Even

16. Because the mitochondrial pool of CoA is small, CoA must be recycled from acetyl-CoA via the formation of ketone bodies. This allows the operation of the β-oxidation pathway, necessary for energy production.

17. **(a)** Glucose yields pyruvate via glycolysis, and pyruvate is the main source of oxaloacetate. Without glucose in the diet, [oxaloacetate] drops and the citric acid cycle slows. **(b)** Odd-numbered; propionate conversion to succinyl-CoA provides intermediates for the citric acid cycle and four-carbon precursors for gluconeogenesis.

18. For the odd-chain heptanoic acid, β oxidation produces propionyl-CoA, which can be converted in several steps to oxaloacetate, a starting material for gluconeogenesis. The even-chain fatty acid cannot support gluconeogenesis, because it is entirely oxidized to acetyl-CoA.

19. β Oxidation of ω-fluorooleate forms fluoroacetyl-CoA, which enters the citric acid cycle and produces fluorocitrate, a powerful inhibitor of aconitase. Inhibition of aconitase shuts down the citric acid cycle. Without reducing equivalents from the citric acid cycle, oxidative phosphorylation (ATP synthesis) is fatally slowed.

20. Ser to Ala: blocks β oxidation in mitochondria. Ser to Asp: blocks fatty acid synthesis, stimulates β oxidation.

21. Response to glucagon or epinephrine would be prolonged, giving a greater mobilization of fatty acids in adipocytes.

22. Enz-FAD, having a more positive standard reduction potential, is a better electron acceptor than NAD^+, and the reaction is driven in the direction of fatty acyl–CoA oxidation. This more favorable equilibrium is obtained at the cost of 1 ATP; only 1.5 ATP are produced per $FADH_2$ oxidized in the respiratory chain (vs. 2.5 per NADH).

23. 9 turns; arachidic acid, a 20-carbon saturated fatty acid, yields 10 molecules of acetyl-CoA, the last two formed in the ninth turn.

24. See Fig. 17–12. [3-^{14}C]Succinyl-CoA is formed, which gives rise to oxaloacetate labeled at C-2 and C-3.

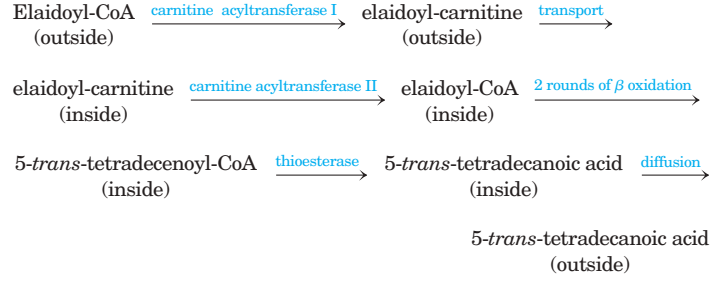
25. Phytanic acid $\rightarrow$ pristanic acid $\rightarrow$ propionyl-CoA $\rightarrow \rightarrow \rightarrow$ succinyl-CoA $\rightarrow$ succinate $\rightarrow$ fumarate $\rightarrow$ malate. All malate carbons would be labeled, but C-1 and C-4 would have only half as much label as C-2 and C-3.

26. ATP hydrolysis in the energy-requiring reactions of a cell takes up water in the reaction ATP + $H_2O \rightarrow$ ADP + P_i; thus, in the steady state, there is no *net* production of H_2O.

27. Methylmalonyl-CoA mutase requires the cobalt-containing cofactor formed from vitamin B_{12}.

28. Mass lost per day is about 0.66 kg, or about 140 kg in 7 months. Ketosis could be avoided by degradation of nonessential body proteins to supply amino acid skeletons for gluconeogenesis.

29. **(a)** Fatty acids are converted to their CoA derivatives by enzymes in the cytoplasm; the acyl-CoAs are then imported into mitochondria for oxidation. Given that the researchers were using isolated mitochondria, they had to use CoA derivatives. **(b)** Stearoyl-CoA was rapidly converted to 9 acetyl-CoA by the β-oxidation pathway. All intermediates reacted rapidly and none were detectable at significant levels. **(c)** Two rounds. Each round removes two carbon atoms, thus two rounds convert an 18-carbon to a 14-carbon fatty acid and 2 acetyl-CoA. **(d)** The K_m is higher for the trans isomer than for the cis, so a higher concentration of trans isomer is required for the same rate of breakdown. Roughly speaking, the trans isomer binds less well than the cis, probably because differences in shape, even though not at the target site for the enzyme, affect substrate binding to the enzyme. **(e)** The substrate for LCAD/VLCAD builds up differently, depending on the particular substrate; this is expected for the rate-limiting step in a pathway. **(f)** The kinetic parameters show that the trans isomer is a poorer substrate than the cis for LCAD, but there is little difference for VLCAD. Because it is a poorer substrate, the trans isomer accumulates to higher levels than the cis. **(g)** One possible pathway is shown below (indicating "inside" and "outside" mitochondria).



(h) It is correct insofar as trans fats are broken down less efficiently than cis fats, and thus trans fats may "leak" out of mitochondria. It is incorrect to say that trans fats are not broken down by cells; they are broken down, but at a slower rate than cis fats.

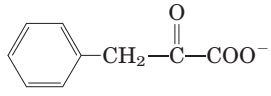
Chapter 18

1.

(a) $^{-}OOC—CH_2—\overset{\overset{O}{\|}}{C}—COO^{-}$ Oxaloacetate

(b) $^{-}OOC—CH_2—CH_2—\overset{\overset{O}{\|}}{C}—COO^{-}$ α-Ketoglutarate

(c) $CH_3—\overset{\overset{O}{\|}}{C}—COO^{-}$ Pyruvate

(d)  Phenylpyruvate

2. This is a coupled-reaction assay. The product of the slow transamination (pyruvate) is rapidly consumed in the subsequent "indicator reaction" catalyzed by lactate dehydrogenase, which consumes NADH. Thus the rate of disappearance of NADH is a measure of the rate of the aminotransferase reaction. The indicator reaction is monitored by observing the decrease in absorption of NADH at 340 nm with a spectrophotometer.

3. Alanine and glutamine play special roles in the transport of amino groups from muscle and from other nonhepatic tissues, respectively, to the liver.

4. No. The nitrogen in alanine can be transferred to oxaloacetate via transamination, to form aspartate.

5. 15 mol of ATP per mole of lactate; 13 mol of ATP per mole of alanine, when nitrogen removal is included

6. **(a)** Fasting resulted in low blood glucose; subsequent administration of the experimental diet led to rapid catabolism of glucogenic amino acids. **(b)** Oxidative deamination caused the rise in NH_3 levels; the absence of arginine (an intermediate in the urea cycle) prevented conversion of NH_3 to urea; arginine is not synthesized in sufficient quantities in the cat to meet the needs imposed by the stress of the experiment. This suggests that arginine is an essential amino acid in the cat's diet. **(c)** Ornithine is converted to arginine by the urea cycle.

7. H_2O + glutamate + $NAD^+ \rightarrow$ α-ketoglutarate + NH_4^+ + NADH + H^+

$NH_4^+ + 2ATP + H_2O + CO_2 \rightarrow$ carbamoyl phosphate + 2ADP + P_i + $3H^+$

Carbamoyl phosphate + ornithine → citrulline + P_i + H^+

Citrulline + aspartate + ATP → argininosuccinate + AMP + PP_i + H^+

Argininosuccinate → arginine + fumarate

Fumarate + H_2O → malate

Malate + NAD^+ → oxaloacetate + NADH + H^+

Oxaloacetate + glutamate → aspartate + α-ketoglutarate

Arginine + H_2O → urea + ornithine

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2 Glutamate + CO_2 + $4H_2O$ + $2NAD^+$ + $3ATP \rightarrow$ 2 α-ketoglutarate + 2NADH + $7H^+$ + urea + 2ADP + AMP + PP_i + $2P_i$ (1)

Additional reactions that need to be considered:

$AMP + ATP \rightarrow 2ADP$ (2)

$O_2 + 8H^+ + 2NADH + 6ADP + 6P_i \rightarrow 2NAD^+ + 6ATP + 8H_2O$ (3)

$H_2O + PP_i \rightarrow 2P_i + H^+$ (4)

Summing equations (1) through (4),

2 Glutamate + CO_2 + O_2 + 2ADP + $2P_i \rightarrow$ 2 α-ketoglutarate + urea + $3H_2O$ + 2ATP

8. The second amino group introduced into urea is transferred from aspartate, which is generated during the transamination of glutamate to oxaloacetate, a reaction catalyzed by aspartate aminotransferase. Approximately one-half of all the amino groups excreted as urea must pass through the aspartate aminotransferase reaction, making this the most highly active aminotransferase.

9. **(a)** A person on a diet consisting only of protein must use amino acids as the principal source of metabolic fuel. Because the catabolism of amino acids requires the removal of nitrogen as urea, the process consumes abnormally large quantities of water to dilute and excrete the urea in the urine. Furthermore, electrolytes in the "liquid protein" must be diluted with water and excreted. If the daily water loss through the kidney is not balanced by a sufficient water intake, a net loss of body water results. **(b)** When considering the nutritional benefits of protein, one must keep in mind the total amount of amino acids needed for protein synthesis and the distribution of amino acids in the dietary protein. Gelatin contains a nutritionally unbalanced distribution of amino acids. As large amounts of gelatin are ingested and the excess amino acids are catabolized, the capacity of the urea cycle may be exceeded, leading to ammonia toxicity. This is further complicated by the dehydration that may result from excretion of large quantities of urea. A combination of these two factors could produce coma and death.

10. Lysine and leucine

11. **(a)** Phenylalanine hydroxylase; a low-phenylalanine diet **(b)** The normal route of phenylalanine metabolism via hydroxylation to tyrosine is blocked, and phenyalanine accumulates. **(c)** Phenylalanine is transformed to phenylpyruvate by transamination, and then to phenyllactate by reduction. The transamination reaction has an equilibrium constant of 1.0, and phenylpyruvate is formed in significant amounts when phenylalanine accumulates. **(d)** Because of the deficiency in production of tyrosine, which is a precursor of melanin, the pigment normally present in hair.

12. Catabolism of the carbon skeletons of valine, methionine, and isoleucine is impaired because a functional methylmalonyl-CoA mutase (a coenzyme B_{12} enzyme) is absent. The physiological effects of loss of this enzyme are described in Table 18–2 and Box 18–2.

13. The vegan diet lacks vitamin B_{12}, leading to the increase in homocysteine and methylmalonate (reflecting the deficiencies in methionine synthase and methylmalonic acid mutase, respectively) in individuals on the diet for several years. Dairy products provide some vitamin B_{12} in the lactovegetarian diet.

14. The genetic forms of pernicious anemia generally arise as a result of defects in the pathway that mediates absorption of dietary vitamin B_{12} (see Box 17–2). Because dietary supplements are not absorbed in the intestine, these conditions are treated by injecting supplementary B_{12} directly into the bloodstream.

15. The mechanism is identical to that for serine dehydratase (see Fig. 18–20a) except that the extra methyl group of threonine is retained, yielding α-ketobutyrate instead of pyruvate.

16. **(a)** $^{15}NH_2—CO—^{15}NH_2$

(b) $^{-}OO^{14}C—CH_2—CH_2—^{14}COO^{-}$

(c) $R—NH—\overset{\overset{^{15}NH}{\|}}{C}—^{15}NH_2$

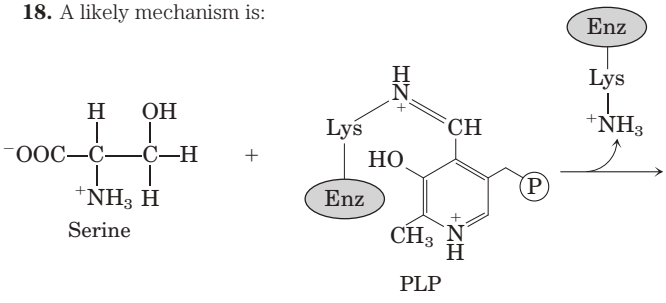
(d) $R—NH—\overset{\overset{O}{\|}}{C}—^{15}NH_2$

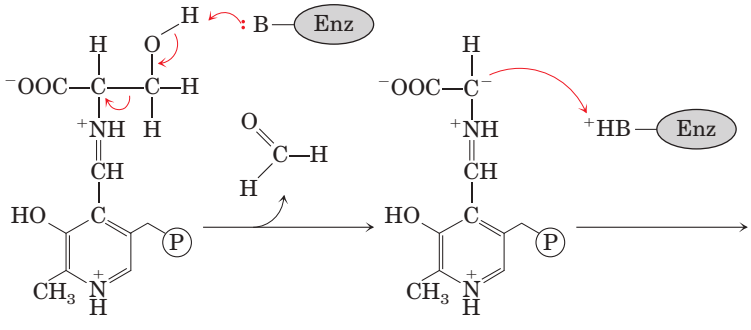
(e) No label

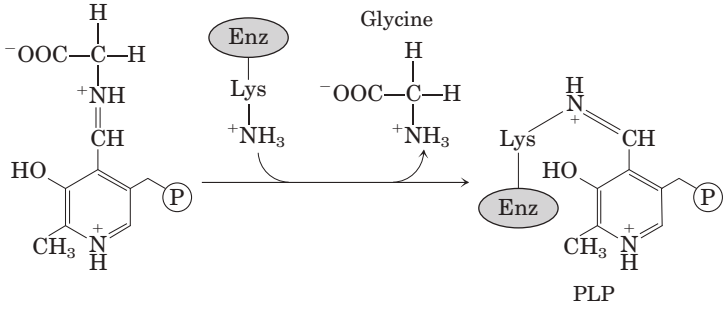
(f) $^{-}OO^{14}C—\overset{\overset{^{15}NH_2}{|}}{\underset{\underset{H}{|}}{C}}—CH_2—^{14}COO^{-}$

17. **(a)** Isoleucine ❶⟶ II ❷⟶ IV ❸⟶ I ❹⟶ V ❺⟶ III ❻⟶ acetyl-CoA + propionyl-CoA **(b)** Step ❶ transamination, no analogous reaction, PLP; ❷ oxidative decarboxylation, analogous to the pyruvate dehydrogenase reaction, NAD^+, TPP, lipoate, FAD; ❸ oxidation, analogous to the succinate dehydrogenase reaction, FAD; ❹ hydration, analogous to the fumarase reaction, no cofactor; ❺ oxidation, analogous to the malate dehydrogenase reaction, NAD^+; ❻ thiolysis (reverse aldol condensation), analogous to the thiolase reaction, CoA.

18. A likely mechanism is:







The formaldehyde (HCHO) produced in the second step reacts rapidly with tetrahydrofolate at the enzyme active site to produce N^5,N^{10}-methylenetetrahydrofolate (see Fig. 18–17).

19. **(a)** Transamination; no analogies; PLP. **(b)** Oxidative decarboxylation; analogous to oxidative decarboxylation of pyruvate to acetyl-CoA prior to entry into the citric acid cycle, and of α-ketoglutarate to succinyl-CoA in the citric acid cycle; NAD^+, FAD, lipoate, and TPP. **(c)** Dehydrogenation (oxidation); analogous to dehydrogenation of succinate to fumarate in the citric acid cycle, and of fatty acyl–CoA to enoyl-CoA in β oxidation; FAD. **(d)** Carboxylation; no analogies in citric acid cycle or β oxidation; ATP and biotin. **(e)** Hydration; analogous to hydration of fumarate to malate in the citric acid cycle, and of enoyl-CoA to 3-hydroxyacyl-CoA in β oxidation; no cofactors. **(f)** Reverse aldol reaction; analogous to reverse of citrate synthase reaction in the citric acid cycle; no cofactors

20. **(a)** Leucine; valine; isoleucine **(b)** Cysteine (derived from cystine). If cysteine were decarboxylated as shown in Fig. 18–6, it would yield $H_3N—CH_2—CH_2—SH$, which could be oxidized to taurine. **(c)** The January 1957 blood shows significantly elevated levels of isoleucine, leucine, methionine, and valine; the January 1957 urine, significantly elevated isoleucine, leucine, taurine, and valine. **(d)** All patients had high levels of isoleucine, leucine, and valine in both blood and urine, suggesting a defect in the breakdown of these amino acids. Given that the urine also contained high levels of the keto forms of these three amino acids, the block in the pathway must occur after deamination but before dehydrogenation (as shown in Fig. 18–28). **(e)** The model does not explain the high levels of methionine in blood and taurine in urine. The high taurine levels may be due to the death of brain cells during the end stage of the disease. However, the reason for high levels of methionine in blood are unclear; the pathway of methionine degradation is not linked with the degradation of branched-chain amino acids. Increased methionine could be a secondary effect of buildup of the other amino acids. It is important to keep in mind that the January 1957 samples were from an individual who was dying, so comparing blood and urine results with those of a healthy individual may not be appropriate. **(f)** The following information is needed (and was eventually obtained by other workers): (1) The dehydrogenase activity is significantly reduced or missing in individuals with maple syrup urine disease. (2) The disease is inherited as a single-gene defect. (3) The defect occurs in a gene encoding all or part of the dehydrogenase. (4) The genetic defect leads to production of inactive enzyme.

Chapter 19

1. *Reaction (1):* (a), (d) NADH; (b), (e) E-FMN; (c) NAD^+/NADH and E-FMN/$FMNH_2$

Reaction (2): (a), (d) E-$FMNH_2$; (b), (e) Fe^{3+}; (c) E-FMN/$FMNH_2$ and Fe^{3+}/Fe^{2+}

Reaction (3): (a), (d) Fe^{2+}; (b), (e) Q; (c) Fe^{3+}/Fe^{2+} and Q/QH_2

2. The side chain makes ubiquinone soluble in lipids and allows it to diffuse in the semifluid membrane.

3. From the difference in standard reduction potential ($\Delta E'°$) for each pair of half-reactions, one can calculate $\Delta G'°$. The oxidation of succinate by FAD is favored by the negative standard free-energy change ($\Delta G'° = -3.7$ kJ/mol). Oxidation by NAD^+ would require a large, positive, standard free-energy change ($\Delta G'° = 68$ kJ/mol).

4. **(a)** All carriers reduced; CN^- blocks the reduction of O_2 catalyzed by cytochrome oxidase. **(b)** All carriers reduced; in the absence of O_2, the reduced carriers are not reoxidized. **(c)** All carriers oxidized. **(d)** Early carriers more reduced; later carriers more oxidized.

5. **(a)** Inhibition of NADH dehydrogenase by rotenone decreases the rate of electron flow through the respiratory chain, which in turn decreases the rate of ATP production. If this reduced rate is unable to meet the organism's ATP requirements, the organism dies. **(b)** Antimycin A strongly inhibits the oxidation of Q in the respiratory chain, reducing the rate of electron transfer and leading to the consequences described in (a). **(c)** Because antimycin A blocks *all* electron flow to oxygen, it is a more potent poison than rotenone, which blocks electron flow from NADH but not from $FADH_2$.

6. **(a)** The rate of electron transfer necessary to meet the ATP demand increases, and thus the P/O ratio decreases. **(b)** High concentrations of uncoupler produce P/O ratios near zero. The P/O ratio decreases, and more fuel must be oxidized to generate the same amount of ATP. The extra heat released by this oxidation raises the body temperature. **(c)** Increased activity of

the respiratory chain in the presence of an uncoupler requires the degradation of additional fuel. By oxidizing more fuel (including fat reserves) to produce the same amount of ATP, the body loses weight. When the P/O ratio approaches zero, the lack of ATP results in death.

7. Valinomycin acts as an uncoupler. It combines with K^+ to form a complex that passes through the inner mitochondrial membrane, dissipating the membrane potential. ATP synthesis decreases, which causes the rate of electron transfer to increase. This results in an increase in the H^+ gradient, O_2 consumption, and amount of heat released.

8. **(a)** The formation of ATP is inhibited. **(b)** The formation of ATP is tightly coupled to electron transfer: 2,4-dinitrophenol is an uncoupler of oxidative phosphorylation. **(c)** Oligomycin

9. Cytosolic malate dehydrogenase plays a key role in the transport of reducing equivalents across the inner mitochondrial membrane via the malate-aspartate shuttle.

10. **(a)** Glycolysis becomes anaerobic. **(b)** Oxygen consumption ceases. **(c)** Lactate formation increases. **(d)** ATP synthesis decreases to 2 ATP/glucose.

11. The steady-state concentration of P_i in the cell is much higher than that of ADP. The P_i released by ATP hydrolysis changes total $[P_i]$ very little.

12. The response to (a) increased [ADP] is faster because the response to (b) reduced pO_2 requires protein synthesis.

13. **(a)** NADH is reoxidized via electron transfer instead of lactic acid fermentation. **(b)** Oxidative phosphorylation is more efficient. **(c)** The high mass-action ratio of the ATP system inhibits phosphofructokinase-1.

14. Fermentation to ethanol could be accomplished in the presence of O_2, which is an advantage because strict anaerobic conditions are difficult to maintain. The Pasteur effect is not observed, since the citric acid cycle and electron-transfer chain are inactive.

15. More-efficient electron transfer between complexes.

16. **(a)** External medium: 4.0×10^{-8} M; matrix: 2.0×10^{-8} M **(b)** $[H^+]$ gradient contributes 1.7 kJ/mol toward ATP synthesis **(c)** 21 **(d)** No **(e)** From the overall transmembrane potential

17. **(a)** 0.91 μmol/s · g **(b)** 5.5 s; to provide a constant level of ATP, regulation of ATP production must be tight and rapid.

18. 53 μmol/s · g. With a steady state [ATP] of 7.0 μmol/g, this is equivalent to 10 turnovers of the ATP pool per second; the reservoir would last about 0.13 s.

19. Reactive oxygen species react with macromolecules, including DNA. If a mitochondrial defect leads to increased production of ROS, the nuclear genes that encode proto-oncogenes can be damaged, producing oncogenes and leading to unregulated cell division and cancer (see Section 12.12).

20. Different extents of heteroplasmy for the defective gene produce different degrees of defective mitochondrial function.

21. The inner mitochondrial membrane is impermeable to NADH, but the reducing equivalents of NADH are transferred (shuttled) through the membrane indirectly: they are transferred to oxaloacetate in the cytosol, the resulting malate is transported into the matrix, and mitochondrial NAD^+ is reduced to NADH.

22. The citric acid cycle is stalled for lack of an acceptor of electrons from NADH. Pyruvate produced by glycolysis cannot enter the cycle as acetyl-CoA; accumulated pyruvate is transaminated to alanine and exported to the liver.

23. Pyruvate dehydrogenase is located in mitochondria, glyceraldehyde 3-phosphate dehydrogenase in the cytosol. The NAD pools are separated by the inner mitochondrial membrane.

24. Complete lack of glucokinase (two defective alleles) makes it impossible to carry out glycolysis at a sufficient rate to raise [ATP] to the threshold required for insulin secretion.

25. Defects in Complex II result in increased production of ROS, damage to DNA, and mutations that lead to unregulated cell division (cancer; see Section 12.12). It is not clear why the cancer tends to occur in the midgut.

26. For the maximum photosynthetic rate, PSI (which absorbs light of 700 nm) and PSII (which absorbs light of 680 nm) must be operating simultaneously.

27. The extra weight comes from the water consumed in the overall reaction.

28. Purple sulfur bacteria use H_2S as the hydrogen donor in photosynthesis. No O_2 is evolved, because the single photosystem lacks the manganese-containing water-splitting complex.

29. 0.44

30. **(a)** Stops **(b)** Slows; some electron flow continues by the cyclic pathway.

31. During illumination, a proton gradient is established. When ADP and P_i are added, ATP synthesis is driven by the gradient, which becomes exhausted in the absence of light.

32. DCMU blocks electron transfer between PSII and the first site of ATP production.

33. In the presence of venturicidin, proton movement through the CF_oCF_1 complex is blocked, and electron flow (oxygen evolution) continues only until the free-energy cost of pumping protons against the rising proton gradient equals the free energy available in a photon. DNP, by dissipating the proton gradient, restores electron flow and oxygen evolution.

34. **(a)** 56 kJ/mol **(b)** 0.29 V

35. From the difference in reduction potentials, one can calculate that $\Delta G'^\circ = 15$ kJ/mol for the redox reaction. Fig. 19–48 shows that the energy of photons in any region of the visible spectrum is more than sufficient to drive this endergonic reaction.

36. 1.35×10^{-77}; the reaction is highly unfavorable! In chloroplasts, the input of light energy overcomes this barrier.

37. −920 kJ/mol

38. No. The electrons from H_2O flow to the artificial electron acceptor Fe^{3+}, not to $NADP^+$.

39. About once every 0.1 s; 1 in 10^8 is excited.

40. Light of 700 nm excites PSI but not PSII; electrons flow from P700 to $NADP^+$, but no electrons flow from P680 to replace them. When light of 680 nm excites PSII, electrons tend to flow to PSI, but the electron carriers between the two photosystems quickly become completely reduced.

41. No. The excited electron from P700 returns to refill the electron "hole" created by illumination. PSII is not needed to supply electrons, and no O_2 is evolved from H_2O. NADPH is not formed, because the excited electron returns to P700.

42. **(a)** (1) The presence of Mg^{2+} supports the hypothesis that chlorophyll is directly involved in catalysis of the phosphorylation reaction: ADP + $P_i \rightarrow$ ATP. (2) Many enzymes (or other proteins) that contain Mg^{2+} are not phosphorylating enzymes, so the presence of Mg^{2+} in chlorophyll does not prove its role in phosphorylation reactions. (3) The presence of Mg^{2+} is essential to chlorophyll's photochemical properties: light absorption and electron transfer. **(b)** (1) Enzymes catalyze reversible reactions, so an isolated enzyme that can, under certain laboratory conditions, catalyze removal of a phosphoryl group could probably, under different conditions (such as in cells), catalyze addition of a phosphoryl group. So it is plausible that chlorophyll could be involved in the phosphorylation of ADP. (2) There are two possible explanations: the chlorophyll protein is a phosphatase only and does not catalyze ADP phosphorylation under cellular conditions, or the crude preparation contains a contaminating phosphatase activity that is unconnected to the photosynthetic reactions. (3) It is likely that the preparation was contaminated with a nonphotosynthetic

phosphatase activity. **(c)** (1) This light inhibition is what one would expect if the chlorophyll protein catalyzed the reaction ADP + P_i + light → ATP. Without light, the reverse reaction, a dephosphorylation, would be favored. In the presence of light, energy is provided and the equilibrium would shift to the right, reducing the phosphatase activity. (2) This inhibition must be an artifact of the isolation or assay methods. (3) It is unlikely that the crude preparation methods in use at the time preserved intact chloroplast membranes, so the inhibition must be an artifact. **(d)** (1) In the presence of light, ATP is synthesized and other phosphorylated intermediates are consumed. (2) In the presence of light, glucose is produced and is metabolized by cellular respiration to produce ATP, with changes in the levels of phosphorylated intermediates. (3) In the presence of light, ATP is produced and other phosphorylated intermediates are consumed. **(e)** Light energy is used to produce ATP (as in the Emerson model) *and* is used to produce reducing power (as in the Rabinowitch model). **(f)** The approximate stoichiometry for photophosphorylation (Chapter 19) is that 8 photons yield 2 NADPH and about 3 ATP. Two NADPH and 3 ATP are required to reduce 1 CO_2 (Chapter 20). Thus, at a minimum, 8 photons are required per CO_2 molecule reduced. This is in good agreement with Rabinowitch's value. **(g)** Because the energy of light is used to produce *both* ATP and NADPH, each photon absorbed contributes more than just 1 ATP for photosynthesis. The process of energy extraction from light is more efficient than Rabinowitch supposed, and plenty of energy is available for this process—even with red light.

Chapter 20

1. Within subcellular organelles, concentrations of specific enzymes and metabolites are elevated; separate pools of cofactors and intermediates are maintained; regulatory mechanisms affect only one set of enzymes and pools.

2. This observation suggests that ATP and NADPH are generated in the light and are essential for CO_2 fixation; conversion stops as the supply of ATP and NADPH becomes exhausted. Furthermore, some enzymes are switched off in the dark.

3. X is 3-phosphoglycerate; Y is ribulose 1,5-bisphosphate.

4. Ribulose 5-phosphate kinase, fructose 1,6-bisphosphatase, sedoheptulose 1,7-bisphosphatase, and glyceraldehyde 3-phosphate dehydrogenase; all are activated by reduction of a critical disulfide bond to a pair of sulfhydryls; iodoacetate reacts irreversibly with free sulfhydryls.

5. To carry out the disulfide exchange reaction that activates the Calvin cycle enzymes, thioredoxin needs both of its sulfhydryl groups.

6. Reductive pentose phosphate pathway regenerates ribulose 1,5-bisphosphate from triose phosphates produced during photosynthesis. Oxidative pentose phosphate pathway provides NADPH for reductive biosynthesis and pentose phosphates for nucleotide synthesis.

7. Both types of "respiration" occur in plants, consume O_2, and produce CO_2. (Mitochondrial respiration also occurs in animals.) Mitochondrial respiration occurs continuously; electrons derived from various fuels are passed through a chain of carriers in the inner mitochondrial membrane to O_2. Photorespiration occurs in chloroplasts, peroxisomes, and mitochondria. Photorespiration occurs during the daytime, when photosynthetic carbon fixation is occurring; mitochondrial respiration occurs primarily at night, or during cloudy days. The path of electron flow in photorespiration is shown in Fig. 20–21; that for mitochondrial respiration, in Fig. 19–19.

8. This hypothesis assumes directed evolution, or evolution with a purpose—ideas not generally accepted by evolutionary biologists. Other processes, such as burning fossil fuels and global deforestation, affect the global atmospheric composition. C_4 plants, by fixing CO_2 under conditions when rubisco prefers O_2 as substrate, also contributes to setting atmospheric CO_2/O_2 ratios.

9. **(a)** Without production of NADPH by the pentose phosphate pathway, cells would be unable to synthesize lipids and other reduced products. **(b)** Without generation of ribulose 1,5-bisphosphate, the Calvin cycle is effectively blocked.

10. In maize, CO_2 is fixed by the C_4 pathway elucidated by Hatch and Slack, in which PEP is carboxylated rapidly to oxaloacetate (some of which undergoes transamination to aspartate) and reduced to malate. Only after subsequent decarboxylation does the CO_2 enter the Calvin cycle.

11. Measure the rate of fixation of ^{14}C carbon dioxide in the light (daytime) and the dark. Greater fixation in the dark identifies the CAM plant. One could also determine the titratable acidity; acids stored in the vacuole during the night can be quantified in this way.

12. Isocitrate dehydrogenase reaction

13. Storage consumes 1 mol of ATP per mole of glucose 6-phosphate; this represents 3.3% of the total ATP available from glucose 6-phosphate metabolism (i.e., the efficiency of storage is 96.7%).

14. [PP_i] is high in the cytosol because the cytosol lacks inorganic pyrophosphatase.

15. **(a)** Low [P_i] in the cytosol and high [triose phosphate] in the chloroplast **(b)** High [triose phosphate] in the cytosol

16. 3-Phosphoglycerate is the primary product of photosynthesis; [P_i] rises when light-driven synthesis of ATP from ADP and P_i slows.

17. **(a)** Sucrose + $(glucose)_n$ → $(glucose)_{n+1}$ + fructose
(b) Fructose generated in the synthesis of dextran is readily imported and metabolized by the bacteria.

18. Species 1 is C_4; species 2, C_3.

19. **(a)** In peripheral chloroplasts **(b), (c)** In central sphere

20. **(a)** By analogy to the oxygenic photosynthesis carried out by plants ($H_2O + CO_2 \rightarrow$ glucose + O_2), the reaction would be $H_2S + O_2 + CO_2 \rightarrow$ glucose + H_2O + S. This is the sum of the reduction of CO_2 by H_2S ($H_2S + CO_2 \rightarrow$ glucose + S) and the energy input ($H_2S + O_2 \rightarrow S + H_2O$). **(b)** The H_2S and CO_2 are produced chemically in deep-sea sediments, but the O_2, like the vast majority of O_2 on Earth, is produced by photosynthesis, which is driven by light energy. **(c)** In the assay used by Robinson et al., ^3H labels the C-1 of ribulose 1,5-bisphosphate, so reaction with CO_2 yields one molecule of [^3H]3-phosphoglycerate and one molecule of unlabeled 3-phosphoglycerate; reaction with O_2 produces one molecule of [^3H]2-phosphoglycolate and one molecule of unlabeled 3-phosphoglycerate. Thus the ratio of [^3H]3-phosphoglycerate to [^3H]2-phosphoglycolate equals the ratio of carboxylation to oxygenation. **(d)** If the ^3H labeled C-5, *both* oxygenation and carboxylation would yield [^3H]3-phosphoglycerate and it would be impossible to distinguish which reaction had produced the labeled product; the reaction could not be used to measure Ω.

(e) Substituting $\frac{[CO_2]}{[O_2]} = \frac{0.00038}{0.2} = 0.0019$ into

$$\frac{V_{carboxylation}}{V_{oxygenation}} = \Omega \frac{[CO_2]}{[O_2]} \text{ gives}$$

$$\frac{V_{carboxylation}}{V_{oxygenation}} = (8.6)(0.0019) = 0.016$$

Therefore, the rate of oxygenation would be roughly 60 times the rate of carboxylation! **(f)** If terrestrial plants had Ω = 8.6, carboxylation would occur at a much lower rate than oxygenation. This would be extremely inefficient, so one would expect the rubisco of terrestrial plants to have an Ω substantially higher than 8.6. In fact, Ω values for land plants vary between 10 and 250. Even with these values, the expected rate of the oxygenation reaction is still very high. **(g)** The rubisco reaction occurs with CO_2 as a gas. At the same

temperature, $^{13}CO_2$ molecules diffuse more slowly than the lighter $^{12}CO_2$ molecules, and thus $^{13}CO_2$ will enter the active site (and become incorporated into substrate) more slowly than $^{12}CO_2$. **(b)** For the relationship to be truly symbiotic, the tube worms must be getting a substantial amount of their carbon from the bacteria. The presence of rubisco in the endosymbionts simply shows that they are capable of chemosynthesis, not that they are supplying the host with a significant fraction of its carbon. On the other hand, showing that the ^{13}C:^{12}C ratio in the host is more similar to that in the endosymbiont than that in other marine animals strongly suggests that the tube worms are getting the majority of their carbon from the bacteria.

Chapter 21

1. **(a)** The 16 carbons of palmitate are derived from 8 acetyl groups of 8 acetyl-CoA molecules. The ^{14}C-labeled acetyl-CoA gives rise to malonyl-CoA labeled at C-1 and C-2. **(b)** The metabolic pool of malonyl-CoA, the source of all palmitate carbons except C-16 and C-15, does not become labeled with small amounts of ^{14}C-labeled acetyl-CoA. Hence, only [15,16-^{14}C] palmitate is formed.

2. Both glucose and fructose are degraded to pyruvate in glycolysis. Pyruvate is converted to acetyl-CoA by the pyruvate dehydrogenase complex. Some of this acetyl-CoA enters the citric acid cycle, which produces reducing equivalents (NADH and NADPH). Mitochondrial electron transfer to O_2 yields ATP.

3. $8\ \text{Acetyl-CoA} + 15\text{ATP} + 14\text{NADPH} + 9H_2O \rightarrow \text{palmitate} + 8\text{CoA} + 15\text{ADP} + 15P_i + 14\text{NADP}^+ + 2H^+$

4. **(a)** 3 deuteriums per palmitate; all located on C-16; all other two-carbon units are derived from unlabeled malonyl-CoA. **(b)** 7 deuteriums per palmitate; located on all *even*-numbered carbons except C-16.

5. By using the three-carbon unit malonyl-CoA, the activated form of acetyl-CoA (recall that malonyl-CoA synthesis requires ATP), metabolism is driven in the direction of fatty acid synthesis by the exergonic release of CO_2.

6. The rate-limiting step in fatty acid synthesis is carboxylation of acetyl-CoA, catalyzed by acetyl-CoA carboxylase. High [citrate] and [isocitrate] indicate that conditions are favorable for fatty acid synthesis: an active citric acid cycle is providing a plentiful supply of ATP, reduced pyridine nucleotides, and acetyl-CoA. Citrate stimulates (increases the V_{max} of) acetyl-CoA carboxylase (a). Because citrate binds more tightly to the filamentous form of the enzyme (the active form), high [citrate] drives the protomer $\rightleftharpoons$ filament equilibrium in the direction of the active form (b). In contrast, palmitoyl-CoA (the end product of fatty acid synthesis) drives the equilibrium in the direction of the inactive (protomer) form. Hence, when the end product of fatty acid synthesis accumulates, the biosynthetic path slows.

7. **(a)** $\text{Acetyl-CoA}_{(mit)} + \text{ATP} + \text{CoA}_{(cyt)} \rightarrow \text{acetyl-CoA}_{(cyt)} + \text{ADP} + P_i + \text{CoA}_{(mit)}$ **(b)** 1 ATP per acetyl group **(c)** Yes

8. The double bond in palmitoleate is introduced by an oxidation catalyzed by fatty acyl–CoA desaturase, a mixed-function oxidase that requires O_2 as a cosubstrate.

9. $3\ \text{Palmitate} + \text{glycerol} + 7\text{ATP} + 4H_2O \rightarrow \text{tripalmitin} + 7\text{ADP} + 7P_i + 7H^+$

10. In adult rats, stored triacylglycerols are maintained at a steady-state level through a balance of the rates of degradation and biosynthesis. Hence, the triacylglycerols of adipose (fat) tissue are constantly turned over, which explains the incorporation of ^{14}C label from dietary glucose.

11. Net reaction:

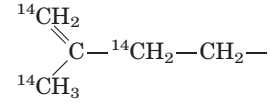
$\text{Dihydroxyacetone phosphate} + \text{NADH} + \text{palmitate} + \text{oleate} + 3\text{ATP} + \text{CTP} + \text{choline} + 4H_2O \rightarrow$

$\text{phosphatidylcholine} + \text{NAD}^+ + 2\text{AMP} + \text{ADP} + H^+ + \text{CMP} + 5P_i$

7ATP per molecule of phosphatidylcholine

12. Methionine deficiency reduces the level of adoMet, which is required for the de novo synthesis of phosphatidylcholine. The salvage pathway does not employ adoMet, but uses available choline. Thus phosphatidylcholine can be synthesized even when the diet is deficient in methionine, as long as choline is available.

13. ^{14}C label appears in three places in the activated isoprene:



14. **(a)** ATP **(b)** UDP-glucose **(c)** CDP-ethanolamine **(d)** UDP-galactose **(e)** fatty acyl–CoA **(f)** *S*-adenosylmethionine **(g)** malonyl-CoA **(h)** Δ^3-isopentenyl pyrophosphate

15. Linoleate is required in the synthesis of prostaglandins. Animals are unable to transform oleate to linoleate, so linoleate is an essential fatty acid. Plants can transform oleate to linoleate, and they provide animals with the required linoleate (see Fig. 21–12).

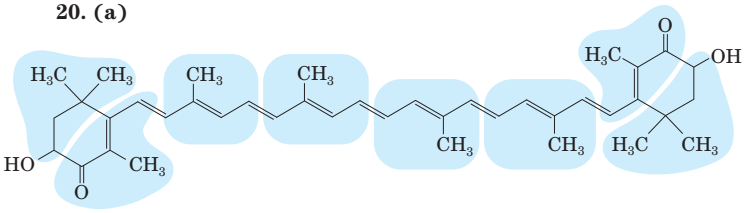
16. The rate-determining step in the biosynthesis of cholesterol is the synthesis of mevalonate, catalyzed by hydroxymethylglutaryl-CoA reductase. This enzyme is allosterically regulated by mevalonate and cholesterol derivatives. High intracellular [cholesterol] also reduces transcription of the gene encoding HMG-CoA reductase.

17. When cholesterol levels decline because of treatment with a statin, cells attempt to compensate by increasing expression of the gene encoding HMG-CoA reductase. The statins are good competitive inhibitors of HMG-CoA reductase activity nonetheless and reduce overall production of cholesterol.

18. Note: There are several plausible alternatives that a student might propose in the absence of a detailed knowledge of the literature on this enzyme. *Thiolase reaction:* Begins with nucleophilic attack of an active-site Cys residue on the first acetyl-CoA substrate, displacing —S-CoA and forming a covalent thioester link between Cys and the acetyl group. A base on the enzyme then extracts a proton from the methyl group of the second acetyl-CoA, leaving a carbanion that attacks the carbonyl carbon of the thioester formed in the first step. The sulfhydryl of the Cys residue is displaced, creating the product acetoacetyl-CoA. *HMG-CoA synthase reaction:* Begins in the same way, with a covalent thioester link formed between the enzyme's Cys residue and the acetyl group of acetyl-CoA, with displacement of the —S-CoA. The —S-CoA dissociates as CoA-SH, and acetoacetyl-CoA binds to the enzyme. A proton is abstracted from the methyl group of the enzyme-linked acetyl, forming a carbanion that attacks the ketone carbonyl of the acetoacetyl-CoA substrate. The carbonyl is converted to a hydroxyl ion in this reaction, and this is protonated to create —OH. The thioester link with the enzyme is then cleaved hydrolytically to generate the HMG-CoA product. *HMG-CoA reductase reaction:* Two successive hydride ions derived from NADPH first displace the —S-CoA, and then reduce the aldehyde to a hydroxyl group.

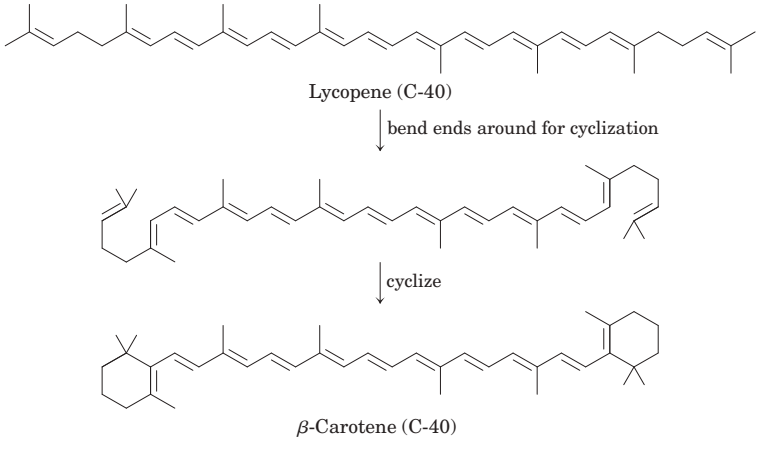
19. Statins inhibit HMG-CoA reductase, an enzyme in the pathway to the synthesis of activated isoprenes, which are precursors of cholesterol and a wide range of isoprenoids, including coenzyme Q (ubiquinone). Hence, statins might reduce the levels of coenzyme Q available for mitochondrial respiration. Ubiquinone is obtained in the diet as well as by direct biosynthesis, but it is not yet clear how much is required and how well dietary sources can substitute for reduced synthesis. Reductions in the levels of particular isoprenoids may account for some side effects of statins.

20. (a)



Astaxanthin

(b) Head-to-head. There are two ways to look at this. First, the "tail" of geranylgeranyl pyrophosphate has a branched dimethyl structure, as do both ends of phytoene. Second, no free —OH is formed by the release of PP_i, indicating that the two —O—Ⓟ—Ⓟ "heads" are linked to form phytoene. **(c)** Four rounds of dehydrogenation convert four single bonds to double bonds. **(d)** No. A count of single and double bonds in the reaction below shows that one double bond is replaced by two single bonds—so, there is no net oxidation or reduction:



(e) Steps ❶ through ❸. The enzyme can convert IPP and DMAP to geranylgeranyl pyrophosphate, but catalyzes no further reactions in the pathway, as confirmed by results with the other substrates. **(f)** Strains 1 through 4 lack *crtE* and have much lower astaxanthin production than strains 5 through 8, all of which overexpress *crtE*. Thus, overexpression of *crtE* leads to a substantial increase in astaxanthin production. Wild-type *E. coli* has some step ❸ activity, but this conversion of farnesyl pyrophosphate to geranylgeranyl pyrophosphate is strongly rate-limiting. **(g)** IPP isomerase. Comparing strains 5 and 6 shows that adding *ispA*, which catalyzes steps ❶ and ❷, has little effect on astaxanthin production, so these steps are not rate-limiting. However, comparing strains 5 and 7 shows that adding *idi* substantially increases astaxanthin production, so IPP isomerase must be the rate-limiting step when *crtE* is overexpressed. **(h)** A low (+) level, comparable to that of strains 5, 6, and 9. Without overexpression of *idi*, production of astaxanthin is limited by low IPP isomerase activity and the resulting limited supply of IPP.

Chapter 22

1. In their symbiotic relationship with the plant, bacteria supply ammonium ion by reducing atmospheric nitrogen, which requires large quantities of ATP.

2. The transfer of nitrogen from NH_3 to carbon skeletons can be catalyzed by (1) glutamine synthetase and (2) glutamate dehydrogenase. The latter enzyme produces glutamate, the amino group donor in all transamination reactions, necessary to the formation of amino acids for protein synthesis.

3. A link between enzyme-bound PLP and the phosphohomoserine substrate is first formed, with rearrangement to generate the ketimine at the α carbon of the substrate. This activates the β carbon for proton abstraction, leading to displacement of the phosphate and formation of a double bond between the β and γ carbons. A rearrangement (beginning with proton abstraction at the pyridoxal carbon adjacent to the substrate amino nitrogen) moves the double bond between the α and β carbons, and converts the ketimine to the aldimine form of PLP. Attack of water at the β carbon is then facilitated by the linked pyridoxal, followed by hydrolysis of the imine link between PLP and the product, to generate threonine.

4. In the mammalian route, toxic ammonium ions are transformed to glutamine, reducing toxic effects on the brain.

5. Glucose + $2CO_2$ + $2NH_3$ → 2 aspartate + $2H^+$ + $2H_2O$

6. The amino-terminal glutaminase domain is quite similar in *all* glutamine amidotransferases. A drug that targeted this active site would probably inhibit many enzymes and thus be prone to producing many more side effects than a more specific inhibitor targeting the unique carboxyl-terminal synthetase active site.

7. If phenylalanine hydroxylase is defective, the biosynthetic route to tyrosine is blocked and tyrosine must be obtained from the diet.

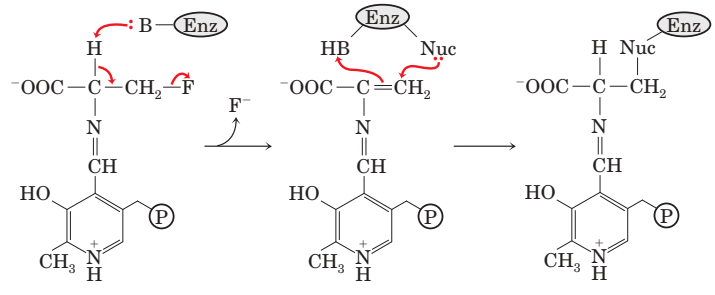
8. In adoMet synthesis, triphosphate is released from ATP. Hydrolysis of the triphosphate renders the reaction thermodynamically more favorable.

9. If the inhibition of glutamine synthase were not concerted, saturating concentrations of histidine would shut down the enzyme and cut off production of glutamine, which the bacterium needs to synthesize other products.

10. Folic acid is a precursor of tetrahydrofolate (see Fig. 18–16), required in the biosynthesis of glycine (see Fig. 22–14), a precursor of porphyrins. A folic acid deficiency therefore impairs hemoglobin synthesis.

11. *For glycine auxotrophs:* adenine and guanine; *for glutamine auxotrophs:* adenine, guanine, and cytosine; *for aspartate auxotrophs:* adenine, guanine, cytosine, and uridine.

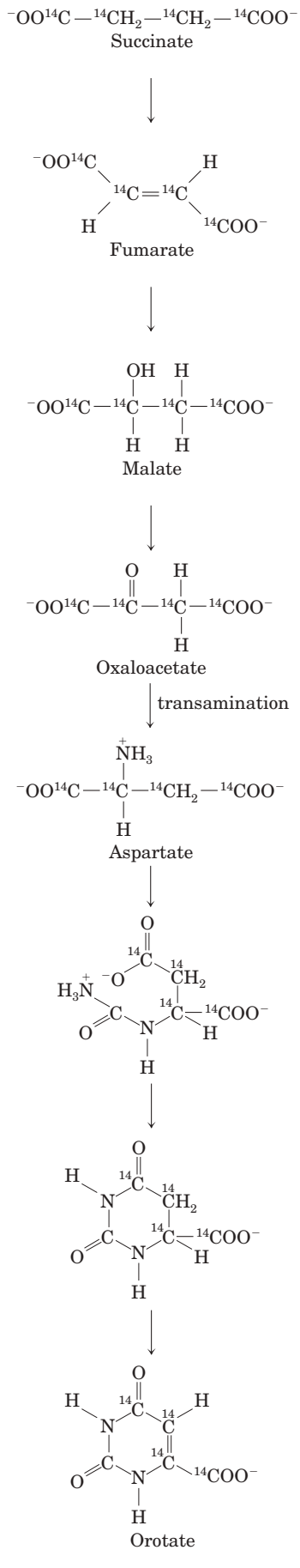
12. (a) See Fig. 18–6, step ❷, for the reaction mechanism of amino acid racemization. The F atom of fluoroalanine is an excellent leaving group. Fluoroalanine causes irreversible (covalent) inhibition of alanine racemase. One plausible mechanism is (Nuc denotes any nucleophilic amino acid side chain in the enzyme active site):



(b) Azaserine (see Fig. 22–51) is an analog of glutamine. The diazoacetyl group is highly reactive and forms covalent bonds with nucleophiles at the active site of a glutamine amidotransferase.

13. (a) As shown in Fig. 18–16, *p*-aminobenzoate is a component of N^5,N^{10}-methylenetetrahydrofolate, the cofactor involved in the transfer of one-carbon units. **(b)** In the presence of sulfanilamide, a structural analog of *p*-aminobenzoate, bacteria are unable to synthesize tetrahydrofolate, a cofactor necessary for converting AICAR to FAICAR; thus AICAR accumulates. **(c)** The competitive inhibition by sulfanilamide of the enzyme involved in tetrahydrofolate biosynthesis is overcome by the addition of excess substrate (*p*-aminobenzoate).

14. The ^{14}C-labeled orotate arises from the following pathway (the first three steps are part of the citric acid cycle):

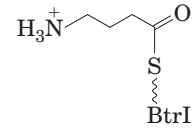


15. Organisms do not store nucleotides to be used as fuel, and they do not completely degrade them, but rather hydrolyze them to release the bases, which can be recovered in salvage pathways. The low C:N ratio of nucleotides makes them poor sources of energy.

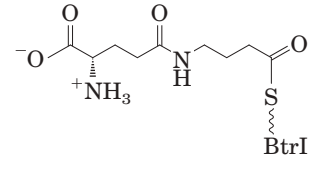
16. Treatment with allopurinol has two consequences. (1) It inhibits conversion of hypoxanthine to uric acid, causing accumulation of hypoxanthine, which is more soluble and more readily excreted; this alleviates the clinical problems associated with AMP degradation. (2) It inhibits conversion of guanine to uric acid, causing accumulation of xanthine, which is less soluble than uric acid; this is the source of xanthine stones. Because the amount of GMP degradation is low relative to AMP degradation, the kidney damage caused by xanthine stones is less than that caused by untreated gout.

17. 5-Phosphoribosyl-1-pyrophosphate; this is the first NH_3 acceptor in the purine biosynthetic pathway.

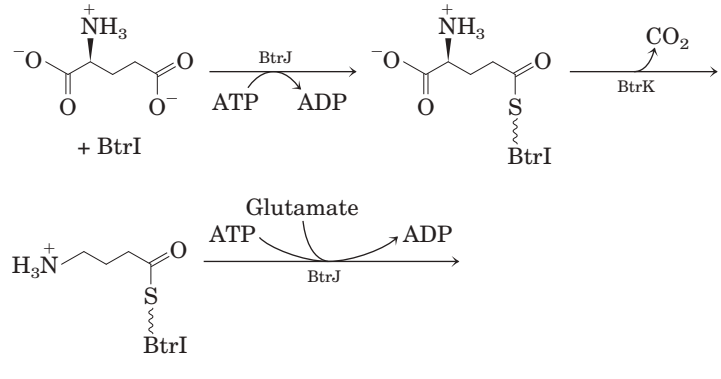
18. **(a)** The α-carboxyl group is removed and an —OH is added to the γ carbon. **(b)** BtrI has sequence homology with acyl carrier proteins. The molecular weight of BtrI increases when incubated under conditions in which CoA could be added to the protein. Adding CoA to a Ser residue would replace an —OH (formula weight (FW) 17) with a 4′-phosphopantetheine group (see Fig. 21–5). This group has the formula $C_{11}H_{21}N_2O_7PS$ (FW 356). Thus, 11,182 − 17 + 356 = 12,151, which is very close to the observed M_r of 12,153. **(c)** The thioester could form with the α-carboxyl group. **(d)** In the most common reaction for removing the α-carboxyl group of an amino acid (see Fig. 18–6c), the carboxyl group must be free. Furthermore, it is difficult to imagine a decarboxylation reaction starting with a carboxyl group in its thioester form. **(e)** 12,240 − 12,281 = 41, close to the M_r of CO_2 (44). Given that BtrK is probably a decarboxylase, its most likely structure is the decarboxylated form:

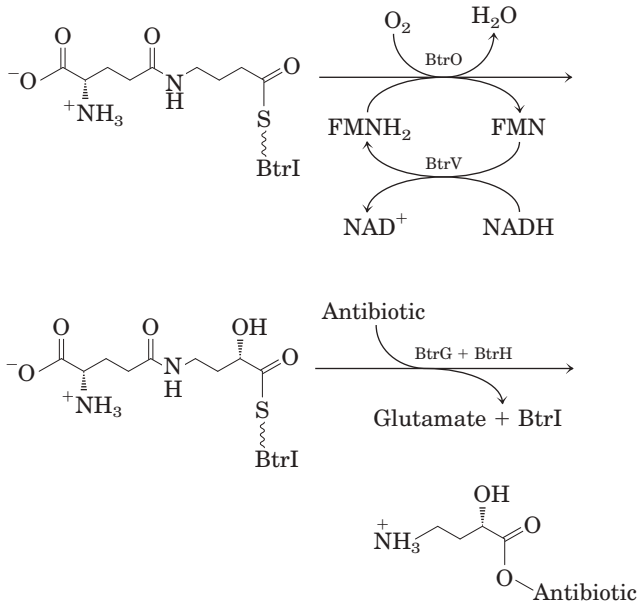


(f) 12,370 − 12,240 = 130. Glutamic acid ($C_5H_9NO_4$; M_r 147), minus the —OH (FW 17) removed in the glutamylation reaction, leaves a glutamyl group of FW 130; thus, γ-glutamylating the molecule above would add 130 to its M_r. BtrJ is capable of γ-glutamylating other substrates, so it may γ-glutamylate the structure above. The most likely site for this is the free amino group, giving the following structure:



(g)





Chapter 23

1. They are recognized by two different receptors, typically found in different cell types, and are coupled to different downstream effects.
2. Steady-state levels of ATP are maintained by phosphoryl group transfer to ADP from phosphocreatine. 1-Fluoro-2,4-dinitrobenzene inhibits creatine kinase.
3. Ammonia is very toxic to nervous tissue, especially the brain. Excess NH_3 is removed by transformation of glutamate to glutamine, which travels to the liver and is subsequently transformed to urea. The additional glutamine arises from the transformation of glucose to α-ketoglutarate, transamination of α-ketoglutarate to glutamate, and conversion of glutamate to glutamine.
4. Glucogenic amino acids are used to make glucose for the brain; others are oxidized in mitochondria via the citric acid cycle.
5. From glucose, by the following route: Glucose $\rightarrow$ dihydroxyacetone phosphate (in glycolysis); dihydroxyacetone phosphate + NADH + $H^+ \rightarrow$ glycerol 3-phosphate + NAD^+ (glycerol 3-phosphate dehydrogenase reaction)
6. **(a)** Increased muscular activity increases the demand for ATP, which is met by increased O_2 consumption. **(b)** After the sprint, lactate produced by anaerobic glycolysis is converted to glucose and glycogen, which requires ATP and therefore O_2.
7. Glucose is the primary fuel of the brain. TPP-dependent oxidative decarboxylation of pyruvate to acetyl-CoA is essential to complete glucose metabolism.
8. 190 m
9. **(a)** Inactivation provides a rapid means to change hormone concentrations. **(b)** Insulin level is maintained by equal rates of synthesis and degradation. **(c)** Changes in the rate of release from storage, rate of transport, and rate of conversion from prohormone to active hormone.
10. Water-soluble hormones bind to receptors on the outer surface of the cell, triggering the formation of a second messenger (e.g., cAMP) inside the cell. Lipid-soluble hormones can pass through the plasma membrane to act on target molecules or receptors directly.
11. **(a)** Heart and skeletal muscle lack glucose 6-phosphatase. Any glucose 6-phosphate produced enters the glycolytic pathway, and under O_2-deficient conditions is converted to lactate via pyruvate. **(b)** In a "fight or flight" situation, the concentration of glycolytic precursors must be high in preparation for muscular activity. Phosphorylated intermediates cannot escape from the cell, because the membrane is not permeable to charged species, and glucose 6-phosphate is not exported on the glucose transporter. The liver, by contrast, must release the glucose necessary to maintain blood glucose level; glucose is formed from glucose 6-phosphate and enters the bloodstream.
12. **(a)** Excessive uptake and use of blood glucose by the liver, leading to hypoglycemia; shutdown of amino acid and fatty acid catabolism **(b)** Little circulating fuel is available for ATP requirements. Brain damage results because glucose is the main source of fuel for the brain.
13. Thyroxine acts as an uncoupler of oxidative phosphorylation. Uncouplers lower the P/O ratio, and the tissue must increase respiration to meet the normal ATP demands. Thermogenesis could also be due to the increased rate of ATP utilization by the thyroid-stimulated tissue, as increased ATP demands are met by increased oxidative phosphorylation and thus respiration.
14. Because prohormones are inactive, they can be stored in quantity in secretory granules. Rapid activation is achieved by enzymatic cleavage in response to an appropriate signal.
15. In animals, glucose can be synthesized from many precursors (see Fig. 14–16). In humans, the principal precursors are glycerol from triacylglycerols and glucogenic amino acids from protein.
16. The *ob/ob* mouse, which is initially obese, will lose weight. The *OB/OB* mouse will retain its normal body weight.
17. BMI = 39.3. For BMI of 25, weight must be 75 kg; must lose 43 kg = 95 lbs.
18. Reduced insulin secretion. Valinomycin has the same effect as opening the K^+ channel, allowing K^+ exit and consequent hyperpolarization.
19. The liver does not receive the insulin message and therefore continues to have high levels of glucose 6-phosphatase and gluconeogenesis, increasing blood glucose both during a fast and after a glucose-containing meal. The elevated blood glucose triggers insulin release from pancreatic β cells, hence the high level of insulin in the blood.
20. Some things to consider: What is the frequency of heart attack attributable to the drug? How does this frequency compare with the number of individuals spared the long-term consequences of type 2 diabetes? Are other, equally effective treatment options with fewer adverse effects available?
21. Without intestinal glucosidase activity, absorption of glucose from dietary glycogen and starch is reduced, blunting the usual rise in blood glucose after the meal. The undigested oligosaccharides are fermented by bacteria in the large intestine, and the gases released cause intestinal discomfort.
22. **(a)** Closing the ATP-gated K^+ channel would depolarize the membrane, leading to increased insulin release. **(b)** Type 2 diabetes results from decreased sensitivity to insulin, not a deficit of insulin production; increasing circulating insulin levels will reduce the symptoms associated with this disease. **(c)** Individuals with type 1 diabetes have deficient pancreatic β cells, so glyburide will have no beneficial effect. **(d)** Iodine, like chlorine (the atom it replaces in the labeled glyburide), is a halogen, but it is a larger atom and has slightly different chemical properties. It is possible that the iodinated glyburide would not bind to SUR. If it bound to another molecule instead, the experiment would result in cloning of the gene for this other, incorrect protein. **(e)** Although a protein has been "purified," the "purified" preparation might be a mixture of several proteins that co-purify under those experimental conditions. In this case, the amino acid sequence could be that of a protein that co-purifies with SUR. Using antibody binding to show that the peptide sequences are present in SUR excludes this possibility. **(f)** Although the cloned gene does encode the 25 amino acid sequence found in SUR, it could be a gene that, coincidentally, encodes the same sequence in another protein. In this case, this

other gene would most likely be expressed in different cells than the *SUR* gene. The mRNA hybridization results are consistent with the putative *SUR* cDNA actually encoding SUR. **(g)** The excess unlabeled glyburide competes with labeled glyburide for the binding site on SUR. As a result, there is significantly less binding of labeled glyburide, so little or no radioactivity is detected in the 140 kDa protein. **(h)** In the absence of excess unlabeled glyburide, labeled 140 kDa protein is found only in the presence of the putative *SUR* cDNA. Excess unlabeled glyburide competes with the labeled glyburide, and no ^{125}I-labeled 140 kDa protein is detected. This shows that the cDNA produces a glyburide-binding protein of the same molecular weight as SUR—strong evidence that the cloned gene encodes the SUR protein. **(i)** Several additional steps are possible, such as: (1) Express the putative *SUR* cDNA in CHO (Chinese hamster ovary) cells and show that the transformed cells have ATP-gated K^+ channel activity. (2) Show that HIT cells with mutations in the putative *SUR* gene lack ATP-gated K^+ channel activity. (3) Show that experimental animals or human patients with mutations in the putative *SUR* gene are unable to secrete insulin.

Chapter 24

1. 6.1×10^4 nm; 290 times longer than the T2 phage head

2. The number of A residues does not equal the number of T residues, nor does the number of G equal the number of C, so the DNA is not a base-paired double helix; the M13 DNA is single-stranded.

3. $M_r = 3.8 \times 10^8$; length = 200 μm; $Lk_0 = 55{,}200$; $Lk = 51{,}900$

4. The exons contain 3 bp/amino acid × 192 amino acids = 576 bp. The remaining 864 bp are in introns, possibly in a leader or signal sequence, and/or in other noncoding DNA.

5. 5,000 bp. **(a)** Doesn't change; *Lk* cannot change without breaking and re-forming the covalent backbone of the DNA. **(b)** Becomes undefined; a circular DNA with a break in one strand has, by definition, no *Lk*. **(c)** Decreases; in the presence of ATP, gyrase underwinds DNA. **(d)** Doesn't change; this assumes that neither of the DNA strands is broken in the heating process.

6. For *Lk* to remain unchanged, the topoisomerase must introduce the same number of positive and negative supercoils.

7. $\sigma = -0.067$; >70% probability

8. **(a)** Undefined; the strands of a nicked DNA could be separated and thus have no *Lk*. **(b)** 476 **(c)** 476; the DNA is already relaxed, so the topoisomerase does not cause a net change. **(d)** 460; gyrase plus ATP reduces the *Lk* in increments of 2. **(e)** 464; eukaryotic type I topoisomerases increase the *Lk* of underwound or negatively supercoiled DNA in increments of 1. **(f)** 460; nucleosome binding does not break any DNA strands and thus cannot change *Lk*.

9. A fundamental structural unit in chromatin repeats about every 200 bp; the DNA is accessible to the nuclease only at 200 bp intervals. The brief treatment was insufficient to cleave the DNA at every accessible point, so a ladder of DNA bands is created in which the DNA fragments are multiples of 200 bp. The thickness of the DNA bands suggests that the distance between cleavage sites varies somewhat. For instance, not all the fragments in the lowest band are exactly 200 bp long.

10. A right-handed helix has a positive *Lk*; a left-handed helix (such as Z-DNA) has a negative *Lk*. Decreasing the *Lk* of a closed circular B-DNA by underwinding it facilitates formation of regions of Z-DNA within certain sequences. (See Chapter 8, p. 291, for a description of sequences that permit the formation of Z-DNA.)

11. **(a)** Both strands must be covalently closed, and the molecule must be either circular or constrained at both ends. **(b)** Formation of cruciforms, left-handed Z-DNA, plectonemic or solenoidal supercoils, and unwinding of the DNA are favored. **(c)** *E. coli* DNA topoisomerase II or DNA gyrase. **(d)** It binds the DNA at a point where it crosses on itself, cleaves both strands of one of the crossing segments, passes the other segment through the break, then reseals the break. The result is a change in *Lk* of −2.

12. Centromere, telomeres, and an autonomous replicating sequence or replication origin

13. The bacterial nucleoid is organized into domains approximately 10,000 bp long. Cleavage by a restriction enzyme relaxes the DNA within a domain, but not outside the domain. Any gene in the cleaved domain for which expression is affected by DNA topology will be affected by the cleavage; genes outside the domain will not.

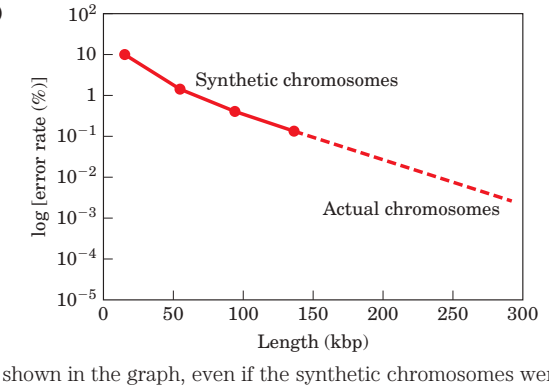
14. **(a)** The lower, faster-migrating band is negatively supercoiled plasmid DNA. The upper band is nicked, relaxed DNA. **(b)** DNA topoisomerase I relaxes the supercoiled DNA. The lower band will disappear, and all of the DNA will converge on the upper band. **(c)** DNA ligase produces little change in the pattern. Some minor additional bands may appear near the upper band, due to the trapping of topoisomers not quite perfectly relaxed by the ligation reaction. **(d)** The upper band will disappear, and all of the DNA will be in the lower band. The supercoiled DNA in the lower band may become even more supercoiled and migrate somewhat faster.

15. **(a)** When DNA ends are sealed to create a relaxed, closed circle, some DNA species are completely relaxed but others are trapped in slightly under- or overwound states. This gives rise to a distribution of topoisomers centered on the most relaxed species. **(b)** Positively supercoiled. **(c)** The DNA that is relaxed despite the addition of dye is DNA with one or both strands broken. DNA isolation procedures inevitably introduce small numbers of strand breaks in some of the closed-circular molecules. **(d)** Approximately −0.05. This is determined by simply comparing native DNA with samples of known σ. In both gels, the native DNA migrates most closely with the sample of $\sigma = -0.049$.

16. 62 million (the genome refers to the haploid genetic content of the cell; the cell is actually diploid, so the number of nucleosomes is doubled). The number comes from 3.1 billion base pairs divided by 200 base pairs per nucleosome (giving 15.5 million nucleosomes), multiplied by two copies of H2A per nucleosome and again multiplied by 2 to account for the diploid state of the cell. The 62 million would double upon replication.

17. **(a)** In nondisjunction, one daughter cell and all of its descendants get two copies of the synthetic chromosome and are white; the other daughter cell and all of its descendants get no copies of the synthetic chromosome and are red. This gives rise to a half-white, half-red colony. **(b)** In chromosome loss, one daughter cell and all of its descendants get one copy of the synthetic chromosome and are pink; the other daughter and all its descendants get no copies of the synthetic chromosome and are red. This gives rise to a half-pink, half-red colony. **(c)** The minimum functional centromere must be smaller than 0.63 kbp, since all fragments of this size or larger confer relative mitotic stability. **(d)** Telomeres are required to fully replicate only linear DNA; a circular molecule can replicate without them. **(e)** The larger the chromosome, the more faithfully it is segregated. The data show neither a minimum size below which the synthetic chromosome is completely unstable, nor a maximum size above which stability no longer changes.

(f)

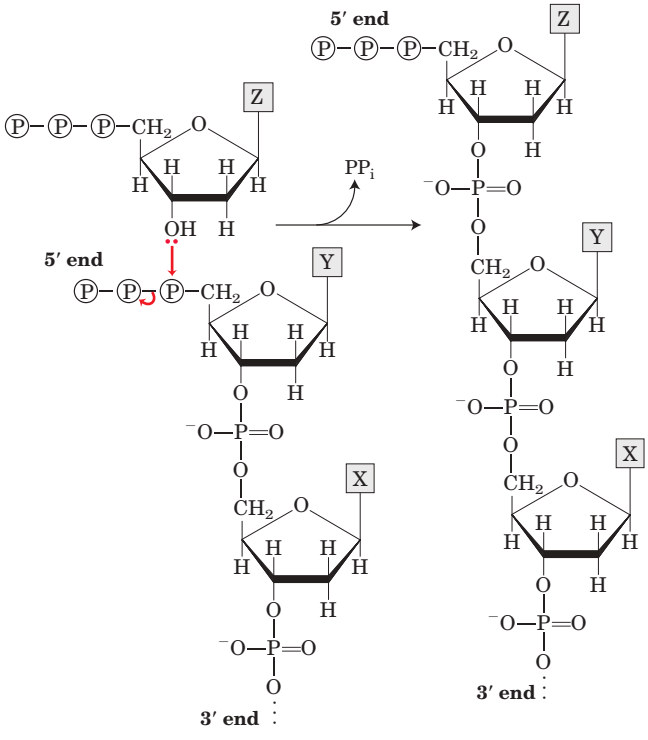


As shown in the graph, even if the synthetic chromosomes were as long as the normal yeast chromosomes, they would not be as

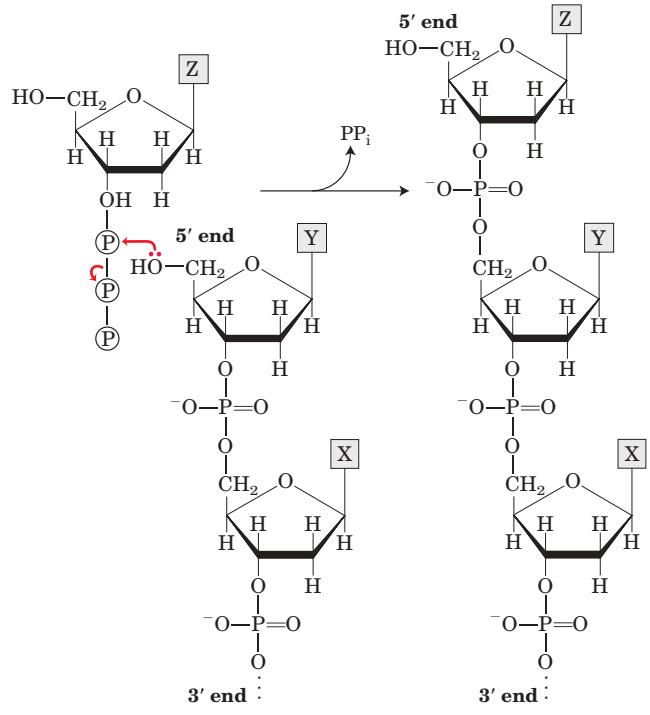
stable. This suggests that other, as yet undiscovered, elements are required for stability.

Chapter 25

1. In random, dispersive replication, in the second generation, all the DNAs would have the same density and would appear as a single band, not the two bands observed in the Meselson-Stahl experiment.
2. In this extension of the Meselson-Stahl experiment, after three generations the molar ratio of ^{15}N–^{14}N DNA to ^{14}N–^{14}N DNA is 2/6 = 0.33.
3. **(a)** 4.42×10^5 turns; **(b)** 40 min. In cells dividing every 20 min, a replicative cycle is initiated every 20 min, each cycle beginning before the prior one is complete. **(c)** 2,000 to 5,000 Okazaki fragments. The fragments are 1,000 to 2,000 nucleotides long and are firmly bound to the template strand by base pairing. Each fragment is quickly joined to the lagging strand, thus preserving the correct order of the fragments.
4. A 28.7%; G 21.3%; C 21.3%; T 28.7%. The DNA strand made from the template strand: A 32.7%; G 18.5%; C 24.1%; T 24.7%; the DNA strand made from the complementary template strand: A 24.7%; G 24.1%; C 18.5%; T 32.7%. It is assumed that the two template strands are replicated completely.
5. **(a)** No. Incorporation of ^{32}P into DNA results from the synthesis of new DNA, which requires the presence of *all four* nucleotide precursors. **(b)** Yes. Although all four nucleotide precursors must be present for DNA synthesis, only one of them has to be radioactive in order for radioactivity to appear in the new DNA. **(c)** No. Radioactivity is incorporated only if the ^{32}P label is in the α phosphate; DNA polymerase cleaves off pyrophosphate—i.e., the β- and γ-phosphate groups.
6. *Mechanism 1:* 3′-OH of an incoming dNTP attacks the α phosphate of the triphosphate at the 5′ end of the growing DNA strand, displacing pyrophosphate. This mechanism uses normal dNTPs, and the growing end of the DNA always has a triphosphate on the 5′ end.



Mechanism 2: This uses a new type of precursor, nucleotide 3′-triphosphates. The growing end of the DNA strand has a 5′-OH, which attacks the α phosphate of an incoming deoxynucleotide 3′-triphosphate, displacing pyrophosphate. Note that this mechanism would require the evolution of new metabolic pathways to supply the needed deoxynucleotide 3′-triphosphates.



7. The DNA polymerase contains a 3′→5′ exonuclease activity that degrades DNA to produce [^{32}P]dNMPs. The activity is not a 5′→3′ exonuclease, because the addition of unlabeled dNTPs inhibits the production of [^{32}P]dNMPs (polymerization activity would suppress a proofreading exonuclease but not an exonuclease operating downstream of the polymerase). Addition of pyrophosphate would generate [^{32}P]dNTPs through reversal of the polymerase reaction.
8. *Leading strand:* Precursors: dATP, dGTP, dCTP, dTTP (also needs a template DNA strand and DNA primer); enzymes and other proteins: DNA gyrase, helicase, single-stranded DNA–binding protein, DNA polymerase III, topoisomerases, and pyrophosphatase. *Lagging strand:* Precursors: ATP, GTP, CTP, UTP, dATP, dGTP, dCTP, dTTP (also needs an RNA primer); enzymes and other proteins: DNA gyrase, helicase, single-stranded DNA–binding protein, primase, DNA polymerase III, DNA polymerase I, DNA ligase, topoisomerases, and pyrophosphatase. NAD^+ is also required as a cofactor for DNA ligase.
9. Mutants with defective DNA ligase produce a DNA duplex in which one of the strands remains in pieces (as Okazaki fragments). When this duplex is denatured, sedimentation results in one fraction containing the intact single strand (the high molecular weight band) and one fraction containing the unspliced fragments (the low molecular weight band).
10. Watson-Crick base pairing between template and leading strand; proofreading and removal of wrongly inserted nucleotides by the 3′-exonuclease activity of DNA polymerase III. Yes—perhaps. Because the factors ensuring fidelity of replication are operative in both the leading and the lagging strands, the lagging strand would probably be made with the same fidelity. However, the greater number of distinct chemical operations involved in making the lagging strand might provide a greater opportunity for errors to arise.
11. ~1,200 bp (600 in each direction)
12. A small fraction (13 of 10^9 cells) of the histidine-requiring mutants spontaneously undergo back-mutation and regain their capacity to synthesize histidine. 2-Aminoanthracene increases

the rate of back-mutations about 1,800-fold and is therefore mutagenic. Since most carcinogens are mutagenic, 2-aminoanthracene is probably carcinogenic.

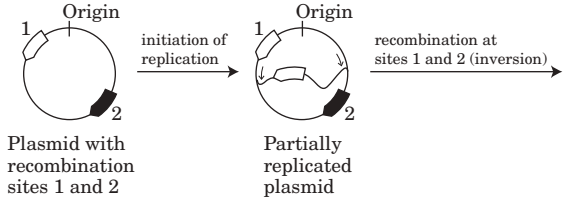
13. Spontaneous deamination of 5-methylcytosine (see Fig. 8–30) produces thymine, and thus a G–T mismatched pair. These are among the most common mismatches in the DNA of eukaryotes. The specialized repair system restores the G≡C pair.

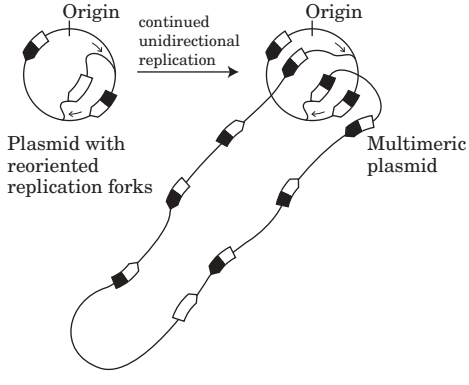
14. **(a)** Ultraviolet irradiation produces pyrimidine dimers; in normal fibroblasts these are excised by cleavage of the damaged strand by a special excinuclease. Thus the denatured single-stranded DNA contains the many fragments caused by the cleavage, and the average molecular weight is lowered. These fragments of single-stranded DNA are absent from the XPG samples, as indicated by the unchanged average molecular weight. **(b)** The absence of fragments in the single-stranded DNA from the XPG cells after irradiation suggests the special excinuclease is defective or missing.

15. During homologous genetic recombination, a Holliday intermediate may be formed almost anywhere within the two paired, homologous chromosomes; the branch point of the intermediate can move extensively by branch migration. In site-specific recombination, the Holliday intermediate is formed between two specific sites, and branch migration is generally restricted by heterologous sequences on either side of the recombination sites.

16. **(a)** Points Y. **(b)** Points X.

17. Once replication has proceeded from the origin to a point where one recombination site has been replicated but the other has not, site-specific recombination not only inverts the DNA between the recombination sites but also changes the direction of one replication fork relative to the other. The forks will chase each other around the DNA circle, generating many tandem copies of the plasmid. The multimeric circle can be resolved to monomers by additional site-specific recombination events.





18. **(a)** Even in the absence of an added mutagen, background mutations occur due to radiation, cellular chemical reactions, and so forth. **(b)** If the DNA is sufficiently damaged, a substantial fraction of gene products are nonfunctional and the cell is nonviable. **(c)** Cells with reduced DNA repair capability are more sensitive to mutagens. Because they less readily repair lesions caused by R7000, uvr$^-$ bacteria have an increased mutation rate and increased chance of lethal effects. **(d)** In the uvr$^+$ strain, the excision-repair system removes DNA bases with attached [^{3}H]R7000, decreasing the ^{3}H in these cells over time. In the uvr$^-$ strain, the DNA is not repaired and the ^{3}H level increases as [^{3}H]R7000 continues to react with the DNA. **(e)** All mutations listed in the table except A═T to G≡C show significant increases over background. Each type of mutation results from a different type of interaction between R7000 and DNA. Because different types of interactions are not equally likely (due to differences in reactivity, steric constraints, etc.), the resulting mutations occur with different frequencies. **(f)** No. Only those that start with a G≡C base pair are explained by this model. Thus A═T to C≡G and A═T to T═A must be due to R7000 attaching to an A or a T. **(g)** R7000-G pairs with A. First, R7000 adds to G≡C to give R7000-G≡C. (Compare this with what happens with the CH_3-G in Fig. 25–27b.) If this is not repaired, one strand is replicated as R7000-G═A, which is repaired to T═A. The other strand is wild-type. If the replication produces R7000-G═T, a similar pathway leads to an A═T base pair. **(h)** No. Compare data in the two tables, and keep in mind that different mutations occur at different frequencies.

A═T to C≡G: moderate in both strains; but better repair in the uvr$^+$ strain

G≡C to A═T: moderate in both; no real difference

G≡C to C═G: higher in uvr$^+$; certainly less repair!

G≡C to T═A: high in both; no real difference

A═T to T═A: high in both; no real difference

A═T to G≡C: low in both; no real difference

Certain adducts may be more readily recognized by the repair apparatus than others and thus are repaired more rapidly and result in fewer mutations.

Chapter 26

1. **(a)** 60 to 100 s; **(b)** 500 to 900 nucleotides

2. A single base error in DNA replication, if not corrected, would cause one of the two daughter cells, and all its progeny, to have a mutated chromosome. A single base error in RNA transcription would not affect the chromosome; it would lead to formation of some defective copies of one protein, but because mRNAs turn over rapidly, most copies of the protein would not be defective. The progeny of this cell would be normal.

3. Normal posttranscriptional processing at the 3′ end (cleavage and polyadenylation) would be inhibited or blocked.

4. Because the template-strand RNA does not encode the enzymes needed to initiate viral infection, it would probably be inert or simply degraded by cellular ribonucleases. Replication of the template-strand RNA and propagation of the virus could occur only if intact RNA replicase (RNA-dependent RNA polymerase) were introduced into the cell along with the template strand.

5. AUGACCAUGAUUACG

6. (1) Use of a template strand of nucleic acid; (2) synthesis in the 5′→3′ direction; (3) use of nucleoside triphosphate substrates, with formation of a phosphodiester bond and displacement of PP_i. Polynucleotide phosphorylase forms phosphodiester bonds but differs in all other listed properties.

7. Generally two: one to cleave the phosphodiester bond at one intron-exon junction, the other to link the resulting free exon end to the exon at the other end of the intron. If the nucleophile in the first step were water, this step would be a hydrolytic event and only one transesterification step would be required to complete the splicing process.

8. Many snoRNAs, required for rRNA modification reactions, are encoded in introns. If splicing does not occur, snoRNAs are not produced.

9. These enzymes lack a 3′→5′ proofreading exonuclease and have a high error rate; the likelihood of a replication error that would inactivate the virus is much less in a small genome than in a large one.

10. **(a)** $4^{32} = 1.8 \times 10^{19}$ **(b)** 0.006% **(c)** For the "unnatural selection" step, use a chromatographic resin with a bound molecule that is a transition-state analog of the ester hydrolysis reaction.

11. Though RNA synthesis is quickly halted by α-amanitin toxin, it takes several days for the critical mRNAs and the proteins in the liver to degrade, causing liver dysfunction and death.

12. **(a)** After lysis of the cells and partial purification of the contents, the protein extract could be subjected to isoelectric focusing. The β subunit could be detected by an antibody-based assay. The difference in amino acid residues between the normal β subunit and the mutated form (i.e., the different charges on the amino acids) would alter the electrophoretic mobility of the mutant protein in an isoelectric focusing gel, relative to the protein from a nonresistant strain. **(b)** Direct DNA sequencing (by the Sanger method).

13. **(a)** 384 nucleotide pairs **(b)** 1,620 nucleotide pairs **(c)** Most of the nucleotides are untranslated regions at the 3′ and 5′ ends of the mRNA. Also, most mRNAs code for a signal sequence (Chapter 27) in their protein products, which is eventually cleaved off to produce the mature and functional protein.

14. **(a)** cDNA is produced by reverse transcription of mRNA; thus, the mRNA sequence is probably CGG. Because the genomic DNA transcribed to make the mRNA has the sequence CAG, the primary transcript most likely has CAG, which is posttranscriptionally modified to CGG. **(b)** The unedited mRNA sequence is the same as that of the DNA (except for U replacing T). Unedited mRNA has the sequence (* indicates site of editing)

```
                                                    *
(5′)---GUCUCUGGUUUUCCUUGGGUGCCUUUAUGCAGCAAGGAUGCGAUAUUUCGCCAAG---(3′)
```

In step 1, primer 1 anneals as shown:

```
                                                    *
(5′)---GUCUCUGGUUUUCCUUGGGUGCCUUUAUGCAGCAAGGAUGCGAUAUUUCGCCAAG---(3′)
                                                    |||||||||||||||||||||||||
                                      Primer 1:  (3′)CGTTCCTACGCTATAAAGCGGTTC(5′)
```

cDNA (underlined) is synthesized from right to left:

```
                                                    *
(5′)---GUCUCUGGUUUUCCUUGGGUGCCUUUAUGCAGCAAGGAUGCGAUAUUUCGCCAAG---(3′)
       |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
(3′)---CAGAGACCAAAAGGAACCCACGGAAATACGTCGTTCCTACGCTATAAAGCGGTTC(5′)
```

Then step 2 yields just the cDNA:

```
                                                    *
(3′)---CAGAGACCAAAAGGAACCCACGGAAATACGTCGTTCCTACGCTATAAAGCGGTTC(5′)
```

In step 3, primer 2 anneals to the cDNA:

```
                Primer 2:  (5′)CCTTGGGTGCCTTTA(3′)
                           |||||||||||||||
(3′)---CAGAGACCAAAAGGAACCCACGGAAATACGTCGTTCCTACGCTATAAAGCGGTTC(5′)
                                                *
```

DNA polymerase adds nucleotides to the 3′ end of this primer. Moving from left to right, it inserts T, G, C, and A. However, because the A from ddATP lacks the 3′ —OH needed to attach the next nucleotide, the chain is not elongated past this point. This A is shown in *italic*; the new DNA is underlined:

```
                Primer 2:  (5′)CCTTGGGTGCCTTTATGCA
                           |||||||||||||||||||
(3′)---CAGAGACCAAAAGGAACCCACGGAAATACGTCGTTCCTACGCTATAAAGCGGTTC(5′)
                                                    *
```

This yields a 19 nucleotide fragment for the unedited transcript. In the edited transcript, the *A is changed to G; in the cDNA this corresponds to C. At the start of step 3:

```
                Primer 2:  (5′)CCTTGGGTGCCTTTA(3′)
                           |||||||||||||||
(3′)---CAGAGACCAAAAGGAACCCACGGAAATACGCCGTTCCTACGCTATAAAGCGGTTC(5′)
                                                  *
```

In this case, DNA polymerase can elongate past the edited base and will stop at the next T in the cDNA. The dideoxy A is *italic*; the new DNA is underlined:

```
                Primer 2:  (5′)CCTTGGGTGCCTTTATGCGGCA
                           ||||||||||||||||||||||
(3′)---CAGAGACCAAAAGGAACCCACGGAAATACGCCGTTCCTACGCTATAAAGCGGTTC(5′)
```

This gives the 22 nucleotide product. **(c)** Treatments (proteases, heat) known to disrupt protein function inhibit the editing activity, whereas treatments (nuclease) that do not affect proteins have little or no effect on editing. A key weakness of this argument is that the protein-disrupting treatments do not completely abolish editing. There could be some background editing or degradation of the mRNA even without the enzyme, or some of the enzyme might survive the treatments. **(d)** Only the α phosphate of NTPs is incorporated into polynucleotides. If the researchers had used the other types of [^{32}P]NTPs, none of the products would have been labeled. **(e)** Because only an A is being edited, only the fate of any A in the sequence is of interest. **(f)** Given that only ATP was labeled, if the entire nucleotide were removed, all radioactivity would have been removed from the mRNA, so only unmodified [^{32}P]AMP would be present on the chromatography plate. **(g)** If the base were removed and replaced, one would expect to see only [^{3}H]AMP. The presence of [^{3}H]IMP indicates that the A to I change occurs without removal of H at positions 2 and 8. The most likely mechanism

is chemical modification of A to I by hydrolytic deamination (see Fig. 22–36). **(h)** CAG is changed to CIG. This codon is read as CGG.

Chapter 27

1. **(a)** Gly–Gln–Ser–Leu–Leu–Ile **(b)** Leu–Asp–Ala–Pro **(c)** His–Asp–Ala–Cys–Cys–Tyr **(d)** Met–Asp–Glu in eukaryotes; fMet–Asp–Glu in bacteria

2. UUAAUGUAU, UUGAUGUAU, CUUAUGUAU, CUCAUGUAU, CUAAUGUAU, CUGAUGUAU, UUAAUGUAC, UUGAUGUAC, CUUAUGUAC, CUCAUGUAC, CUAAUGUAC, CUGAUGUAC

3. No. Because nearly all the amino acids have more than one codon (e.g., Leu has six), any given polypeptide can be coded for by a number of different base sequences. However, some amino acids are encoded by only one codon and those with multiple codons often share the same nucleotide at two of the three positions, so *certain parts* of the mRNA sequence encoding a protein of known amino acid sequence can be predicted with high certainty.

4. **(a)** (5′)CGACGGCGCGAAGUCAGGGGUGUUAAG(3′)

(b) Arg–Arg–Arg–Glu–Val–Arg–Gly–Val–Lys

(c) No. The complementary antiparallel strands in double-helical DNA do not have the same base sequence in the 5′→3′ direction. RNA is transcribed from only one specific strand of duplex DNA. The RNA polymerase must therefore recognize and bind to the correct strand.

5. There are two tRNAs for methionine: $tRNA^{fMet}$, which is the initiating tRNA, and $tRNA^{Met}$, which can insert a Met residue in interior positions in a polypeptide. Only fMet-$tRNA^{fMet}$ is recognized by the initiation factor IF-2 and is aligned with the initiating AUG positioned at the ribosomal P site in the initiation complex. AUG codons in the interior of the mRNA can bind and incorporate only Met-$tRNA^{Met}$.

6. Allow polynucleotide phosphorylase to act on a mixture of UDP and CDP in which UDP has, say, five times the concentration of CDP. The result would be a synthetic RNA polymer with many UUU triplets (coding for Phe), a smaller number of UUC (Phe), UCU (Ser), and CUU (Leu), a much smaller number of UCC (Ser), CUC (Leu), and CCU (Pro), and the smallest number of CCC (Pro).

7. A minimum of 583 ATP equivalents (based on 4 per amino acid residue added, except that there are only 145 translocation steps). Correction of each error requires 2 ATP equivalents. For glycogen synthesis, 292 ATP equivalents. The extra energy cost for β-globin synthesis reflects the cost of the information content of the protein. At least 20 activating enzymes, 70 ribosomal proteins, 4 rRNAs, 32 or more tRNAs, an mRNA, and 10 or more auxiliary enzymes must be made by the eukaryotic cell in order to synthesize a protein from amino acids. The synthesis of an (α1→4) chain of glycogen from glucose requires only 4 or 5 enzymes (Chapter 15).

8.

Glycine codons	Anticodons
(5′)GGU	(5′)ACC, GCC, ICC
(5′)GGC	(5′)GCC, ICC
(5′)GGA	(5′)UCC, ICC
(5′)GGG	(5′)CCC, UCC

(a) The 3′ and middle position **(b)** Pairings with anticodons (5′)GCC, ICC, and UCC **(c)** Pairings with anticodons (5′)ACC and CCC

9. (a), (c), (e), and (g) only; (b), (d), and (f) cannot be the result of single-base mutations: (b) and (f) would require substitutions of two bases, and (d) would require substitutions of all three bases.

10. (5′)AUGAUAUUGCUAUCUUGGACU

Changes:	C	C	AU	U	C	C
	U			C	A	A
				G	G	G

14 of 63 possible one-base changes would result in no coding change.

11. The two DNA codons for Glu are GAA and GAG, and the four DNA codons for Val are GTT, GTC, GTA, and GTG. A single base change in GAA to form GTA or in GAG to form GTG could account for the Glu → Val replacement in sickle-cell hemoglobin. Much less likely are two-base changes, from GAA to GTG, GTT, or GTC; and from GAG to GTA, GTT, or GTC.

12. Isoleucine is similar in structure to several other amino acids, particularly valine. Distinguishing between valine and isoleucine in the aminoacylation process requires the second filter of a proofreading function. Histidine has a structure unlike that of any other amino acid, and this structure provides opportunities for binding specificity adequate to ensure accurate aminoacylation of the cognate tRNA.

13. **(a)** The Ala-tRNA synthetase recognizes the G^3–U^{70} base pair in the amino acid arm of $tRNA^{Ala}$. **(b)** The mutant $tRNA^{Ala}$ would insert Ala residues at codons encoding Pro. **(c)** A mutation that might have similar effects is an alteration in $tRNA^{Pro}$ that allowed it to be recognized and aminoacylated by Ala-tRNA synthetase. **(d)** Most of the proteins in the cell would be inactivated, so these would be lethal mutations and hence never observed. This represents a powerful selective pressure for maintaining the genetic code.

14. *IF-2:* The 70S ribosome would form, but initiation factors would not be released and elongation could not start. *EF-Tu:* The second aminoacyl-tRNA would bind to the ribosomal A site, but no peptide bond would form. *EF-G:* The first peptide bond would form, but the ribosome would not move along the mRNA to vacate the A site for binding of a new EF-Tu–tRNA.

15. The amino acid most recently added to a growing polypeptide chain is the only one covalently attached to a tRNA and thus is the only link between the polypeptide and the mRNA encoding it. A proofreading activity would sever this link, halting synthesis of the polypeptide and releasing it from the mRNA.

16. The protein would be directed into the ER, and from there the targeting would depend on additional signals. SRP binds the amino-terminal signal early in protein synthesis and directs the nascent polypeptide and ribosome to receptors in the ER. Because the protein is translocated into the lumen of the ER as it is synthesized, the NLS is never accessible to the proteins involved in nuclear targeting.

17. Trigger factor is a molecular chaperone that stabilizes an unfolded and translocation-competent conformation of ProOmpA.

18. DNA with a minimum of 5,784 bp; some of the coding sequences must be nested or overlapping.

19. **(a)** The helices associate through hydrophobic and van der Waals interactions. **(b)** R groups 3, 6, 7, and 10 extend to the left; 1, 2, 4, 5, 8, and 9 extend to the right. **(c)** One possible sequence is

1 2 3 4 5 6 7 8 9 10

N–Phe–Ile–Glu–Val–Met–Asn–Ser–Ala–Phe–Gln–*C*

(d) One possible DNA sequence for the amino acid sequence in (c) is

Nontemplate strand

(5′)TTTATTGAAGTAATGAATAGTGCATTCCAG(3′)

(3′)AAATAACTTCATTACTTATCACGTAAGGTC(5′)

Template strand

(e) Phe, Leu, Ile, Met, and Val. All are hydrophobic, but the set does not include *all* the hydrophobic amino acids; Trp, Pro, Ala, and Gly are missing. **(f)** Tyr, His, Gln, Asn, Lys, Asp, and Glu. All of these are hydrophilic, although Tyr is less hydrophilic than the others. The set does not include *all* the hydrophilic amino acids; Ser, Thr, and Arg are missing. **(g)** Omitting T from the mixture excludes codons starting or ending with T—thus excluding Tyr, which is not very hydrophilic, and, more importantly, excluding the two possible stop codons (TAA and TAG). No other amino acids in the NAN set are excluded by omitting T. **(h)** Misfolded proteins are often degraded in the cell. Therefore, if a synthetic gene has produced a protein that forms a band on the SDS gel, it is likely that this protein is folded properly. **(i)** Protein folding depends on more than hydrophobic and van der Waals interactions. There are many reasons why a synthesized random-sequence protein might not fold into the four-helix structure. For example, hydrogen bonds between hydrophilic side chains could disrupt the structure. Also, not all sequences have an equal propensity to form an α helix.

Chapter 28

1. **(a)** Tryptophan synthase levels remain high in spite of the presence of tryptophan. **(b)** Levels again remain high. **(c)** Levels rapidly decrease, preventing wasteful synthesis of tryptophan.

2. The *E. coli* cells will produce β-galactosidase when they are subjected to high levels of a DNA-damaging agent, such as UV light. Under such conditions, RecA binds to single-stranded chromosomal DNA and facilitates the autocatalytic cleavage of the LexA repressor, releasing LexA from its binding site and allowing transcription of downstream genes.

3. **(a)** Constitutive, low-level expression of the operon; most mutations in the operator would make the repressor less likely to bind. **(b)** Either constitutive expression, as in (a), or constant repression, if the mutation destroyed the capability to bind to lactose and related compounds and hence the response to inducers. **(c)** Either increased or decreased expression of the operon (under conditions in which it is induced), depending on whether the mutation made the promoter more or less similar, respectively, to the consensus *E. coli* promoter.

4. 7,000 copies

5. 8×10^{-9} M, about 10^5 times greater than the dissociation constant. With 10 copies of active repressor in the cell, the operator site is always bound by the repressor molecule.

6. **(a)–(e)** Each condition decreases expression of *lac* operon genes.

7. **(a)** Less attenuation of transcription. The ribosome completing the translation of sequence 1 would no longer overlap and block sequence 2; sequence 2 would always be available to pair with sequence 3, preventing formation of the attenuator structure. **(b)** More attenuation of transcription. Sequence 2 would pair less efficiently with sequence 3; the attenuator structure would be formed more often, even when sequence 2 was not blocked by a ribosome. **(c)** No attenuation of transcription. The only regulation would be that afforded by the Trp repressor. **(d)** Attenuation loses its sensitivity to Trp tRNA. It might become sensitive to His tRNA. **(e)** Attenuation would rarely, if ever, occur. Sequences 2 and 3 always block formation of the attenuator. **(f)** Constant attenuation of transcription. Attenuator always forms, regardless of the availability of tryptophan.

8. Induction of the SOS response could not occur, making the cells more sensitive to high levels of DNA damage.

9. Each *Salmonella* cell would have flagella made up of both types of flagellar protein, and the cell would be vulnerable to antibodies generated in response to either protein.

10. A dissociable factor necessary for activity (e.g., a specificity factor similar to the σ subunit of the *E. coli* enzyme) may have been lost during purification of the polymerase.

11.

Gal4 protein

Gal4 DNA-binding domain	Gal4 activator domain

Engineered protein

Lac repressor DNA-binding domain	Gal4 activator domain

The engineered protein cannot bind to the Gal4 binding site in the *GAL* gene (UAS_G) because it lacks the Gal4 DNA-binding domain. Modify the Gal4p DNA binding site to give it the nucleotide sequence to which the Lac repressor normally binds (using methods described in Chapter 9).

12. Methylamine. The reaction proceeds with attack of water on the guanidinium carbon of the modified arginine.

13. The *bcd* mRNA needed for development is contributed to the egg by the mother. The egg develops normally even if its genotype is bcd^-/bcd^-, as long as the mother has one normal *bcd* gene and the bcd^- allele is recessive. However, the adult bcd^-/bcd^- female will be sterile because she has no normal *bcd* mRNA to contribute to her own eggs.

14. **(a)** For 10% expression (90% repression), 10% of the repressor has bound inducer and 90% is free and available to bind the operator. The calculation uses Eqn 5–8 (p. 161), with $\theta = 0.1$ and $K_d = 10^{-4}$ M.

$$\theta = \frac{[\text{IPTG}]}{[\text{IPTG}] + K_d} = \frac{[\text{IPTG}]}{[\text{IPTG}] + 10^{-4}\ \text{M}}$$

$$0.1 = \frac{[\text{IPTG}]}{[\text{IPTG}] + 10^{-4}\ \text{M}} \text{ so } 0.9\,[\text{IPTG}] = 10^{-5} \text{ or } [\text{IPTG}] = 1.1 \times 10^{-5}\ \text{M}$$

For 90% expression, 90% of the repressor has bound inducer, so $\theta = 0.9$. Entering the values for θ and K_d in Eqn 5–8 gives [IPTG] $= 9 \times 10^{-4}$ M. Thus, gene expression varies 10-fold over a roughly 10-fold [IPTG] range. **(b)** You would expect the protein levels to be low before induction, rise during induction, and then decay as synthesis stops and the proteins are degraded. **(c)** As shown in (a), the *lac* operon has more levels of expression than just on or off; thus it does not have characteristic A. As shown in (b), expression of the *lac* operon subsides once the inducer is removed; thus it lacks characteristic B. **(d)** *GFP-on:* rep^{ts} and GFP are expressed at high levels; rep^{ts} represses OP_λ, so no LacI protein is produced. *GFP-off:* LacI is expressed at a high level; LacI represses OP_{lac}, so rep^{ts} and GFP are not produced. **(e)** IPTG treatment switches the system from GFP-off to GFP-on. IPTG has an effect only when LacI is present, so affects only the GFP-off state. Adding IPTG relieves the repression of OP_{lac}, allowing high-level expression of rep^{ts}, which turns off expression of LacI, and high-level expression of GFP. **(f)** Heat treatment switches the system from GFP-on to GFP-off. Heat has an effect only when rep^{ts} is present, so affects only the GFP-on state. Heat inactivates rep^{ts} and relieves the repression of OP_λ, allowing high-level expression of LacI. LacI then acts at OP_{lac} to repress synthesis of rep^{ts} and GFP. **(g)** *Characteristic A:* The system is not stable in the intermediate state. At some point, one repressor will act more strongly than the other due to chance fluctuations in expression; this shuts off expression of the other repressor and locks the system in one state. *Characteristic B:* Once one repressor is expressed, it prevents the synthesis of the other; thus the system remains in one state even after the switching stimulus has been removed. **(h)** At no time does any cell express an intermediate level of GFP—this is a confirmation of characteristic A. At the intermediate concentration (X) of inducer, some cells have switched to GFP-on while others have not yet made the switch and remain in the GFP-off state; none are in between. The bimodal distribution of expression levels at [IPTG] = X is caused by the mixed population of GFP-on and GFP-off cells.

Glossary

a

ABC transporters: Plasma membrane proteins with sequences that make up *A*TP-*b*inding *c*assettes; serve to transport a large variety of substrates, including inorganic ions, lipids, and nonpolar drugs, out of the cell, using ATP as the energy source.

absolute configuration: The configuration of four different substituent groups around an asymmetric carbon atom, in relation to D- and L-glyceraldehyde.

absorption: Transport of the products of digestion from the intestinal tract into the blood.

acceptor control: Regulation of the rate of respiration by the availability of ADP as phosphate group acceptor.

accessory pigments: Visible light–absorbing pigments (carotenoids, xanthophylls, and phycobilins) in plants and photosynthetic bacteria that complement chlorophylls in trapping energy from sunlight.

acid dissociation constant: The dissociation constant (K_a) of an acid, describing its dissociation into its conjugate base and a proton.

acidosis: A metabolic condition in which the capacity of the body to buffer H^+ is diminished; usually accompanied by decreased blood pH.

actin: A protein that makes up the thin filaments of muscle; also an important component of the cytoskeleton of many eukaryotic cells.

action spectrum: A plot of the efficiency of light at promoting a light-dependent process such as photosynthesis as a function of wavelength.

activation energy ($\Delta G^{\ddagger}$): The amount of energy (in joules) required to convert all the molecules in 1 mol of a reacting substance from the ground state to the transition state.

activator: (1) A DNA-binding protein that positively regulates the expression of one or more genes; that is, transcription rates increase when an activator is bound to the DNA. (2) A positive modulator of an allosteric enzyme.

active site: The region of an enzyme surface that binds the substrate molecule and catalytically transforms it; also known as the catalytic site.

active transport: Energy-requiring transport of a solute across a membrane in the direction of increasing concentration.

activity: The true thermodynamic activity or potential of a substance, as distinct from its molar concentration.

acyl phosphate: Any molecule with the general chemical form $R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}O{-}OPO_3^{2-}$.

adaptor proteins: Signaling proteins, generally without their own enzymatic activities, that have binding sites for two or more cellular components and serve to bring those components together.

adenosine 3′,5′-cyclic monophosphate: *See* cyclic AMP.

***S*-adenosylmethionine (adoMet):** An enzymatic cofactor involved in methyl group transfers.

adipocyte: An animal cell specialized for the storage of fats (triacylglycerols).

adipose tissue: Connective tissue specialized for the storage of large amounts of triacylglycerols. *See also* brown adipose tissue; white adipose tissue.

ADP (adenosine diphosphate): A ribonucleoside 5′-diphosphate serving as phosphate group acceptor in the cell energy cycle.

aerobe: An organism that lives in air and uses oxygen as the terminal electron acceptor in respiration.

aerobic: Requiring or occurring in the presence of oxygen.

agonist: A compound, typically a hormone or neurotransmitter, that elicits a physiological response when it binds to its specific receptor.

alcohol fermentation: *See* ethanol fermentation.

aldose: A simple sugar in which the carbonyl carbon atom is an aldehyde; that is, the carbonyl carbon is at one end of the carbon chain.

alkalosis: A metabolic condition in which the capacity of the body to buffer OH^- is diminished; usually accompanied by an increase in blood pH.

allosteric enzyme: A regulatory enzyme with catalytic activity modulated by the noncovalent binding of a specific metabolite at a site other than the active site.

allosteric protein: A protein (generally with multiple subunits) with multiple ligand-binding sites, such that ligand binding at one site affects ligand binding at another.

allosteric site: The specific site on the surface of an allosteric enzyme molecule to which the modulator or effector molecule is bound.

α helix: A helical conformation of a polypeptide chain, usually right-handed, with maximal intrachain hydrogen bonding; one of the most common secondary structures in proteins.

α oxidation: An alternative path for the oxidation of β-methyl fatty acids in peroxisomes.

Ames test: A simple bacterial test for carcinogenicity, based on the assumption that carcinogens are mutagens.

amino acid activation: ATP-dependent enzymatic esterification of the carboxyl group of an amino acid to the 3′-hydroxyl group of its corresponding tRNA.

amino acids: α-Amino–substituted carboxylic acids, the building blocks of proteins.

aminoacyl-tRNA: An aminoacyl ester of a tRNA.

aminoacyl-tRNA synthetases: Enzymes that catalyze synthesis of an aminoacyl-tRNA at the expense of ATP energy.

amino-terminal residue: The only amino acid residue in a polypeptide chain with a free α-amino group; defines the amino terminus of the polypeptide.

aminotransferases: Enzymes that catalyze the transfer of amino groups from α-amino to α-keto acids; also called transaminases.

ammonotelic: Excreting excess nitrogen in the form of ammonia.

AMP-activated protein kinase (AMPK): A protein kinase activated by 5′-adenosine monophosphate (AMP). AMPK action generally shifts metabolism away from biosynthesis toward energy production.

amphibolic pathway: A metabolic pathway used in both catabolism and anabolism.

amphipathic: Containing both polar and nonpolar domains.

amphitropic proteins: Proteins that associate reversibly with the membrane and thus can be found in the cytosol, in the membrane, or in both places.

ampholyte: A substance that can act as either a base or an acid.

amphoteric: Capable of donating and accepting protons, thus able to serve as an acid or a base.

AMPK: *See* AMP-activated protein kinase.

amyloidoses: A variety of progressive conditions characterized by abnormal deposits of misfolded proteins in one or more organs or tissues.

anabolism: The phase of intermediary metabolism concerned with the energy-requiring biosynthesis of cell components from smaller precursors.

anaerobe: An organism that lives without oxygen. Obligate anaerobes die when exposed to oxygen.

anaerobic: Occurring in the absence of air or oxygen.

analyte: A molecule to be analyzed by mass spectrometry.

anammox: Anaerobic oxidation of ammonia to N_2, using nitrite as electron acceptor; carried out by specialized chemolithotrophic bacteria.

anaplerotic reaction: An enzyme-catalyzed reaction that can replenish the supply of intermediates in the citric acid cycle.

angstrom (Å): A unit of length (10^{-8} cm) used to indicate molecular dimensions.

anhydride: The product of the condensation of two carboxyl or phosphate groups in which the elements of water are eliminated to form a compound with the general structure R—X(=O)—O—X(=O)—R, where X is either carbon or phosphorus.

anion-exchange resin: A polymeric resin with fixed cationic groups, used in the chromatographic separation of anions.

anomeric carbon: The carbon atom in a sugar at the new stereocenter formed when a sugar cyclizes to form a hemiacetal. This is the carbonyl carbon of aldehydes and ketones.

anomers: Two stereoisomers of a given sugar that differ only in the configuration about the carbonyl (anomeric) carbon atom.

antagonist: A compound that interferes with the physiological action of another substance (the agonist), usually at a hormone or neurotransmitter receptor.

antibiotic: One of many different organic compounds that are formed and secreted by various species of microorganisms and plants, are toxic to other species, and presumably have a defensive function.

antibody: A defense protein synthesized by the immune system of vertebrates. *See also* immunoglobulin.

anticodon: A specific sequence of three nucleotides in a tRNA, complementary to a codon for an amino acid in an mRNA.

antigen: A molecule capable of eliciting the synthesis of a specific antibody in vertebrates.

antiparallel: Describes two linear polymers that are opposite in polarity or orientation.

antiport: Cotransport of two solutes across a membrane in opposite directions.

apoenzyme: The protein portion of an enzyme, exclusive of any organic or inorganic cofactors or prosthetic groups that might be required for catalytic activity.

apolipoprotein: The protein component of a lipoprotein.

apoprotein: The protein portion of a protein, exclusive of any organic or inorganic cofactors or prosthetic groups that might be required for activity.

apoptosis: (app′-a-toe′-sis) Programmed cell death in which a cell brings about its own death and lysis, in response to a signal from outside or programmed in its genes, by systematically degrading its own macromolecules.

aptamer: Oligonucleotide that binds specifically to one molecular target, usually selected by an iterative cycle of affinity-based enrichment (SELEX).

aquaporin (AQP): A member of a family of integral membrane proteins that mediate the flow of water across membranes.

Archaea: One of the five kingdoms of living organisms; includes many species that thrive in extreme environments of high ionic strength, high temperature, or low pH.

asymmetric carbon atom: A carbon atom that is covalently bonded to four different groups and thus may exist in two different tetrahedral configurations.

ATP (adenosine triphosphate): A ribonucleoside 5′-triphosphate functioning as a phosphate group donor in the cellular energy cycle; carries chemical energy between metabolic pathways by serving as a shared intermediate coupling endergonic and exergonic reactions.

ATPase: An enzyme that hydrolyzes ATP to yield ADP and phosphate, usually coupled to a process requiring energy.

ATP synthase: An enzyme complex that forms ATP from ADP and phosphate during oxidative phosphorylation in the inner mitochondrial membrane or the bacterial plasma membrane, and during photophosphorylation in chloroplasts.

attenuator: An RNA sequence involved in regulating the expression of certain genes; functions as a transcription terminator.

autophagy: Catabolic lysosomal degradation of cellular proteins and other components.

autophosphorylation: Strictly, the phosphorylation of an amino acid residue in a protein that is catalyzed by the same protein molecule; often extended to include phosphorylation of one subunit of a homodimer by the other subunit.

autotroph: An organism that can synthesize its own complex molecules from very simple carbon and nitrogen sources, such as carbon dioxide and ammonia.

auxin: A plant growth hormone.

auxotrophic mutant (auxotroph): A mutant organism defective in the synthesis of a particular biomolecule, which must therefore be supplied for the organism's growth.

Avogadro's number (N): The number of molecules in a gram molecular weight (a mole) of any compound (6.02×10^{23}).

b

Bacteria: One of the five kingdoms of living organisms; bacteria have a plasma membrane but no internal organelles or nucleus.

bacteriophage: A virus capable of replicating in a bacterial cell; also called phage.

baculovirus: Any of a group of double-stranded DNA viruses that infect invertebrates, particularly insects, and are widely used for purposes of protein expression in biotechnology.

basal metabolic rate: An animal's rate of oxygen consumption when at complete rest, long after a meal.

base pair: Two nucleotides in nucleic acid chains that are paired by hydrogen bonding of their bases; for example, A with T or U, and G with C.

BAT: *See* brown adipose tissue.

B cell: *See* B lymphocyte.

β conformation: An extended, zigzag arrangement of a polypeptide chain; a common secondary structure in proteins.

β oxidation: Oxidative degradation of fatty acids into acetyl-CoA by successive oxidations at the β-carbon atom; as distinct from ω oxidation.

β turn: A type of protein secondary structure consisting of four amino acid residues arranged in a tight turn so that the polypeptide turns back on itself.

bilayer: A double layer of oriented amphipathic lipid molecules, forming the basic structure of biological membranes. The hydrocarbon tails face inward to form a continuous nonpolar phase.

bile acids: Polar derivatives of cholesterol, secreted by the liver into the intestine, that serve to emulsify dietary fats, facilitating lipase action on them.

bile salts: Amphipathic steroid derivatives with detergent properties, participating in digestion and absorption of lipids.

binding energy: The energy derived from noncovalent interactions between enzyme and substrate or receptor and ligand.

binding site: The crevice or pocket on a protein in which a ligand binds.

bioassay: A method for measuring the amount of a biologically active substance (such as a hormone) in a sample by quantifying the biological response to aliquots of that sample.

bioinformatics: The computerized analysis of biological data, using methods derived from statistics, linguistics, mathematics, chemistry, biochemistry, and physics. The data are often nucleic acid or protein sequence or structural data, but can also involve experimental data from many sources, patient statistics, and materials in the scientific literature. Bioinformatics research focuses on methods for data storage, retrieval, and analysis.

biosphere: All the living matter on or in the earth, the seas, and the atmosphere.

biotin: A vitamin; an enzymatic cofactor involved in carboxylation reactions.

B lymphocyte (B cell): One of a class of blood cells (lymphocytes), responsible for the production of circulating antibodies.

bond energy: The energy required to break a bond.

branch migration: Movement of the branch point in a branched DNA formed from two DNA molecules with identical sequences. *See also* Holliday intermediate.

brown adipose tissue (BAT): Thermogenic adipose tissue rich in mitochondria that contain the uncoupling protein thermogenin, which uncouples electron transfer through the respiratory chain from ATP synthesis. *Compare* white adipose tissue.

buffer: A system capable of resisting changes in pH, consisting of a conjugate acid-base pair in which the ratio of proton acceptor to proton donor is near unity.

c

calorie: The amount of heat required to raise the temperature of 1.0 g of water from 14.5 to 15.5 °C. One calorie (cal) equals 4.18 joules (J).

Calvin cycle: The cyclic pathway in plants that fixes carbon dioxide and produces triose phosphates.

CAM plants: Succulent plants of hot, dry climates, in which CO_2 is fixed into oxaloacetate in the dark, then fixed by rubisco in the light when stomata close to exclude O_2.

cAMP: *See* cyclic AMP.

cAMP receptor protein (CRP): In bacteria, a specific regulatory protein that controls initiation of transcription of the genes that produce the enzymes required for the cell to use some other nutrient when glucose is lacking; also called catabolite gene activator protein (CAP).

CAP: *See* cAMP receptor protein.

capsid: The protein coat of a virion or virus particle.

carbanion: A negatively charged carbon atom.

carbocation: A positively charged carbon atom; also called a carbonium ion.

carbohydrate: A polyhydroxy aldehyde or ketone, or substance that yields such a compound on hydrolysis. Many carbohydrates have the empirical formula $(CH_2O)_n$; some also contain nitrogen, phosphorus, or sulfur.

carbon-assimilation reactions: Reaction sequence in which atmospheric CO_2 is converted into organic compounds.

carbon-fixation reactions: The reactions, catalyzed by rubisco during photosynthesis or by other carboxylases, in which atmospheric CO_2 is initially incorporated (fixed) into an organic compound.

carbonium ion: *See* carbocation.

carboxyl-terminal residue: The only amino acid residue in a polypeptide chain with a free α-carboxyl group; defines the carboxyl terminus of the polypeptide.

cardiolipin: A membrane phospholipid in which two phosphatidic acid moieties share a single glycerol head group.

carnitine shuttle: Mechanism for moving fatty acids from the cytosol to the mitochondrial matrix as fatty esters of carnitine.

carotenoids: Lipid-soluble photosynthetic pigments made up of isoprene units.

cascade: *See* enzyme cascade.

catabolism: The phase of intermediary metabolism concerned with the energy-yielding degradation of nutrient molecules.

catabolite gene activator protein (CAP): *See* cAMP receptor protein.

catalytic site: *See* active site.

catecholamines: Hormones, such as epinephrine, that are amino derivatives of catechol.

catenane: Two or more circular polymeric molecules interlinked by one or more noncovalent topological links, resembling the links of a chain.

cation-exchange resin: An insoluble polymer with fixed negative charges, used in the chromatographic separation of cationic substances.

cDNA: *See* complementary DNA.

cDNA library: A collection of cloned DNA fragments derived entirely from the complement of mRNA being expressed in a particular organism or cell type under a defined set of conditions.

cellular differentiation: The process in which a precursor cell becomes specialized to carry out a particular function, by acquiring a new complement of proteins and RNA.

central dogma: The organizing principle of molecular biology: genetic information flows from DNA to RNA to protein.

centromere: A specialized site in a chromosome, serving as the attachment point for the mitotic or meiotic spindle.

cerebroside: Sphingolipid containing one sugar residue as a head group.

channeling: The direct transfer of a reaction product (common intermediate) from the active site of an enzyme to the active site of the enzyme catalyzing the next step in a pathway.

chaperone: Any of several classes of proteins or protein complexes that catalyze the accurate folding of proteins in all cells.

chaperonin: One of two major classes of chaperones found in virtually all organisms; a complex of proteins that functions in protein folding, either GroES/GroEL in bacteria or Hsp60 in eukaryotes.

chemiosmotic coupling: Coupling of ATP synthesis to electron transfer via a transmembrane difference in charge and pH.

chemiosmotic theory: The theory that energy derived from electron transfer reactions is temporarily stored as a transmembrane difference in charge and pH, which subsequently drives the formation of ATP in oxidative phosphorylation and photophosphorylation.

chemotaxis: A cell's sensing of and movement toward or away from a specific chemical agent.

chemotroph: An organism that obtains energy by metabolizing organic compounds derived from other organisms.

chiral center: An atom with substituents arranged so that the molecule is not superposable on its mirror image.

chiral compound: A compound that contains an asymmetric center (chiral atom or chiral center) and thus can occur in two nonsuperposable mirror-image forms (enantiomers).

chlorophylls: A family of green pigments that function as receptors of light energy in photosynthesis; magnesium-porphyrin complexes.

chloroplast: Chlorophyll-containing photosynthetic organelle in some eukaryotic cells.

chondroitin sulfate: One of a family of sulfated glycosaminoglycans, a major component of the extracellular matrix.

chromatin: A filamentous complex of DNA, histones, and other proteins, constituting the eukaryotic chromosome.

chromatography: A process in which complex mixtures of molecules are separated by many repeated partitionings between a flowing (mobile) phase and a stationary phase.

chromatophore: A compound or moiety (natural or synthetic) that absorbs visible or ultraviolet light.

chromosome: A single large DNA molecule and its associated proteins, containing many genes; stores and transmits genetic information.

chylomicron: A plasma lipoprotein consisting of a large droplet of triacylglycerols stabilized by a coat of protein and phospholipid; carries lipids from the intestine to the tissues.

circular dichroism spectroscopy: A method used to characterize the degree of folding in a protein, based on differences in the absorption of right-handed versus left-handed circularly polarized light.

cis and trans isomers: *See* geometric isomers.

cistron: A unit of DNA or RNA corresponding to one gene.

citric acid cycle: A cyclic pathway for the oxidation of acetyl residues to carbon dioxide, in which formation of citrate is the first step; also known as the Krebs cycle or tricarboxylic acid cycle.

clones: The descendants of a single cell.

cloning: The production of large numbers of identical DNA molecules, cells, or organisms from a single ancestral DNA molecule, cell, or organism.

closed system: A system that exchanges neither matter nor energy with the surroundings. *See also* system.

cobalamin: *See* coenzyme B_{12}.

coding strand: In DNA transcription, the DNA strand identical in base sequence to the RNA transcribed from it, with U in the RNA in place of T in the DNA; as distinct from the template strand. Also called the nontemplate strand.

codon: A sequence of three adjacent nucleotides in a nucleic acid that codes for a specific amino acid.

coenzyme: An organic cofactor required for the action of certain enzymes; often has a vitamin component.

coenzyme A: A pantothenic acid–containing coenzyme that serves as an acyl group carrier in certain enzymatic reactions.

coenzyme B_{12}: An enzymatic cofactor derived from the vitamin cobalamin, involved in certain types of carbon skeletal rearrangements.

cofactor: An inorganic ion or a coenzyme required for enzyme activity.

cognate: Describes two biomolecules that normally interact; for example, an enzyme and its usual substrate, or a receptor and its usual ligand.

cohesive ends: *See* sticky ends.

cointegrate: An intermediate in the migration of certain DNA transposons in which the donor DNA and target DNA are covalently attached.

colligative properties: Properties of a solution that depend on the number of solute particles per unit volume; for example, freezing-point depression.

combinatorial control: Use of combinations of a limited repertoire of regulatory proteins

to provide gene-specific regulation of many individual genes.

competitive inhibition: A type of enzyme inhibition reversed by increasing the substrate concentration; a competitive inhibitor generally competes with the normal substrate or ligand for a protein's binding site.

complementary: Having a molecular surface with chemical groups arranged to interact specifically with chemical groups on another molecule.

complementary DNA (cDNA): A DNA complementary to a specific mRNA, used in DNA cloning; usually made by reverse transcriptase.

condensation: A reaction type in which two compounds are joined with the elimination of water.

configuration: The spatial arrangement of an organic molecule that is conferred by the presence of either (1) double bonds, about which there is no freedom of rotation, or (2) chiral centers, around which substituent groups are arranged in a specific sequence. Configurational isomers cannot be interconverted without breaking one or more covalent bonds.

conformation: A spatial arrangement of substituent groups that are free to assume different positions in space, without breaking any bonds, because of the freedom of bond rotation.

conjugate acid-base pair: A proton donor and its corresponding deprotonated species; for example, acetic acid (donor) and acetate (acceptor).

conjugated protein: A protein containing one or more prosthetic groups.

conjugate redox pair: An electron donor and its corresponding electron acceptor form; for example, Cu^+ (donor) and Cu^{2+} (acceptor), or NADH (donor) and NAD^+ (acceptor).

consensus sequence: A DNA or amino acid sequence consisting of the residues that most commonly occur at each position in a set of similar sequences.

conservative substitution: Replacement of an amino acid residue in a polypeptide by another residue with similar properties; for example, substitution of Glu by Asp.

constitutive enzymes: Enzymes required at all times by a cell and present at some constant level; for example, many enzymes of the central metabolic pathways. Sometimes called housekeeping enzymes.

contig: A series of overlapping clones or a continuous sequence defining an uninterrupted section of a chromosome.

contour length: The length of a helical polymeric molecule as measured along its helical axis.

cooperativity: The characteristic of an enzyme or other protein in which binding of the first molecule of a ligand changes the affinity for the second molecule. In positive cooperativity, the affinity for the second ligand molecule increases; in negative cooperativity, it decreases.

cotransport: The simultaneous transport, by a single transporter, of two solutes across a membrane. *See also* antiport; symport.

coupled reactions: Two chemical reactions that have a common intermediate and thus a means of energy transfer from one to the other.

covalent bond: A chemical bond that involves sharing of electron pairs.

C_4 plants: Plants (generally tropical) in which CO_2 is first fixed into a four-carbon compound (oxaloacetate or malate) before entering the Calvin cycle via rubisco.

cristae: Infoldings of the inner mitochondrial membrane.

CRP: *See* cAMP receptor protein.

cruciform: Secondary structure in double-stranded RNA or DNA in which the double helix is denatured at palindromic repeat sequences in each strand, and each separated strand is paired internally to form opposing hairpin structures. *See also* hairpin.

cyclic AMP (cAMP, adenosine 3′, 5′-cyclic monophosphate): A second messenger; its formation in a cell by adenylyl cyclase is stimulated by certain hormones or other molecular signals.

cyclic electron flow: In chloroplasts, the light-induced flow of electrons originating from and returning to photosystem I.

cyclic photophosphorylation: ATP synthesis driven by cyclic electron flow through photosystem I.

cyclin: One of a family of proteins that activate cyclin-dependent protein kinases and thereby regulate the cell cycle.

cytochrome P-450: A family of heme-containing enzymes, with a characteristic absorption band at 450 nm, that participate in biological hydroxylations with O_2.

cytochromes: Heme proteins serving as electron carriers in respiration, photosynthesis, and other oxidation-reduction reactions.

cytokine: One of a family of small secreted proteins (such as interleukins or interferons) that activate cell division or differentiation by binding to plasma membrane receptors in target cells.

cytokinesis: The final separation of daughter cells following mitosis.

cytoplasm: The portion of a cell's contents outside the nucleus but within the plasma membrane; includes organelles such as mitochondria.

cytoskeleton: The filamentous network that provides structure and organization to the cytoplasm; includes actin filaments, microtubules, and intermediate filaments.

cytosol: The continuous aqueous phase of the cytoplasm, with its dissolved solutes; excludes the organelles such as mitochondria.

d

dalton: Unit of atomic or molecular weight; 1 dalton (Da) is the weight of a hydrogen atom (1.66×10^{-24} g).

dark reactions: *See* carbon-assimilation reactions.

deamination: The enzymatic removal of amino groups from biomolecules such as amino acids or nucleotides.

degenerate code: A code in which a single element in one language is specified by more than one element in a second language.

dehydrogenases: Enzymes that catalyze the removal of pairs of hydrogen atoms from substrates.

deletion mutation: A mutation resulting from the deletion of one or more nucleotides from a gene or chromosome.

ΔG: *See* free-energy change.

$\Delta G^{\ddagger}$: *See* activation energy.

$\Delta G'^{\circ}$: *See* standard free-energy change.

denaturation: Partial or complete unfolding of the specific native conformation of a polypeptide chain, protein, or nucleic acid such that the function of the molecule is lost.

denatured protein: A protein that has lost enough of its native conformation by exposure to a destabilizing agent such as heat or detergent that its function is lost.

de novo pathway: Pathway for the synthesis of a biomolecule, such as a nucleotide, from simple precursors; as distinct from a salvage pathway.

deoxyribonucleic acid: *See* DNA.

deoxyribonucleotides: Nucleotides containing 2-deoxy-D-ribose as the pentose component.

desaturases: Enzymes that catalyze the introduction of double bonds into the hydrocarbon portion of fatty acids.

desensitization: Universal process by which sensory mechanisms cease to respond after prolonged exposure to the specific stimulus they detect.

desolvation: In aqueous solution, the release of bound water surrounding a solute.

diabetes mellitus: A group of metabolic diseases with symptoms that result from a deficiency in insulin production or utilization; characterized by a failure in glucose transport from the blood into cells at normal glucose concentrations.

dialysis: Removal of small molecules from a solution of a macromolecule by their diffusion through a semipermeable membrane into a suitably buffered solution.

differential centrifugation: Separation of cell organelles or other particles of different size by their different rates of sedimentation in a centrifugal field.

differentiation: Specialization of cell structure and function during growth and development.

diffusion: The net movement of molecules in the direction of lower concentration.

digestion: Enzymatic hydrolysis of major nutrients in the gastrointestinal system to yield their simpler components.

diploid: Having two sets of genetic information; describes a cell with two chromosomes of each type. *Compare* haploid.

disaccharide: A carbohydrate consisting of two covalently joined monosaccharide units.

dissociation constant: An equilibrium constant (K_d) for the dissociation of a complex of two or more biomolecules into its components;

for example, dissociation of a substrate from an enzyme.

disulfide bond: A covalent bond involving the oxidative linkage of two Cys residues, from the same or different polypeptide chains, forming a cystine residue.

DNA (deoxyribonucleic acid): A polynucleotide with a specific sequence of deoxyribonucleotide units covalently joined through 3′,5′-phosphodiester bonds; serves as the carrier of genetic information.

DNA chimera: DNA containing genetic information derived from two different species.

DNA chip: Informal term for a DNA microarray, referring to the small size of typical microarrays.

DNA cloning: *See* cloning.

DNA library: A collection of cloned DNA fragments.

DNA ligases: Enzymes that creates a phosphodiester bond between the 3′ end of one DNA segment and the 5′ end of another.

DNA looping: The interaction of proteins bound at distant sites on a DNA molecule so that the intervening DNA forms a loop.

DNA microarray: A collection of DNA sequences immobilized on a solid surface, with individual sequences laid out in patterned arrays that can be probed by hybridization.

DNA polymerase: An enzyme that catalyzes template-dependent synthesis of DNA from its deoxyribonucleoside 5′-triphosphate precursors.

DNA supercoiling: The coiling of DNA upon itself, generally as a result of bending, underwinding, or overwinding of the DNA helix.

DNA transposition: *See* transposition.

domain: A distinct structural unit of a polypeptide; domains may have separate functions and may fold as independent, compact units.

double helix: The natural coiled conformation of two complementary, antiparallel DNA chains.

double-reciprocal plot: A plot of $1/V_0$ versus 1/[S], which allows a more accurate determination of V_{max} and K_m than a plot of V_0 versus [S]; also called the Lineweaver-Burk plot.

e

***E′°*:** *See* standard reduction potential.

ECM: *See* extracellular matrix.

electrochemical gradient: The resultant of the gradients of concentration and of electric charge of an ion across a membrane; the driving force for oxidative phosphorylation and photophosphorylation.

electrochemical potential: The energy required to maintain a separation of charge and of concentration across a membrane.

electrogenic: Contributing to an electrical potential across a membrane.

electron acceptor: A substance that receives electrons in an oxidation-reduction reaction.

electron carrier: A protein, such as a flavoprotein or a cytochrome, that can reversibly gain and lose electrons; functions in the transfer of electrons from organic nutrients to oxygen or some other terminal acceptor.

electron donor: A substance that donates electrons in an oxidation-reduction reaction.

electron transfer: Movement of electrons from electron donor to electron acceptor; especially, from substrates to oxygen via the carriers of the respiratory (electron-transfer) chain.

electrophile: An electron-deficient group with a strong tendency to accept electrons from an electron-rich group (nucleophile).

electrophoresis: Movement of charged solutes in response to an electrical field; often used to separate mixtures of ions, proteins, or nucleic acids.

elongation factors: (1) Proteins that function in the elongation phase of eukaryotic transcription. (2) Specific proteins required in the elongation of polypeptide chains by ribosomes.

eluate: The effluent from a chromatographic column.

enantiomers: Stereoisomers that are nonsuperposable mirror images of each other.

endergonic reaction: A chemical reaction that consumes energy (that is, for which ΔG is positive).

endocrine: Pertaining to cellular secretions that enter the bloodstream and have their effects on distant tissues.

endocytosis: The uptake of extracellular material by its inclusion in a vesicle (endosome) formed by invagination of the plasma membrane.

endonucleases: Enzymes that hydrolyze the interior phosphodiester bonds of a nucleic acid—that is, act at bonds other than the terminal bonds.

endoplasmic reticulum: An extensive system of double membranes in the cytoplasm of eukaryotic cells; it encloses secretory channels and is often studded with ribosomes (rough endoplasmic reticulum).

endothermic reaction: A chemical reaction that takes up heat (that is, for which ΔH is positive).

end-product inhibition: *See* feedback inhibition.

enhancers: DNA sequences that facilitate the expression of a given gene; may be located a few hundred, or even thousand, base pairs away from the gene.

enthalpy (H): The heat content of a system.

enthalpy change (ΔH): For a reaction, approximately equal to the difference between the energy used to break bonds and the energy gained by the formation of new ones.

entropy (S): The extent of randomness or disorder in a system.

enzyme: A biomolecule, either protein or RNA, that catalyzes a specific chemical reaction. It does not affect the equilibrium of the catalyzed reaction; it enhances the rate of the reaction by providing a reaction path with a lower activation energy.

enzyme cascade: A series of reactions, often involved in regulatory events, in which one enzyme activates another (often by phosphorylation), which activates a third, and so on. The effect of a catalyst activating a catalyst is a large amplification of the signal that initiated the cascade.

epigenetic: Describes any inherited characteristic of a living organism that is acquired by means that do not involve the nucleotide sequence of the parental chromosomes; for example, covalent modifications of histones.

epimerases: Enzymes that catalyze the reversible interconversion of two epimers.

epimers: Two stereoisomers differing in configuration at one asymmetric center in a compound having two or more asymmetric centers.

epithelial cell: Any cell that forms part of the outer covering of an organism or organ.

epitope: An antigenic determinant; the particular chemical group or groups in a macromolecule (antigen) to which a given antibody binds.

epitope tag: A protein sequence or domain bound by some well-characterized antibody.

equilibrium: The state of a system in which no further net change is occurring; the free energy is at a minimum.

equilibrium constant (K_{eq}): A constant, characteristic for each chemical reaction, that relates the specific concentrations of all reactants and products at equilibrium at a given temperature and pressure.

erythrocyte: A cell containing large amounts of hemoglobin and specialized for oxygen transport; a red blood cell.

essential amino acids: Amino acids that cannot be synthesized by humans (and other vertebrates) and must be obtained from the diet.

essential fatty acids: The group of polyunsaturated fatty acids produced by plants, but not by humans; required in the human diet.

ethanol fermentation: The anaerobic conversion of glucose to ethanol via glycolysis; also called alcohol fermentation. *See also* fermentation.

euchromatin: The regions of interphase chromosomes that stain diffusely, as opposed to the more condensed, heavily staining, heterochromatin. These are often regions in which genes are being actively expressed.

eukaryote: A unicellular or multicellular organism with cells having a membrane-bounded nucleus, multiple chromosomes, and internal organelles.

excited state: An energy-rich state of an atom or molecule, produced by the absorption of light energy; as distinct from ground state.

exergonic reaction: A chemical reaction that proceeds with the release of free energy (that is, for which ΔG is negative).

exocytosis: The fusion of an intracellular vesicle with the plasma membrane, releasing the vesicle contents to the extracellular space.

exon: The segment of a eukaryotic gene that encodes a portion of the final product of the gene; a segment of RNA that remains after posttranscriptional processing and is

transcribed into a protein or incorporated into the structure of an RNA. *See also* intron.

exonucleases: Enzymes that hydrolyze only those phosphodiester bonds that are in the terminal positions of a nucleic acid.

exothermic reaction: A chemical reaction that releases heat (that is, for which ΔH is negative).

expression vector: *See* vector.

extracellular matrix (ECM): An interwoven combination of glycosaminoglycans, proteoglycans, and proteins, just outside the plasma membrane, that provides cell anchorage, positional recognition, and traction during cell migration.

extrahepatic: Describes all tissues outside the liver; implies the centrality of the liver in metabolism.

f

facilitated diffusion: *See* passive transport.

FAD (flavin adenine dinucleotide): The coenzyme of some oxidation-reduction enzymes; contains riboflavin.

F_1 ATPase: The multiprotein subunit of ATP synthase that has the ATP-synthesizing catalytic sites. It interacts with the F_o subunit of ATP synthase, coupling proton movement to ATP synthesis.

fatty acid: A long-chain aliphatic carboxylic acid found in natural fats and oils; also a component of membrane phospholipids and glycolipids.

feedback inhibition: Inhibition of an allosteric enzyme at the beginning of a metabolic sequence by the end product of the sequence; also known as end-product inhibition.

fermentation: Energy-yielding anaerobic breakdown of a nutrient molecule, such as glucose, without net oxidation; yields lactate, ethanol, or some other simple product.

fibrin: A protein factor that forms the cross-linked fibers in blood clots.

fibrinogen: The inactive precursor protein of fibrin.

fibroblast: A cell of the connective tissue that secretes connective tissue proteins such as collagen.

fibrous proteins: Insoluble proteins that serve a protective or structural role; contain polypeptide chains that generally share a common secondary structure.

first law of thermodynamics: The law stating that, in all processes, the total energy of the universe remains constant.

Fischer projection formulas: A method for representing molecules that shows the configuration of groups around chiral centers; also known as projection formulas.

5′ end: The end of a nucleic acid that lacks a nucleotide bound at the 5′ position of the terminal residue.

flagellum: A cell appendage used in propulsion. Bacterial flagella have a much simpler structure than eukaryotic flagella, which are similar to cilia.

flavin-linked dehydrogenases: Dehydrogenases requiring one of the riboflavin coenzymes, FMN or FAD.

flavin nucleotides: Nucleotide coenzymes (FMN and FAD) containing riboflavin.

flavoprotein: An enzyme containing a flavin nucleotide as a tightly bound prosthetic group.

flippases: Membrane proteins in the ABC transporter family that catalyze the movement of phospholipids from the extracellular leaflet to the cytosolic leaflet of a membrane bilayer.

floppases: Membrane proteins in the ABC transporter family that catalyze movement of phospholipids from the cytosolic leaflet to the extracellular leaflet of a membrane bilayer.

fluid mosaic model: A model describing biological membranes as a fluid lipid bilayer with embedded proteins; the bilayer exhibits both structural and functional asymmetry.

fluorescence: Emission of light by excited molecules as they revert to the ground state.

fluorescence recovery after photobleaching: *See* FRAP.

fluorescence resonance energy transfer: *See* FRET.

FMN (flavin mononucleotide): Riboflavin phosphate, a coenzyme of certain oxidation-reduction enzymes.

fold: *See* motif.

footprinting: A technique for identifying the nucleic acid sequence bound by a DNA- or RNA-binding protein.

fraction: A portion of a biological sample that has been subjected to a procedure designed to separate macromolecules based on a property such as solubility, net charge, molecular weight, or function.

fractionation: The process of separating the proteins or other components of a complex molecular mixture into fractions based on differences in properties such as solubility, net charge, molecular weight, or function.

frame shift: A mutation caused by insertion or deletion of one or more paired nucleotides, changing the reading frame of codons during protein synthesis; the polypeptide product has a garbled amino acid sequence beginning at the mutated codon.

FRAP (fluorescence recovery after photobleaching): A technique used to quantify the diffusion of membrane components (lipids or proteins) in the plane of the bilayer.

free energy (G): The component of the total energy of a system that can do work at constant temperature and pressure.

free energy of activation ($\Delta G^{\ddagger}$): *See* activation energy.

free-energy change (ΔG): The amount of free energy released (negative ΔG) or absorbed (positive ΔG) in a reaction at constant temperature and pressure.

free radical: *See* radical.

FRET (fluorescence resonance energy transfer): A technique for estimating the distance between two proteins or two domains of a protein by measuring the nonradiative transfer of energy between reporter chromophores when one is excited and the fluorescence emitted from the other is quantified.

functional group: The specific atom or group of atoms that confers a particular chemical property on a biomolecule.

fusion protein: (1) One of a family of proteins that facilitate membrane fusion. (2) The protein product of a gene created by the fusion of two distinct genes or portions of genes.

futile cycle: A cycle of enzyme-catalyzed reactions that results in release of thermal energy by the hydrolysis of ATP.

g

G_i: *See* inhibitory G protein.

G_s: *See* stimulatory G protein.

gametes: Reproductive cells with a haploid gene content; sperm or egg cells.

ganglioside: Sphingolipid containing a complex oligosaccharide as a head group; especially common in nervous tissue.

GEFs: *See* guanosine nucleotide–exchange factors.

gel filtration: *See* size-exclusion chromatography.

gene: A chromosomal segment that codes for a single functional polypeptide chain or RNA molecule.

gene expression: Transcription, and in the case of proteins, translation, to yield the product of a gene; a gene is expressed when its biological product is present and active.

gene fusion: The enzymatic attachment of one gene, or part of a gene, to another.

general acid-base catalysis: Catalysis involving proton transfer(s) to or from a molecule other than water.

genetic code: The set of triplet code words in DNA (or mRNA) coding for the amino acids of proteins.

genetic engineering: Any process by which genetic material, particularly DNA, is altered by a molecular biologist.

genetic map: A diagram showing the relative sequence and position of specific genes along a chromosome.

genome: All the genetic information encoded in a cell or virus.

genomic library: A DNA library containing DNA segments that represent all (or most) of the sequences in an organism's genome.

genomics: A science devoted broadly to the understanding of cellular and organism genomes.

genotype: The genetic constitution of an organism, as distinct from its physical characteristics, or phenotype.

geometric isomers: Isomers related by rotation about a double bond; also called cis and trans isomers.

germ-line cell: A type of animal cell that is formed early in embryogenesis and may multiply by mitosis or produce by meiosis cells that develop into gametes (egg or sperm cells).

GFP: *See* green fluorescent protein.

globular proteins: Soluble proteins with a globular (somewhat rounded) shape.

glucogenic: Capable of being converted into glucose or glycogen by the process of gluconeogenesis.

gluconeogenesis: The biosynthesis of a carbohydrate from simpler, noncarbohydrate precursors such as oxaloacetate or pyruvate.

GLUT: Designation for a family of membrane proteins that transport glucose.

glycan: A polymer of monosaccharide units joined by glycosidic bonds; polysaccharide.

glyceroneogenesis: The synthesis in adipocytes of glycerol 3-phosphate from pyruvate for use in triacylglycerol synthesis.

glycerophospholipid: An amphipathic lipid with a glycerol backbone; fatty acids are ester-linked to C-1 and C-2 of glycerol, and a polar alcohol is attached through a phosphodiester linkage to C-3.

glycoconjugate: A compound containing a carbohydrate component bound covalently to a protein or lipid, forming a glycoprotein or glycolipid.

glycogenesis: The process of converting glucose to glycogen.

glycogenin: The protein that both primes the synthesis of new glycogen chains and catalyzes the polymerization of the first few sugar residues of each chain before glycogen synthase continues the extension.

glycogenolysis: The enzymatic breakdown of stored (not dietary) glycogen.

glycolate pathway: The metabolic pathway in photosynthetic organisms that converts glycolate produced during photorespiration into 3-phosphoglycerate.

glycolipid: A lipid containing a carbohydrate group.

glycolysis: The catabolic pathway by which a molecule of glucose is broken down into two molecules of pyruvate.

glycome: The full complement of carbohydrates and carbohydrate-containing molecules of a cell or tissue under a particular set of conditions.

glycomics: The systematic characterization of the glycome.

glycoprotein: A protein containing a carbohydrate group.

glycosaminoglycan: A heteropolysaccharide of two alternating units: one is either *N*-acetylglucosamine or *N*-acetylgalactosamine; the other is a uronic acid (usually glucuronic acid). Formerly called a mucopolysaccharide.

glycosidic bonds: *See O*-glyosidic bonds.

glycosphingolipid: An amphipathic lipid with a sphingosine backbone to which are attached a long-chain fatty acid and a polar alcohol.

glyoxylate cycle: A variant of the citric acid cycle, for the net conversion of acetate into succinate and, eventually, new carbohydrate; present in bacteria and some plant cells.

glyoxysome: A specialized peroxisome containing the enzymes of the glyoxylate cycle; found in cells of germinating seeds.

Golgi complex: A complex membranous organelle of eukaryotic cells; functions in the post-translational modification of proteins and their secretion from the cell or incorporation into the plasma membrane or organellar membranes.

GPCRs: *See* G protein–coupled receptors.

GPI-anchored protein: A protein held to the outer monolayer of the plasma membrane by its covalent attachment through a short oligosaccharide chain to a phosphatidylinositol molecule in the membrane.

G protein–coupled receptor kinases (GRKs): A family of protein kinases that phosphorylate Ser and Thr residues near the carboxyl terminus of G protein–coupled receptors, initiating their internalization.

G protein–coupled receptors (GPCRs): A large family of membrane receptor proteins with seven transmembrane helical segments, often associating with G proteins to transduce an extracellular signal into a change in cellular metabolism; also called heptahelical receptors.

G proteins: A large family of GTP-binding proteins that act in intracellular signaling pathways and in membrane trafficking. Active when GTP is bound, they self-inactivate by converting GTP to GDP. Also called guanosine nucleotide–binding proteins.

gram molecular weight: For a compound, the weight in grams that is numerically equal to its molecular weight; the weight of one mole.

grana: Stacks of thylakoids, flattened membranous sacs or disks, in chloroplasts.

green fluorescent protein (GFP): A small protein from a marine organism that produces a bright fluorescence in the green region of the visible spectrum. Fusion proteins with GFP are commonly used to determine the subcellular location of the fused protein by fluorescence microscopy.

ground state: The normal, stable form of an atom or molecule; as distinct from the excited state.

group transfer potential: A measure of the ability of a compound to donate an activated group (such as a phosphate or acyl group); generally expressed as the standard free energy of hydrolysis.

growth factors: Proteins or other molecules that act from outside a cell to stimulate cell growth and division.

GTPase activator proteins (GAPs): Regulatory proteins that bind activated G proteins and stimulate their intrinsic GTPase activity, speeding their self-inactivation.

guanosine nucleotide–binding proteins: *See* G proteins.

guanosine nucleotide–exchange factors (GEFs): Regulatory proteins that bind to and activate G proteins by stimulating the exchange of bound GDP for GTP.

h

hairpin: Secondary structure in single-stranded RNA or DNA, in which complementary parts of a palindromic repeat fold back and are paired to form an antiparallel duplex helix that is closed at one end.

half-life: The time required for the disappearance or decay of one-half of a given component in a system.

haploid: Having a single set of genetic information; describes a cell with one chromosome of each type. *Compare* diploid.

haplotype: A combination of alleles of different genes located sufficiently close together on a chromosome that they tend to be inherited together.

hapten: A small molecule that, when linked to a larger molecule, elicits an immune response.

Haworth perspective formulas: A method for representing cyclic chemical structures so as to define the configuration of each substituent group; commonly used for representing sugars.

helicases: Enzymes that catalyze the separation of strands in a DNA molecule before replication.

heme: The iron-porphyrin prosthetic group of heme proteins.

heme protein: A protein containing a heme as a prosthetic group.

hemoglobin: A heme protein in erythrocytes; functions in oxygen transport.

Henderson-Hasselbalch equation: An equation relating the pH, the pK_a, and the ratio of the concentrations of proton-acceptor (A^-) and proton-donor (HA) species in a solution:

$$pH = pK_a + \log \frac{[A^-]}{[HA]}.$$

heparan sulfate: A sulfated polymer of alternating *N*-acetylglucosamine and a uronic acid, either glucuronic or iduronic acid; typically found in the extracellular matrix.

hepatocyte: The major cell type of liver tissue.

heptahelical receptors: *See* G protein–coupled receptors.

heteropolysaccharide: A polysaccharide containing more than one type of sugar.

heterotroph: An organism that requires complex nutrient molecules, such as glucose, as a source of energy and carbon.

heterotropic: Describes an allosteric modulator that is distinct from the normal ligand.

heterotropic enzyme: An allosteric enzyme requiring a modulator other than its substrate.

hexose: A simple sugar with a backbone containing six carbon atoms.

hexose monophosphate pathway: *See* pentose phosphate pathway.

high-performance liquid chromatography (HPLC): Chromatographic procedure, often conducted at relatively high pressures using automated equipment, which permits refined and highly reproducible profiles.

Hill coefficient: A measure of cooperative interaction between protein subunits.

Hill reaction: The evolution of oxygen and photoreduction of an artificial electron acceptor by a chloroplast preparation in the absence of carbon dioxide.

histones: The family of basic proteins that associate tightly with DNA in the chromosomes of all eukaryotic cells.

Holliday intermediate: An intermediate in genetic recombination in which two double-stranded DNA molecules are joined by a reciprocal crossover involving one strand of each molecule.

holoenzyme: A catalytically active enzyme, including all necessary subunits, prosthetic groups, and cofactors.

homeobox: A conserved DNA sequence of 180 base pairs that encodes a protein domain found in many proteins that play a regulatory role in development.

homeodomain: The protein domain encoded by the homeobox; a regulatory unit that determines the segmentation of a body plan.

homeostasis: The maintenance of a dynamic steady state by regulatory mechanisms that compensate for changes in external circumstances.

homeotic genes: Genes that regulate development of the pattern of segments in the *Drosophila* body plan; similar genes are found in most vertebrates.

homologs: Genes or proteins that possess a clear sequence and functional relationship to each other.

homologous genetic recombination: Recombination between two DNA molecules of similar sequence, occurring in all cells; occurs during meiosis and mitosis in eukaryotes.

homologous proteins: Proteins having similar sequences and functions in different species; for example, the hemoglobins.

homotropic: Describes an allosteric modulator that is identical to the normal ligand.

homotropic enzyme: An allosteric enzyme that uses its substrate as a modulator.

hormone: A chemical substance synthesized in small amounts by an endocrine tissue and carried in the blood to another tissue, where it acts as a messenger to regulate the function of the target tissue or organ.

hormone receptor: A protein in, or on the surface of, target cells that binds a specific hormone and initiates the cellular response.

hormone response element (HRE): A short (12 to 20 bp) DNA sequence that binds receptors for steroid, retinoid, thyroid, and vitamin D hormones, altering the expression of the contiguous genes. Each hormone has a consensus sequence preferred by the cognate receptor.

HPLC: *See* high-performance liquid chromatography.

HRE: *See* hormone response element.

hyaluronan: A high molecular weight, acidic polysaccharide typically composed of the alternating disaccharide GlcUA(β1→3)GlcNAc; a major component of the extracellular matrix, forming larger complexes (proteoglycans) with proteins and other acidic polysaccharides. Also called hyaluronic acid.

hydrogen bond: A weak electrostatic attraction between one electronegative atom (such as oxygen or nitrogen) and a hydrogen atom covalently linked to a second electronegative atom.

hydrolases: Enzymes (proteases, lipases, phosphatases, nucleases, for example) that catalyze hydrolysis reactions.

hydrolysis: Cleavage of a bond, such as an anhydride or peptide bond, by the addition of the elements of water, yielding two or more products.

hydronium ion: The hydrated hydrogen ion (H_3O^+).

hydropathy index: A scale that expresses the relative hydrophobic and hydrophilic tendencies of a chemical group.

hydrophilic: Polar or charged; describes molecules or groups that associate with (dissolve easily in) water.

hydrophobic: Nonpolar; describes molecules or groups that are insoluble in water.

hydrophobic interactions: The association of nonpolar groups or compounds with each other in aqueous systems, driven by the tendency of the surrounding water molecules to seek their most stable (disordered) state.

hyperchromic effect: The large increase in light absorption at 260 nm occurring as a double-helical DNA unwinds (melts).

hypoxia: The metabolic condition in which the supply of oxygen is severely limited.

i

immune response: The capacity of a vertebrate to generate antibodies to an antigen, a macromolecule foreign to the organism.

immunoblotting: A technique that employs antibodies to detect the presence of a protein in a biological sample after the proteins in the sample have been separated by gel electrophoresis, transferred to a membrane and immobilized; also called Western blotting.

immunoglobulin: An antibody protein generated against, and capable of binding specifically to, an antigen.

induced fit: A change in the conformation of an enzyme in response to substrate binding that renders the enzyme catalytically active; also used to denote changes in the conformation of any macromolecule in response to ligand binding such that the binding site of the macromolecule better conforms to the shape of the ligand.

inducer: A signal molecule that, when bound to a regulatory protein, produces an increase in the expression of a given gene.

induction: An increase in the expression of a gene in response to a change in the activity of a regulatory protein.

informational macromolecules: Biomolecules containing information in the form of specific sequences of different monomers; for example, many proteins, lipids, polysaccharides, and nucleic acids.

inhibitory G protein (G_i): A trimeric GTP-binding protein that, when activated by an associated plasma membrane receptor, inhibits a neighboring membrane enzyme such as adenylyl cyclase. Compare stimulatory G protein (G_s).

initiation codon: AUG (sometimes GUG or, even more rarely, UUG in bacteria and archaea); codes for the first amino acid in a polypeptide sequence: *N*-formylmethionine in bacteria; methionine in archaea and eukaryotes.

initiation complex: A complex of a ribosome with an mRNA and the initiating Met-tRNA^{Met} or fMet-tRNA^{fMet}, ready for the elongation steps.

inorganic pyrophosphatase: An enzyme that hydrolyzes a molecule of inorganic pyrophosphate to yield two molecules of (ortho) phosphate; also known as pyrophosphatase.

insertion mutation: A mutation caused by insertion of one or more extra bases, or a mutagen, between successive bases in DNA.

insertion sequence: Specific base sequences at either end of a transposable segment of DNA.

in situ: "In position"; that is, in its natural position or location.

integral proteins: Proteins firmly bound to a membrane by hydrophobic interactions; as distinct from peripheral proteins.

integrin: One of a large family of heterodimeric transmembrane proteins that mediate adhesion of cells to other cells or to the extracellular matrix.

intercalation: Insertion between stacked aromatic or planar rings; for example, the insertion of a planar molecule between two successive bases in a nucleic acid.

intermediary metabolism: In cells, the enzyme-catalyzed reactions that extract chemical energy from nutrient molecules and use it to synthesize and assemble cell components.

intrinsically disordered proteins: Proteins, or segments of proteins, that lack a definable three-dimensional structure in solution.

intron: A sequence of nucleotides in a gene that is transcribed but excised before the gene is translated; also called intervening sequence. *See also* exon.

in vitro: "In glass"; that is, in the test tube.

in vivo: "In life"; that is, in the living cell or organism.

ion channel: An integral protein that provides for the regulated transport of a specific ion, or ions, across a membrane.

ion-exchange chromatography: A process for separating complex mixtures of ionic compounds by many repeated partitionings between a flowing (mobile) phase and a stationary phase consisting of a polymeric resin that contains fixed charged groups.

ionizing radiation: A type of radiation, such as x rays, that causes loss of electrons from some organic molecules, thus making them more reactive.

ionophore: A compound that binds one or more metal ions and is capable of diffusing across a membrane, carrying the bound ion.

ion product of water (K_w): The product of the concentrations of H^+ and OH^- in pure water: $K_w = [H^+][OH^-] = 1 \times 10^{-14}$ at 25 °C.

iron-sulfur protein: One of a large family of electron-transfer proteins in which the electron carrier is one or more iron ions associated with two or more sulfur atoms of Cys residues or of inorganic sulfide.

isoelectric focusing: An electrophoretic method for separating macromolecules on the basis of isoelectric pH.

isoelectric pH (isoelectric point, pI): The pH at which a solute has no net electric charge and thus does not move in an electric field.

isoenzymes: *See* isozymes.

isomerases: Enzymes that catalyze the transformation of compounds into their positional isomers.

isomers: Any two molecules with the same molecular formula but a different arrangement of molecular groups.

isoprene: The hydrocarbon 2-methyl-1,3-butadiene, a recurring structural unit of terpenoids.

isoprenoid: Any of a large number of natural products synthesized by enzymatic polymerization of two or more isoprene units; also called terpenoid.

isozymes: Multiple forms of an enzyme that catalyze the same reaction but differ in amino acid sequence, substrate affinity, V_{max}, and/or regulatory properties; also called isoenzymes.

k

ketogenic: Yielding acetyl-CoA, a precursor for ketone body formation, as a breakdown product.

ketone bodies: Acetoacetate, D-β-hydroxybutyrate, and acetone; water-soluble fuels normally exported by the liver but overproduced during fasting or in untreated diabetes mellitus.

ketose: A simple monosaccharide in which the carbonyl group is a ketone.

ketosis: A condition in which the concentration of ketone bodies in the blood, tissues, and urine is abnormally high.

kinases: Enzymes that catalyze the phosphorylation of certain molecules by ATP.

kinetics: The study of reaction rates.

Krebs cycle: *See* citric acid cycle.

K_t ($K_{transport}$): A kinetic parameter for a membrane transporter analogous to the Michaelis constant, K_m, for an enzymatic reaction. The rate of substrate uptake is half-maximal when the substrate concentration equals the K_t.

l

lagging strand: The DNA strand that, during replication, must be synthesized in the direction opposite to that in which the replication fork moves.

law of mass action: The law stating that the rate of any given chemical reaction is proportional to the product of the activities (or concentrations) of the reactants.

leader: A short sequence near the amino terminus of a protein or the 5′ end of an RNA that has a specialized targeting or regulatory function.

leading strand: The DNA strand that, during replication, is synthesized in the same direction as the replication fork moves.

leaky mutant: A mutant gene that gives rise to a product with a detectable level of biological activity.

leaving group: The departing or displaced molecular group in a unimolecular elimination or bimolecular substitution reaction.

lectin: A protein that binds a carbohydrate, commonly an oligosaccharide, with very high affinity and specificity, mediating cell-cell interactions.

lethal mutation: A mutation that inactivates a biological function essential to the life of the cell or organism.

leucine zipper: A protein structural motif involved in protein-protein interactions in many eukaryotic regulatory proteins; consists of two interacting α helices in which Leu residues in every seventh position are a prominent feature of the interacting surfaces.

leukocyte: White blood cell; involved in the immune response in mammals.

leukotriene: Any of a class of signaling lipids derived from arachidonate in the noncyclic pathway; modulate smooth muscle activity.

ligand: A small molecule that binds specifically to a larger one; for example, a hormone is the ligand for its specific protein receptor.

ligases: Enzymes that catalyze condensation reactions in which two atoms are joined using the energy of ATP or another energy-rich compound.

light-dependent reactions: The reactions of photosynthesis that require light and cannot occur in the dark; also known as light reactions.

Lineweaver-Burk equation: An algebraic transform of the Michaelis-Menten equation, allowing determination of V_{max} and K_m by extrapolation of [S] to infinity:

$$\frac{1}{V_0} = \frac{K_m}{V_{max}[S]} + \frac{1}{V_{max}}.$$

linking number: The number of times one closed circular DNA strand is wound about another; the number of topological links holding the circles together.

lipases: Enzymes that catalyze the hydrolysis of triacylglycerols.

lipid: A small water-insoluble biomolecule generally containing fatty acids, sterols, or isoprenoid compounds.

lipidome: The full complement of lipid-containing molecules in a cell, organ, or tissue under a particular set of conditions.

lipidomics: The systematic characterization of the lipidome.

lipoate (lipoic acid): A vitamin for some microorganisms; an intermediate carrier of hydrogen atoms and acyl groups in α-keto acid dehydrogenases.

lipoprotein: A lipid-protein aggregate that serves to carry water-insoluble lipids in the blood. The protein component alone is an apolipoprotein.

liposome: A small, spherical vesicle composed of a phospholipid bilayer, forming spontaneously when phospholipids are suspended in an aqueous buffer.

lyases: Enzymes that catalyze the removal of a group from a molecule to form a double bond, or the addition of a group to a double bond.

lymphocytes: A subclass of leukocytes involved in the immune response. *See also* B lymphocytes; T lymphocytes.

lysis: Destruction of a plasma membrane or (in bacteria) cell wall, releasing the cellular contents and killing the cell.

lysosome: A membrane-bounded organelle of eukaryotic cells; it contains many hydrolytic enzymes and serves as a degrading and recycling center for unneeded components.

m

macromolecule: A molecule having a molecular weight in the range of a few thousand to many millions.

mass-action ratio (Q): For the reaction $aA + bB \rightleftharpoons cC + dD$, the ratio $[C]^c[D]^d/[A]^a[B]^b$.

matrix: The space enclosed by the inner membrane of the mitochondrion.

mechanistic target of rapamycin complex 1: *See* mTORC1.

meiosis: A type of cell division in which diploid cells give rise to haploid cells destined to become gametes or spores.

membrane potential (V_m): The difference in electrical potential across a biological membrane, commonly measured by the insertion of a microelectrode. Typical membrane potentials vary from −25 mV (by convention, the negative sign indicates that the inside is negative relative to the outside) to greater than −100 mV across some plant vacuolar membranes.

membrane transport: Movement of a polar solute across a membrane via a specific membrane protein (a transporter).

messenger RNA (mRNA): A class of RNA molecules, each of which is complementary to one strand of DNA; carries the genetic message from the chromosome to the ribosomes.

metabolic control: The mechanisms by which the flux through a metabolic pathway is changed to reflect a cell's altered circumstances.

metabolic regulation: The mechanisms by which a cell resists changes in the concentration of individual metabolites that would otherwise occur when metabolic control mechanisms alter the flux through a pathway.

metabolic syndrome: A combination of medical conditions that together predispose to cardiovascular disease and type 2 diabetes. They include high blood pressure, high concentrations of LDL and triacylglycerol in the

blood, slightly elevated fasting blood glucose concentration, and obesity.

metabolism: The entire set of enzyme-catalyzed transformations of organic molecules in living cells; the sum of anabolism and catabolism.

metabolite: A chemical intermediate in the enzyme-catalyzed reactions of metabolism.

metabolome: The complete set of small-molecule metabolites (metabolic intermediates, signals, secondary metabolites) present in a given cell or tissue under specific conditions.

metabolomics: The systematic characterization of the metabolome of a cell or tissue.

metabolon: A supramolecular assembly of sequential metabolic enzymes.

metalloprotein: A protein with a metal ion as its prosthetic group.

metamerism: Division of the body into segments, as in insects, for example.

micelle: An aggregate of amphipathic molecules in water, with the nonpolar portions in the interior and the polar portions at the exterior surface, exposed to water.

Michaelis constant (K_m): The substrate concentration at which an enzyme-catalyzed reaction proceeds at one-half its maximum velocity.

Michaelis-Menten equation: The equation describing the hyperbolic dependence of the initial reaction velocity, V_0, on substrate concentration, [S], in many enzyme-catalyzed reactions:

$$V_0 = \frac{V_{max}[S]}{K_m + [S]}.$$

Michaelis-Menten kinetics: A kinetic pattern in which the initial rate of an enzyme-catalyzed reaction exhibits a hyperbolic dependence on substrate concentration.

microRNA: A class of small RNA molecules (20 to 25 nucleotides after processing is complete) involved in gene silencing by inhibiting translation and/or promoting the degradation of particular mRNAs.

microsomes: Membranous vesicles formed by fragmentation of the endoplasmic reticulum of eukaryotic cells; recovered by differential centrifugation.

miRNA: *See* microRNA.

mismatch: A base pair in a nucleic acid that cannot form a normal Watson-Crick pair.

mismatch repair: An enzymatic system for repairing base mismatches in DNA.

mitochondrion: Membrane-bounded organelle of eukaryotic cells; contains the enzyme systems required for the citric acid cycle, fatty acid oxidation, electron transfer, and oxidative phosphorylation.

mitosis: In eukaryotic cells, the multistep process that results in the replication of chromosomes and cell division.

mixed-function oxygenases: Enzymes (a monooxygenase, for example) that catalyze reactions in which two reductants—one of which is generally NADPH, the other the substrate—are oxidized. One oxygen atom is incorporated into the product, the other is reduced to H_2O. These enzymes often use cytochrome P-450 to carry electrons from NADPH to O_2.

mixed inhibition: The reversible inhibition pattern resulting when an inhibitor molecule can bind to either the free enzyme or the enzyme-substrate complex (not necessarily with the same affinity).

modulator: A metabolite that, when bound to the allosteric site of an enzyme, alters its kinetic characteristics.

molar solution: One mole of solute dissolved in water to give a total volume of 1,000 mL.

mole: One gram molecular weight of a compound. *See also* Avogadro's number.

monocistronic mRNA: An mRNA that can be translated into only one protein.

monoclonal antibodies: Antibodies produced by a cloned hybridoma cell, which therefore are identical and directed against the same epitope of the antigen. (Hybridoma cells are stable antibody-producing cell lines that grow well in tissue culture; created by fusing an antibody-producing B cell with a myeloma cell.)

monosaccharide: A carbohydrate consisting of a single sugar unit.

moonlighting enzymes: Enzymes that play two distinct roles, at least one of which is catalytic; the other may be catalytic, regulatory, or structural.

motif: Any distinct folding pattern for elements of secondary structure, observed in one or more proteins. A motif can be simple or complex, and can represent all or just a small part of a polypeptide chain. Also called a fold or supersecondary structure.

mRNA: *See* messenger RNA.

mTORC1 (mechanistic target of rapamycin complex 1): A multiprotein complex of mTOR (mechanistic target of rapamycin) and several regulatory subunits, which together have activity as a Ser/Thr protein kinase. Stimulated by nutrients and energy-sufficient conditions, it triggers cell growth and proliferation.

mucopolysaccharide: *See* glycosaminoglycan.

multidrug transporters: Plasma membrane transporters in the ABC transporter family that expel several commonly used antitumor drugs, thereby interfering with antitumor therapy.

multienzyme system: A group of related enzymes participating in a given metabolic pathway.

mutarotation: The change in specific rotation of a pyranose or furanose sugar or glycoside accompanying the equilibration of its α- and β-anomeric forms.

mutases: Enzymes that catalyze the transposition of functional groups.

mutation: An inheritable change in the nucleotide sequence of a chromosome.

myocyte: A muscle cell.

myofibril: A unit of thick and thin filaments of muscle fibers.

myosin: A contractile protein; the major component of the thick filaments of muscle and other actin-myosin systems.

n

NAD, NADP (nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate): Nicotinamide-containing coenzymes functioning as carriers of hydrogen atoms and electrons in some oxidation-reduction reactions.

Na^+K^+ ATPase: The electrogenic ATP-driven active transporter in the plasma membrane of most animal cells that pumps three Na^+ outward for every two K^+ moved inward.

native conformation: The biologically active conformation of a macromolecule.

ncRNA (noncoding RNA): Any RNA that does not encode instructions for a protein product.

negative cooperativity: A property of some multisubunit enzymes or proteins in which binding of a ligand or substrate to one subunit impairs binding to another subunit.

negative feedback: Regulation of a biochemical pathway in which a reaction product inhibits an earlier step in the pathway.

neuron: A cell of nervous tissue specialized for transmission of a nerve impulse.

neurotransmitter: A low molecular weight compound (usually containing nitrogen) secreted from the axon terminal of a neuron and bound by a specific receptor on the next neuron or on a myocyte; serves to transmit a nerve impulse.

nitrogenase complex: A system of enzymes capable of reducing atmospheric nitrogen to ammonia in the presence of ATP.

nitrogen cycle: The cycling of various forms of biologically available nitrogen through the plant, animal, and microbial worlds, and through the atmosphere and geosphere.

nitrogen fixation: Conversion of atmospheric nitrogen (N_2) into a reduced, biologically available form by nitrogen-fixing organisms.

NMR: *See* nuclear magnetic resonance spectroscopy.

noncoding RNA: *See* ncRNA.

noncyclic electron flow: The light-induced flow of electrons from water to $NADP^+$ in oxygen-evolving photosynthesis; involves both photosystems I and II.

nonessential amino acids: Amino acids that can be made by humans and other vertebrates from simpler precursors and are thus not required in the diet.

nonheme iron proteins: Proteins, usually acting in oxidation-reduction reactions, containing iron but no porphyrin groups.

nonpolar: Hydrophobic; describes molecules or groups that are poorly soluble in water.

nonsense codon: A codon that does not specify an amino acid, but signals the termination of a polypeptide chain.

nonsense mutation: A mutation that results in the premature termination of a polypeptide chain.

nonsense suppressor: A mutation, usually in the gene for a tRNA, that causes an amino acid to be inserted into a polypeptide in response to a termination codon.

nontemplate strand: *See* coding strand.

nuclear magnetic resonance (NMR) spectroscopy: A technique that utilizes certain quantum mechanical properties of atomic nuclei to study the structure and dynamics of the molecules of which they are a part.

nucleases: Enzymes that hydrolyze the internucleotide (phosphodiester) linkages of nucleic acids.

nucleic acids: Biologically occurring polynucleotides in which the nucleotide residues are linked in a specific sequence by phosphodiester bonds; DNA and RNA.

nucleoid: In bacteria, the nuclear zone that contains the chromosome but has no surrounding membrane.

nucleolus: In eukaryotic cells, a densely staining structure in the nucleus; involved in rRNA synthesis and ribosome formation.

nucleophile: An electron-rich group with a strong tendency to donate electrons to an electron-deficient nucleus (electrophile); the entering reactant in a bimolecular substitution reaction.

nucleoplasm: The portion of a eukaryotic cell's contents enclosed by the nuclear membrane.

nucleoside: A compound consisting of a purine or pyrimidine base covalently linked to a pentose.

nucleoside diphosphate kinase: An enzyme that catalyzes the transfer of the terminal phosphate of a nucleoside 5′-triphosphate to a nucleoside 5′-diphosphate.

nucleoside diphosphate sugar: A coenzymelike carrier of a sugar molecule, functioning in the enzymatic synthesis of polysaccharides and sugar derivatives.

nucleoside monophosphate kinase: An enzyme that catalyzes the transfer of the terminal phosphate of ATP to a nucleoside 5′-monophosphate.

nucleosome: In eukaryotes, structural unit for packaging chromatin; consists of a DNA strand wound around a histone core.

nucleotide: A nucleoside phosphorylated at one of its pentose hydroxyl groups.

nucleus: In eukaryotes, a membrane-bounded organelle that contains chromosomes.

o

***O*-glycosidic bonds:** Bonds between a sugar and another molecule (typically an alcohol, purine, pyrimidine, or sugar) through an intervening oxygen.

oligomer: A short polymer, usually of amino acids, sugars, or nucleotides; the definition of "short" is somewhat arbitrary, but usually fewer than 50 subunits.

oligomeric protein: A multisubunit protein having two or more identical polypeptide chains.

oligonucleotide: A short polymer of nucleotides (usually fewer than 50).

oligopeptide: A few amino acids joined by peptide bonds.

oligosaccharide: Several monosaccharide groups joined by glycosidic bonds.

***ω* oxidation:** An alternative mode of fatty acid oxidation in which the initial oxidation is at the carbon most distant from the carboxyl carbon; as distinct from β oxidation.

oncogene: A cancer-causing gene; any of several mutant genes that cause cells to exhibit rapid, uncontrolled proliferation. *See also* proto-oncogene.

open reading frame (ORF): A group of contiguous nonoverlapping nucleotide codons in a DNA or RNA molecule that does not include a termination codon.

open system: A system that exchanges matter and energy with its surroundings. *See also* system.

operator: A region of DNA that interacts with a repressor protein to control the expression of a gene or group of genes.

operon: A unit of genetic expression consisting of one or more related genes and the operator and promoter sequences that regulate their transcription.

opsin: The protein portion of the visual pigment, which becomes rhodopsin with the addition of the chromophore retinal.

optical activity: The capacity of a substance to rotate the plane of plane-polarized light.

optimum pH: The characteristic pH at which an enzyme has maximal catalytic activity.

orexigenic: Tending to increase appetite and food consumption.

ORF: *See* open reading frame.

organelles: Membrane-bounded structures found in eukaryotic cells; contain enzymes and other components required for specialized cell functions.

origin: The nucleotide sequence or site in DNA where DNA replication is initiated.

orthologs: Genes or proteins from different species that possess a clear sequence and functional relationship to each other.

osmosis: Bulk flow of water through a semipermeable membrane into another aqueous compartment containing solute at a higher concentration.

osmotic pressure: Pressure generated by the osmotic flow of water through a semipermeable membrane into an aqueous compartment containing solute at a higher concentration.

oxidases: Enzymes that catalyze oxidation reactions in which molecular oxygen serves as the electron acceptor, but neither of the oxygen atoms is incorporated into the product. *Compare* oxygenases.

oxidation: The loss of electrons from a compound.

oxidation-reduction reaction: A reaction in which electrons are transferred from a donor to an acceptor molecule; also called a redox reaction.

oxidative phosphorylation: The enzymatic phosphorylation of ADP to ATP coupled to electron transfer from a substrate to molecular oxygen.

oxidizing agent (oxidant): The acceptor of electrons in an oxidation-reduction reaction.

oxygenases: Enzymes that catalyze reactions in which oxygen atoms are directly incorporated into the product, forming a hydroxyl or carboxyl group. In reactions catalyzed by a monooxygenase, only one of the two O atoms is incorporated; the other is reduced to H_2O. In reactions catalyzed by a dioxygenase, both O atoms are incorporated into the product. *Compare* oxidases.

oxygenic photosynthesis: Light-driven ATP and NADPH synthesis in organisms that use water as the electron source, producing O_2.

p

palindrome: A segment of duplex DNA in which the base sequences of the two strands exhibit twofold rotational symmetry about an axis.

paradigm: In biochemistry, an experimental model or example.

paralogs: Genes or proteins present in the same species that possess a clear sequence and functional relationship to each other.

partition coefficient: A constant that expresses the ratio in which a given solute will be partitioned or distributed between two given immiscible liquids at equilibrium.

passive transport: Diffusion of a polar substance across a biological membrane through a protein transporter; also called facilitated diffusion.

pathogenic: Disease-causing.

PCR: *See* polymerase chain reaction.

PDB (Protein Data Bank): An international database (www.pdb.org) that archives the data describing the three-dimensional structure of nearly all macromolecules for which structures have been published.

pentose: A simple sugar with a backbone containing five carbon atoms.

pentose phosphate pathway: A pathway present in most organisms that serves to interconvert hexoses and pentoses and is a source of reducing equivalents (NADPH) and pentoses for biosynthetic processes; it begins with glucose 6-phosphate and includes 6-phosphogluconate as an intermediate. Also called the phosphogluconate pathway and the hexose monophosphate pathway.

peptidases: Enzymes that hydrolyze peptide bonds.

peptide: Two or more amino acids covalently joined by peptide bonds.

peptide bond: A substituted amide linkage between the α-amino group of one amino acid and the α-carboxyl group of another, with the elimination of the elements of water.

peptidoglycan: A major component of bacterial cell walls; generally consists of parallel heteropolysaccharides cross-linked by short peptides.

peptidyl transferase: The enzyme activity that synthesizes the peptide bonds of proteins; a ribozyme, part of the rRNA of the large ribosomal subunit.

peripheral proteins: Proteins loosely or reversibly bound to a membrane by hydrogen bonds or electrostatic forces; generally water soluble once released from the membrane. *Compare* integral proteins.

permeases: *See* transporters.

peroxisome: Membrane-bounded organelle of eukaryotic cells; contains peroxide-forming and peroxide-destroying enzymes.

peroxisome proliferator-activated receptor: *See* PPAR.

pH: The negative logarithm of the hydrogen ion concentration of an aqueous solution.

phage: *See* bacteriophage.

phenotype: The observable characteristics of an organism.

phosphatases: Enzymes that cleave phosphate esters by hydrolysis, the addition of the elements of water.

phosphodiester linkage: A chemical grouping that contains two alcohols esterified to one molecule of phosphoric acid, which thus serves as a bridge between them.

phosphogluconate pathway: *See* pentose phosphate pathway.

phospholipid: A lipid containing one or more phosphate groups.

phosphorolysis: Cleavage of a compound with phosphate as the attacking group; analogous to hydrolysis.

phosphorylases: Enzymes that catalyze phosphorolysis.

phosphorylation: Formation of a phosphate derivative of a biomolecule, usually by enzymatic transfer of a phosphoryl group from ATP.

phosphorylation potential (ΔG_p): The actual free-energy change of ATP hydrolysis under the nonstandard conditions prevailing in a cell.

photochemical reaction center: The part of a photosynthetic complex where the energy of an absorbed photon causes charge separation, initiating electron transfer.

photon: The ultimate unit (a quantum) of light energy.

photophosphorylation: The enzymatic formation of ATP from ADP coupled to the light-dependent transfer of electrons in photosynthetic cells.

photoreduction: The light-induced reduction of an electron acceptor in photosynthetic cells.

photorespiration: Oxygen consumption occurring in illuminated temperate-zone plants, largely due to oxidation of phosphoglycolate.

photosynthesis: The use of light energy to produce carbohydrates from carbon dioxide and a reducing agent such as water. *Compare* oxygenic photosynthesis.

photosynthetic phosphorylation: *See* photophosphorylation.

photosystem: In photosynthetic cells, a functional set of light-absorbing pigments and its reaction center, where the energy of an absorbed photon is transduced into a separation of electric charges.

phototroph: An organism that can use the energy of light to synthesize its own fuels from simple molecules such as carbon dioxide, oxygen, and water; as distinct from a chemotroph.

pI: *See* isoelectric pH.

pK_a: The negative logarithm of an equilibrium constant.

plasmalogen: A phospholipid with an alkenyl ether substituent on C-1 of glycerol.

plasma membrane: The exterior membrane surrounding the cytoplasm of a cell.

plasma proteins: The proteins present in blood plasma.

plasmid: An extrachromosomal, independently replicating, small circular DNA molecule; commonly employed in genetic engineering.

plastid: In plants, a self-replicating organelle; may differentiate into a chloroplast or amyloplast.

platelets: Small, enucleated cells that initiate blood clotting; they arise from bone marrow cells called megakaryocytes. Also known as thrombocytes.

pleated sheet: The side-by-side, hydrogen-bonded arrangement of polypeptide chains in the extended β conformation.

plectonemic: Describes a structure in a molecular polymer that has a net twisting of strands about each other in some simple and regular way.

PLP: *See* pyridoxal phosphate.

polar: Hydrophilic, or "water-loving"; describes molecules or groups that are soluble in water.

polarity: (1) In chemistry, the nonuniform distribution of electrons in a molecule; polar molecules are usually soluble in water. (2) In molecular biology, the distinction between the 5′ and 3′ ends of nucleic acids.

poly(A) tail: A length of adenosine residues added to the 3′ end of many mRNAs in eukaryotes (and sometimes in bacteria).

polycistronic mRNA: A contiguous mRNA with more than two genes that can be translated into proteins.

polyclonal antibodies: A heterogeneous pool of antibodies produced in an animal by different B lymphocytes in response to an antigen. Different antibodies in the pool recognize different parts of the antigen.

polylinker: A short, often synthetic, fragment of DNA containing recognition sequences for several restriction endonucleases.

polymerase chain reaction (PCR): A repetitive laboratory procedure that results in a geometric amplification of a specific DNA sequence.

polymorphic: Describes a protein for which amino acid sequence variants exist in a population of organisms, but the variations do not destroy the protein's function.

polynucleotide: A covalently linked sequence of nucleotides in which the 3′ hydroxyl of the pentose of one nucleotide residue is joined by a phosphodiester bond to the 5′ hydroxyl of the pentose of the next residue.

polypeptide: A long chain of amino acids linked by peptide bonds; the molecular weight is generally less than 10,000.

polyribosome: *See* polysome.

polysaccharide: A linear or branched polymer of monosaccharide units linked by glycosidic bonds.

polysome: A complex of an mRNA molecule and two or more ribosomes; also called polyribosome.

polyunsaturated fatty acid: *See* PUFA.

P/O ratio: The number of moles of ATP formed in oxidative phosphorylation per $\frac{1}{2}O_2$ reduced (thus, per pair of electrons passed to O_2). Experimental values used in this text are 2.5 for passage of electrons from NADH to O_2, and 1.5 for passage of electrons from FADH to O_2.

porphyria: Inherited condition resulting from the lack of one or more enzymes required to synthesize porphyrins.

porphyrin: Complex nitrogenous compound containing four substituted pyrroles covalently joined into a ring; often complexed with a central metal atom.

positive cooperativity: A property of some multisubunit enzymes or proteins in which binding of a ligand or substrate to one subunit facilitates binding to another subunit.

positive-inside rule: General observation that most plasma membrane proteins are oriented so that most of their positively charged residues (Lys and Arg) are on the cytosolic face.

posttranscriptional processing: The enzymatic processing of the primary RNA transcript to produce functional RNAs, including mRNAs, tRNAs, rRNAs, and many other classes of RNAs.

posttranslational modification: Enzymatic processing of a polypeptide chain after translation from its mRNA.

PPAR (peroxisome proliferator-activated receptor): A family of nuclear transcription factors, activated by lipidic ligands, that alter the expression of specific genes, including those encoding enzymes of lipid synthesis and breakdown.

primary structure: A description of the covalent backbone of a polymer (macromolecule), including the sequence of monomeric subunits and any interchain and intrachain covalent bonds.

primary transcript: The immediate RNA product of transcription before any posttranscriptional processing reactions.

primases: Enzymes that catalyze the formation of RNA oligonucleotides used as primers by DNA polymerases.

primer: A short oligomer (of sugars or nucleotides, for example) to which an enzyme adds additional monomeric subunits.

primer terminus: The end of a primer to which monomeric subunits are added.

priming: (1) In protein phosphorylation, the phosphorylation of an amino acid residue that becomes the binding site and point of reference for phosphorylation of other residues in the same protein. (2) In DNA replication, the synthesis of a short oligonucleotide to which DNA polymerases can add additional nucleotides.

primosome: An enzyme complex that synthesizes the primers required for lagging strand DNA synthesis.

processivity: For any enzyme that catalyzes the synthesis of a biological polymer, the property of adding multiple subunits to the polymer without dissociating from the substrate.

prochiral molecule: A symmetric molecule that can react asymmetrically with an enzyme having an asymmetric active site, generating a chiral product.

projection formulas: *See* Fischer projection formulas.

prokaryote: A term used historically to refer to any species in the kingdoms Bacteria and Archaea. The differences between bacteria (formerly referred to as "eubacteria") and archaea are sufficiently great that the inclusive term is of marginal usefulness. A tendency to use "prokaryote" when referring only to bacteria is common and misleading; "prokaryote" also implies an ancestral relationship to eukaryotes, which is incorrect. In this text, "prokaryote" and "prokaryotic" are not used.

promoter: A DNA sequence at which RNA polymerase may bind, leading to initiation of transcription.

proofreading: The correction of errors in the synthesis of an information-containing biopolymer by removing incorrect monomeric subunits after they have been covalently added to the growing polymer.

prostaglandin: One of a class of polyunsaturated, cyclic lipids derived from arachidonate that act as paracrine hormones.

prosthetic group: A metal ion or an organic compound (other than an amino acid) that is covalently bound to a protein and is essential to its activity.

proteases: Enzymes that catalyze the hydrolytic cleavage of peptide bonds in proteins.

proteasome: Supramolecular assembly of enzymatic complexes that function in the degradation of damaged or unneeded cellular proteins.

protein: A macromolecule composed of one or more polypeptide chains, each with a characteristic sequence of amino acids linked by peptide bonds.

Protein Data Bank: *See* PDB.

protein kinases: Enzymes that transfer the terminal phosphoryl group of ATP or another nucleoside triphosphate to a Ser, Thr, Tyr, Asp, or His side chain in a target protein, thereby regulating the activity or other properties of that protein.

protein phosphatases: Enzymes that hydrolyze a phosphate ester or anhydride bond on a protein, releasing inorganic phosphate, P_i.

protein targeting: The process by which newly synthesized proteins are sorted and transported to their proper locations in the cell.

proteoglycan: A hybrid macromolecule consisting of a heteropolysaccharide joined to a polypeptide; the polysaccharide is the major component.

proteome: The full complement of proteins expressed in a given cell, or the complete complement of proteins that can be expressed by a given genome.

proteomics: Broadly, the study of the protein complement of a cell or organism.

proteostasis: The maintenance of a cellular steady-state collection of proteins that are required for cell functions under a given set of conditions.

protomer: A general term describing any repeated unit of one or more stably associated protein subunits in a larger protein structure. If a protomer has multiple subunits, the subunits may be identical or different.

proton acceptor: An anionic compound capable of accepting a proton from a proton donor; that is, a base.

proton donor: The donor of a proton in an acid-base reaction; that is, an acid.

proton-motive force: The electrochemical potential inherent in a transmembrane gradient of H^+ concentration; used in oxidative phosphorylation and photophosphorylation to drive ATP synthesis.

proto-oncogene: A cellular gene, usually encoding a regulatory protein, that can be converted into an oncogene by mutation.

PUFA (polyunsaturated fatty acid): A fatty acid with more than one double bond, generally nonconjugated.

purine: A nitrogenous heterocyclic base found in nucleotides and nucleic acids; contains fused pyrimidine and imidazole rings.

puromycin: An antibiotic that inhibits polypeptide synthesis by being incorporated into a growing polypeptide chain, causing its premature termination.

pyridine nucleotide: A nucleotide coenzyme containing the pyridine derivative nicotinamide; NAD or NADP.

pyridoxal phosphate (PLP): A coenzyme containing the vitamin pyridoxine (vitamin B_6); functions in reactions involving amino group transfer.

pyrimidine: A nitrogenous heterocyclic base found in nucleotides and nucleic acids.

pyrimidine dimer: A covalently joined dimer of two adjacent pyrimidine residues in DNA, induced by absorption of UV light; most commonly derived from two adjacent thymines (a thymine dimer).

pyrophosphatase: *See* inorganic pyrophosphatase.

q

***Q*:** *See* mass-action ratio.

quantitative PCR (qPCR): A PCR procedure that allows the determination of how much of the amplified template was in the original sample.

quantum: The ultimate unit of energy.

quaternary structure: The three-dimensional structure of a multisubunit protein, particularly the manner in which the subunits fit together.

r

racemic mixture (racemate): An equimolar mixture of the D and L stereoisomers of an optically active compound.

radical: An atom or group of atoms possessing an unpaired electron; also called a free radical.

radioactive isotope: An isotopic form of an element with an unstable nucleus that stabilizes itself by emitting ionizing radiation.

radioimmunoassay (RIA): A sensitive, quantitative method for detecting trace amounts of a biomolecule, based on its capacity to displace a radioactive form of the molecule from combination with its specific antibody.

Ras superfamily of G proteins: Small (M_r ~20,000), monomeric guanosine nucleotide–binding proteins that regulate signaling and membrane trafficking pathways. Inactive with GDP bound, they are activated by displacement of GDP by GTP, then inactivated by their intrinsic GTPase. Also called small G proteins.

rate constant: The proportionality constant that relates the velocity of a chemical reaction to the concentration(s) of the reactant(s).

rate-limiting step: (1) Generally, the step in an enzymatic reaction with the greatest activation energy or the transition state of highest free energy. (2) The slowest step in a metabolic pathway.

reaction intermediate: Any chemical species in a reaction pathway that has a finite chemical lifetime.

reactive oxygen species (ROS): Highly reactive products of the partial reduction of O_2, including hydrogen peroxide (H_2O_2), superoxide ($^{\bullet}O_2^-$), and hydroxyl free radical $^{\bullet}OH$, produced as minor byproducts during oxidative phosphorylation.

reading frame: A contiguous, nonoverlapping set of three-nucleotide codons in DNA or RNA.

receptor Tyr kinase (RTK): A large family of plasma membrane proteins with ligand-binding sites on the extracellular domain, a single transmembrane helix, and a cytoplasmic domain with protein Tyr kinase activity controlled by the extracellular ligand.

recombinant DNA: DNA formed by the joining of genes into new combinations.

recombination: Any enzymatic process by which the linear arrangement of nucleic acid sequences in a chromosome is altered by cleavage and rejoining.

recombinational DNA repair: Recombinational processes directed at the repair of DNA strand breaks or cross-links, especially at inactivated replication forks.

redox pair: An electron donor and its corresponding oxidized form; for example, NADH and NAD^+.

redox reaction: *See* oxidation-reduction reaction.

reducing agent (reductant): The electron donor in an oxidation-reduction reaction.

reducing end: The end of a polysaccharide having a terminal sugar with a free anomeric carbon; the terminal residue can act as a reducing sugar.

reducing equivalent: A general term for an electron or an electron equivalent in the form of a hydrogen atom or a hydride ion.

reducing sugar: A sugar in which the carbonyl (anomeric) carbon is not involved in a glycosidic bond and can therefore undergo oxidation.

reduction: The gain of electrons by a compound or ion.

regulator of G protein signaling (RGS): Protein structural domain that stimulates the GTPase activity of heterotrimeric G proteins.

regulatory cascade: A multistep regulatory pathway in which a signal leads to activation of a series of proteins in succession, with each protein in the succession catalytically activating the next, such that the original signal is amplified exponentially.

regulatory enzyme: An enzyme with a regulatory function, through its capacity to undergo a change in catalytic activity by allosteric mechanisms or by covalent modification.

regulatory gene: A gene that gives rise to a product involved in the regulation of the expression of another gene; for example, a gene encoding a repressor protein.

regulatory sequence: A DNA sequence involved in regulating the expression of a gene; for example, a promoter or operator.

regulon: A group of genes or operons that are coordinately regulated even though some, or all, may be spatially distant in the chromosome or genome.

relaxed DNA: Any DNA that exists in its most stable and unstrained structure, typically the B form under most cellular conditions.

release factors: Protein factors of the cytosol required for the release of a completed polypeptide chain from a ribosome; also known as termination factors.

renaturation: Refolding of an unfolded (denatured) globular protein so as to restore its native structure and function.

replication: Synthesis of daughter nucleic acid molecules identical to the parental nucleic acid.

replication fork: The Y-shaped structure generally found at the point where DNA is being synthesized.

replicative form: Any of the full-length structural forms of a viral chromosome that serve as distinct replication intermediates.

replisome: The multiprotein complex that promotes DNA synthesis at the replication fork.

repressible enzyme: In bacteria, an enzyme whose synthesis is inhibited when its reaction product is readily available to the cell.

repression: A decrease in the expression of a gene in response to a change in the activity of a regulatory protein.

repressor: The protein that binds to the regulatory sequence or operator for a gene, blocking its transcription.

residue: A single unit in a polymer; for example, an amino acid in a polypeptide chain. The term reflects the fact that sugars, nucleotides, and amino acids lose a few atoms (generally the elements of water) when incorporated in their respective polymers.

respiration: Any metabolic process that leads to the uptake of oxygen and the release of CO_2.

respiration-linked phosphorylation: ATP formation from ADP and P_i, driven by electron flow through a series of membrane-bound carriers, with a proton gradient as the direct source of energy driving rotational catalysis by ATP synthase.

respiratory chain: The electron-transfer chain; a sequence of electron-carrying proteins that transfers electrons from substrates to molecular oxygen in aerobic cells.

response element: A region of DNA, near (upstream from) a gene, that is bound by specific proteins that influence the rate of transcription of the gene.

restriction endonucleases: Site-specific endodeoxyribonucleases that cleave both strands of DNA at points in or near the specific site recognized by the enzyme; important tools in genetic engineering.

restriction fragment: A segment of double-stranded DNA produced by the action of a restriction endonuclease on a larger DNA.

retinal: A 20-carbon isoprene aldehyde derived from carotene, which serves as the light-sensitive component of the visual pigment rhodopsin. Illumination converts 11-*cis*-retinal to all-*trans*-retinal.

retrovirus: An RNA virus containing a reverse transcriptase.

reverse transcriptase: An RNA-directed DNA polymerase in retroviruses; capable of making DNA complementary to an RNA.

reversible inhibition: Inhibition by a molecule that binds reversibly to the enzyme, such that the enzyme activity returns when the inhibitor is no longer present.

R group: (1) Formally, an abbreviation denoting any alkyl group. (2) Occasionally, used in a more general sense to denote virtually any organic substituent (the R groups of amino acids, for example).

RGS: *See* regulator of G protein signaling

rhodopsin: The visual pigment, composed of the protein opsin and the chromophore retinal.

RIA: *See* radioimmunoassay.

ribonuclease: A nuclease that catalyzes the hydrolysis of certain internucleotide linkages of RNA.

ribonucleic acid: *See* RNA.

ribonucleotide: A nucleotide containing D-ribose as its pentose component.

ribosomal RNA (rRNA): A class of RNA molecules serving as components of ribosomes.

ribosome: A supramolecular complex of rRNAs and proteins, approximately 18 to 22 nm in diameter; the site of protein synthesis.

riboswitch: A structured segment of an mRNA that binds to a specific ligand and affects the translation or processing of the mRNA.

ribozymes: Ribonucleic acid molecules with catalytic activities; RNA enzymes.

ribulose 1,5-bisphosphate carboxylase/oxygenase (rubisco): The enzyme that fixes inorganic CO_2 into organic form (3-phosphoglycerate) in those organisms (plants and some microorganisms) capable of CO_2 fixation.

Rieske iron-sulfur protein: A type of iron-sulfur protein in which two of the ligands to the central iron ion are His side chains; act in many electron-transfer sequences, including oxidative phosphorylation and photophosphorylation.

RNA (ribonucleic acid): A polyribonucleotide of a specific sequence linked by successive 3′,5′-phosphodiester bonds.

RNA editing: Posttranscriptional modification of an mRNA that alters the meaning of one or more codons during translation.

RNA polymerase: An enzyme that catalyzes the formation of RNA from ribonucleoside 5′-triphosphates, using a strand of DNA or RNA as a template.

RNA splicing: Removal of introns and joining of exons in a primary transcript.

ROS: *See* reactive oxygen species.

rRNA: *See* ribosomal RNA.

RTK: *See* receptor Tyr kinase.

rubisco: *See* ribulose 1,5-bisphosphate carboxylase/oxygenase.

S

salvage pathway: Pathway for synthesis of a biomolecule, such as a nucleotide, from intermediates in the degradative pathway for the biomolecule; a recycling pathway, as distinct from a de novo pathway.

sarcomere: A functional and structural unit of the muscle contractile system.

satellite DNA: Highly repeated, nontranslated segments of DNA in eukaryotic chromosomes; most often associated with the centromeric region. Its function is unknown. Also called simple-sequence DNA.

saturated fatty acid: A fatty acid containing a fully saturated alkyl chain.

scaffold proteins: Noncatalytic proteins that nucleate formation of multienzyme complexes by providing two or more specific binding sites for those proteins.

scramblases: Membrane proteins that catalyze the movement of phospholipids across the membrane bilayer, leading to uniform

distribution of a lipid between the two membrane leaflets.

secondary metabolism: Pathways that lead to specialized products not found in every living cell.

secondary structure: The local spatial arrangement of the main-chain atoms in a segment of a polypeptide chain; also applied to polynucleotide structure.

second law of thermodynamics: The law stating that, in any chemical or physical process, the entropy of the universe tends to increase.

second messenger: An effector molecule synthesized in a cell in response to an external signal (first messenger) such as a hormone.

sedimentation coefficient: A physical constant specifying the rate of sedimentation of a particle in a centrifugal field under specified conditions.

selectins: A large family of membrane proteins, lectins that bind oligosaccharides on other cells tightly and specifically and serve to carry signals across the plasma membrane.

SELEX: A method for rapid experimental identification of nucleic acid sequences (usually RNA) that have particular catalytic or ligand-binding properties.

sequence polymorphisms: Any alterations in genomic sequence (base-pair changes, insertions, deletions, rearrangements) that help distinguish subsets of individuals in a population or distinguish one species from another.

serine proteases: One of four major classes of proteases, featuring a reaction mechanism in which an active-site Ser residue acts as a covalent catalyst.

Shine-Dalgarno sequence: A sequence in an mRNA that is required for binding bacterial ribosomes.

short tandem repeat (STR): A short (typically 3 to 6 bp) DNA sequence, repeated many times in tandem at a particular location in a chromosome.

SH2 domain: A protein domain that binds tightly to a phosphotyrosine residue in certain proteins such as the receptor Tyr kinases, initiating the formation of a multiprotein complex that acts in a signaling pathway.

shuttle vector: A recombinant DNA vector that can be replicated in two or more different host species. *See also* vector.

sickle-cell anemia: A human disease characterized by defective hemoglobin molecules in individuals homozygous for a mutant allele coding for the β chain of hemoglobin.

σ: (1) *See* superhelical density. (2) A subunit of the bacterial RNA polymerase that confers specifity for certain promoters; usually designated by a superscript indicating its size (for example, σ^{70} has a molecular weight of 70,000).

signal sequence: An amino acid sequence, often at the amino terminus, that signals the cellular fate or destination of a newly synthesized protein.

signal transduction: The process by which an extracellular signal (chemical, mechanical, or electrical) is amplified and converted to a cellular response.

silent mutation: A mutation in a gene that causes no detectable change in the biological characteristics of the gene product.

simple diffusion: The movement of solute molecules across a membrane to a region of lower concentration, unassisted by a protein transporter.

simple protein: A protein yielding only amino acids on hydrolysis.

simple sequence DNA: *See* satellite DNA.

single nucleotide polymorphism (SNP): A genomic base-pair change that helps distinguish one species from another or one subset of individuals in a population.

site-directed mutagenesis: A set of methods used to create specific alterations in the sequence of a gene.

site-specific recombination: A type of genetic recombination that occurs only at specific sequences.

size-exclusion chromatography: A procedure for the separation of molecules by size, based on the capacity of porous polymers to exclude solutes above a certain size; also called gel filtration.

small G proteins: *See* Ras superfamily of G proteins.

small nuclear RNA (snRNA): A class of short RNAs, typically 100 to 200 nucleotides long, found in the nucleus and involved in the splicing of eukaryotic mRNAs.

small nucleolar RNA (snoRNA): A class of short RNAs, generally 60 to 300 nucleotides long, that guide the modification of rRNAs in the nucleolus.

SNP: *See* single nucleotide polymorphism.

somatic cells: All body cells except the germline cells.

SOS response: In bacteria, a coordinated induction of a variety of genes in response to high levels of DNA damage.

Southern blot: A DNA hybridization procedure in which one or more specific DNA fragments are detected in a larger population by hybridization to a complementary, labeled nucleic acid probe.

specific acid-base catalysis: Acid or base catalysis involving the constituents of water (hydroxide or hydronium ions).

specific activity: The number of micromoles (μmol) of a substrate transformed by an enzyme preparation per minute per milligram of protein at 25 °C; a measure of enzyme purity.

specificity: The ability of an enzyme or receptor to discriminate among competing substrates or ligands.

specific rotation: The rotation, in degrees, of the plane of plane-polarized light (D-line of sodium) by an optically active compound at 25 °C, with a specified concentration and light path.

sphingolipid: An amphipathic lipid with a sphingosine backbone to which are attached a long-chain fatty acid and a polar alcohol.

spliceosome: A complex of RNAs and proteins involved in the splicing of mRNAs in eukaryotic cells.

splicing: *See* RNA splicing.

standard free-energy change (ΔG°): The free-energy change for a reaction occurring under a set of standard conditions: temperature, 298 K; pressure, 1 atm or 101.3 kPa; and all solutes at 1 M concentration. $\Delta G'^\circ$ denotes the standard free-energy change at pH 7.0 in 55.5 M water.

standard reduction potential (E'°): The electromotive force exhibited at an electrode by 1 M concentrations of a reducing agent and its oxidized form at 25 °C and pH 7.0; a measure of the relative tendency of the reducing agent to lose electrons.

statin: Any of a class of drugs used to reduce blood cholesterol in humans; act by inhibiting the enzyme HMG-CoA reductase, an early step in sterol synthesis.

steady state: A nonequilibrium state of a system through which matter is flowing and in which all components remain at a constant concentration.

stem cells: The common, self-regenerating cells in bone marrow that give rise to differentiated blood cells such as erythrocytes and lymphocytes.

stereoisomers: Compounds that have the same composition and the same order of atomic connections but different molecular arrangements.

sterol: A lipid containing the steroid nucleus.

sticky ends: Two DNA ends in the same DNA molecule, or in different molecules, with short overhanging single-stranded segments that are complementary to one another, facilitating ligation of the ends; also known as cohesive ends.

stimulatory G protein (G_s): A trimeric regulatory GTP-binding protein that, when activated by an associated plasma membrane receptor, stimulates a neighboring membrane enzyme such as adenylyl cyclase. Its effects oppose those of G_i.

stop codons: *See* termination codons.

STR: *See* short tandem repeat.

stroma: The space and aqueous solution enclosed within the inner membrane of a chloroplast, not including the contents in the thylakoid membranes.

structural gene: A gene coding for a protein or RNA molecule; as distinct from a regulatory gene.

substitution mutation: A mutation caused by the replacement of one base by another.

substrate: The specific compound acted upon by an enzyme.

substrate channeling: Movement of the chemical intermediates in a series of enzyme-catalyzed reactions from the active site of one enzyme to that of the next enzyme in the

pathway, without leaving the surface of a protein complex that includes both enzymes.

substrate-level phosphorylation: Phosphorylation of ADP or some other nucleoside 5′-diphosphate coupled to the dehydrogenation of an organic substrate; independent of the electron-transfer chain.

suicide inactivator: A relatively inert molecule that is transformed by an enzyme, at its active site, into a reactive substance that irreversibly inactivates the enzyme.

sulfonylurea drugs: A group of oral medications used in the treatment of type 2 diabetes; act by closing K^+ channels in pancreatic β cells, stimulating insulin secretion.

supercoil: The twisting of a helical (coiled) molecule on itself; a coiled coil.

supercoiled DNA: DNA that twists upon itself because it is under- or overwound (and thereby strained) relative to B-form DNA.

superhelical density (σ): In a helical molecule such as DNA, the number of supercoils (superhelical turns) relative to the number of coils (turns) in the relaxed molecule.

supersecondary structure: *See* motif.

suppressor mutation: A mutation that totally or partially restores a function lost by a primary mutation; located at a site different from the site of the primary mutation.

Svedberg (S): A unit of measure of the rate at which a particle sediments in a centrifugal field.

symbionts: Two or more organisms that are mutually interdependent; usually living in physical association.

symport: Cotransport of solutes across a membrane in the same direction.

synteny: Conserved gene order along the chromosomes of different species.

synthases: Enzymes that catalyze condensation reactions in which no nucleoside triphosphate is required as an energy source.

synthetases: Enzymes that catalyze condensation reactions using ATP or another nucleoside triphosphate as an energy source.

system: An isolated collection of matter; all other matter in the universe apart from the system is called the surroundings.

systems biology: The study of complex biochemical systems, integrating the functions of several to all of the macromolecules in a cell (RNA, DNA, proteins).

t

tag: An extra segment of protein that is fused via modification of its gene to a protein of interest, usually for purposes of purification.

T cell: *See* T lymphocyte.

telomere: Specialized nucleic acid structure found at the ends of linear eukaryotic chromosomes.

template: A macromolecular mold or pattern for the synthesis of an informational macromolecule.

template strand: A strand of nucleic acid used by a polymerase as a template to synthesize a complementary strand, as distinct from the coding strand.

terminal transferase: An enzyme that catalyzes the addition of nucleotide residues of a single kind to the 3′ end of DNA chains.

termination codons: UAA, UAG, and UGA; in protein synthesis, these codons signal the termination of a polypeptide chain. Also known as stop codons.

termination factors: *See* release factors.

termination sequence: A DNA sequence, at the end of a transcriptional unit, that signals the end of transcription.

tertiary structure: The three-dimensional conformation of a polymer in its native folded state.

tetrahydrobiopterin: The reduced coenzyme form of biopterin.

tetrahydrofolate: The reduced, active coenzyme form of the vitamin folate.

thermogenesis: The biological generation of heat by muscle activity (shivering), uncoupled oxidative phosphorylation, or the operation of futile cycles.

thermogenin: A protein of the inner mitochondrial membrane in brown adipose tissue that allows transmembrane movement of protons, short-circuiting the normal use of protons to drive ATP synthesis and dissipating the energy of substrate oxidation as heat; also called uncoupling protein 1 (UCP1).

thiamine pyrophosphate (TPP): The active coenzyme form of vitamin B_1; involved in aldehyde transfer reactions.

thioester: An ester of a carboxylic acid with a thiol or mercaptan.

3′ end: The end of a nucleic acid that lacks a nucleotide bound at the 3′ position of the terminal residue.

thrombocytes: *See* platelets.

thromboxane: Any of a class of molecules derived from arachidonate and involved in platelet aggregation during blood clotting.

thylakoid: Closed cisterna, or disk, formed by the pigment-bearing internal membranes of chloroplasts.

thymine dimer: *See* pyrimidine dimer.

tissue culture: Method by which cells derived from multicellular organisms are grown in liquid media.

titration curve: A plot of pH versus the equivalents of base added during titration of an acid.

T lymphocyte (T cell): One of a class of blood cells (lymphocytes) of thymic origin, involved in cell-mediated immune reactions.

tocopherol: Any of several forms of vitamin E.

topoisomerases: Enzymes that introduce positive or negative supercoils in closed, circular duplex DNA.

topoisomers: Different forms of a covalently closed, circular DNA molecule that differ only in their linking number.

topology: The study of the properties of an object that do not change under continuous deformations such as twisting or bending.

TPP: *See* thiamine pyrophosphate.

trace element: A chemical element required by an organism in only trace amounts.

transaminases: *See* aminotransferases.

transamination: Enzymatic transfer of an amino group from an α-amino acid to an α-keto acid.

transcription: The enzymatic process whereby the genetic information contained in one strand of DNA is used to specify a complementary sequence of bases in an mRNA chain.

transcriptional control: The regulation of a protein's synthesis by regulation of the formation of its mRNA.

transcription factor: In eukaryotes, a protein that affects the regulation and transcription initiation of a gene by binding to a regulatory sequence near or within the gene and interacting with RNA polymerase and/or other transcription factors.

transcriptome: The entire complement of RNA transcripts present in a given cell or tissue under specific conditions.

transducin: The trimeric G protein activated when light is absorbed by visual rhodopsin; activated transducin activates cGMP phosphodiesterase.

transduction: (1) Generally, the conversion of energy or information from one form to another. (2) The transfer of genetic information from one cell to another by means of a viral vector.

transfer RNA (tRNA): A class of RNA molecules (M_r 25,000 to 30,000), each of which combines covalently with a specific amino acid as the first step in protein synthesis.

transformation: Introduction of an exogenous DNA into a cell, causing the cell to acquire a new phenotype.

transgenic: Describes an organism that has genes from another organism incorporated in its genome as a result of recombinant DNA procedures.

transition state: An activated form of a molecule in which the molecule has undergone a partial chemical reaction; the highest point on the reaction coordinate.

transition-state analog: A stable molecule that resembles the transition state of a particular reaction, and therefore binds the enzyme that catalyzes the reaction more tightly than does the substrate in the ES complex.

translation: The process in which the genetic information present in an mRNA molecule specifies the sequence of amino acids during protein synthesis.

translational control: The regulation of a protein's synthesis by regulation of the rate of its translation on the ribosome.

translational frameshifting: A programmed change in the reading frame during translation of an mRNA on a ribosome, occurring by any of several mechanisms.

translational repressor: A repressor that binds to an mRNA, blocking translation.

translocase: (1) An enzyme that catalyzes membrane transport. (2) An enzyme that causes a movement such as the movement of a ribosome along an mRNA.

transpiration: Passage of water from the roots of a plant to the atmosphere via the vascular system and the stomata of the leaves.

transporters: Proteins that span a membrane and transport specific nutrients, metabolites, ions, or proteins across the membrane; sometimes called permeases.

transposition: The movement of a gene or set of genes from one site in the genome to another.

transposon (transposable element): A segment of DNA that can move from one position in the genome to another.

triacylglycerol: An ester of glycerol with three molecules of fatty acid; also called a triglyceride or neutral fat.

tricarboxylic acid cycle: *See* citric acid cycle.

trimeric G proteins: Members of the G protein family with three subunits, which function in a variety of signaling pathways. Inactive with GDP bound, they are activated by associated receptors as bound GDP is displaced by GTP, then inactivated by their intrinsic GTPase activity.

triose: A simple sugar with a backbone containing three carbon atoms.

tRNA: *See* transfer RNA.

tropic hormone (tropin): A peptide hormone that stimulates a specific target gland to secrete its hormone; for example, thyrotropin produced by the pituitary stimulates secretion of thyroxine by the thyroid.

t-SNAREs: Protein receptors in a targeted membrane (typically the plasma membrane) that bind to v-SNAREs in the membrane of a secretory vesicle and mediate fusion of the vesicle and target membranes.

tumor suppressor gene: One of a class of genes that encode proteins that normally regulate the cell cycle by suppressing cell division. Mutation of one copy of the gene is usually without effect, but when both copies are defective, the cell is allowed to continue dividing without limitation, producing a tumor.

turnover number: The number of times an enzyme molecule transforms a substrate molecule per unit time, under conditions giving maximal activity at substrate concentrations that are saturating.

two-component signaling systems: Signal-transducing systems found in bacteria and plants, composed of a receptor His kinase that phosphorylates an internal His residue when occupied by its ligand. It then catalyzes phosphoryl transfer to a second component, the response regulator, which, when phosphorylated, alters the output of the signaling system.

u

ubiquitin: A small, highly conserved eukaryotic protein that targets an intracellular protein for degradation by proteasomes. Several ubiquitin molecules are covalently attached in tandem to a Lys residue in the target protein by a specific ubiquitinating enzyme.

ultraviolet (UV) radiation: Electromagnetic radiation in the region of 200 to 400 nm.

uncompetitive inhibition: The reversible inhibition pattern resulting when an inhibitor molecule can bind to the enzyme-substrate complex but not to the free enzyme.

uncoupling agent: A substance that uncouples phosphorylation of ADP from electron transfer; for example, 2,4-dinitrophenol.

uncoupling protein 1: *See* thermogenin.

uniport: A transport system that carries only one solute, as distinct from cotransport.

unsaturated fatty acid: A fatty acid containing one or more double bonds.

urea cycle: A cyclic metabolic pathway in vertebrate liver, synthesizing urea from amino groups and carbon dioxide.

ureotelic: Excreting excess nitrogen in the form of urea.

uricotelic: Excreting excess nitrogen in the form of urate (uric acid).

v

V_{max}: The maximum velocity of an enzymatic reaction when the binding site is saturated with substrate.

van der Waals interaction: Weak intermolecular forces between molecules as a result of each inducing polarization in the other.

vector: A DNA molecule known to replicate autonomously in a host cell, to which a segment of DNA may be spliced to allow its replication; for example, a plasmid or an artificial chromosome.

vectorial: Describes an enzymatic reaction or transport process in which the protein has a specific orientation in a biological membrane such that the substrate is moved from one side of the membrane to the other as it is converted into product.

vectorial metabolism: Metabolic transformations in which the location (not the chemical composition) of a substrate changes relative to the plasma membrane or a membrane between two cellular compartments. Transporters catalyze vectorial reactions, as do the proton pumps of oxidative phosphorylation and photophosphorylation.

vesicle: A small, spherical membrane-bounded particle with an internal aqueous compartment that contains components such as hormones or neurotransmitters to be moved within or out of a cell.

viral vector: A viral DNA altered so that it can act as a vector for recombinant DNA.

virion: A virus particle.

virus: A self-replicating, infectious, nucleic acid–protein complex that requires an intact host cell for its replication; its genome is either DNA or RNA.

vitamin: An organic substance required in small quantities in the diet of some species; generally functions as a component of a coenzyme.

v-SNAREs: Protein receptors in the membrane of a secretory vesicle (typically the plasma membrane) that bind to t-SNAREs in a targeted membrane (typically the plasma membrane) of a secretory vesicle and mediate fusion of the vesicle and target membranes.

w

Western blotting: *See* immunoblotting.

white adipose tissue (WAT): Nonthermogenic adipose tissue rich in triacylglycerols stored and mobilized in response to hormonal signals. Transfer of electrons in the mitochondrial respiratory chain is tightly coupled to ATP synthesis. *Compare* brown adipose tissue.

wild type: The normal (unmutated) genotype or phenotype.

wobble: The relatively loose base pairing between the base at the 3′ end of a codon and the complementary base at the 5′ end of the anticodon.

x

x-ray crystallography: The analysis of x-ray diffraction patterns of a crystalline compound, used to determine the molecule's three-dimensional structure.

z

zinc finger: A specialized protein motif involved in DNA recognition by some DNA-binding proteins; characterized by a single atom of zinc coordinated to four Cys residues or to two His and two Cys residues.

Z scheme: The path of electrons in oxygenic photosynthesis from water through photosystem II and the cytochrome b_6f complex to photosystem I and finally to NADPH. When the sequence of electron carriers is plotted against their reduction potentials, the path of electrons looks like a sideways Z.

zwitterion: A dipolar ion with spatially separated positive and negative charges.

zymogen: An inactive precursor of an enzyme; for example, pepsinogen, the precursor of pepsin.

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Credits

Molecular Models

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ATOMIC COORDINATES Unless indicated, all atomic coordinates were obtained from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB), www.pdb.org. See Berman, H.M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T.N., Weissig, H., Shindyalov, I.N., & Bourne, P.E. (2000) The Protein Data Bank. *Nucleic Acids Res*. 28, 235–242. The RCSB PDB is a member of the worldwide PDB (wwPDB), www.wwpdb.org. See Berman, H., Henrick, K., & Nakamura, H. (2003) Announcing the worldwide Protein Data Bank. *Nat. Struct. Biol.* 10, 980.

Some structures were generated using PyMOL, pymol.sourceforge.net; Sybyl 6.2, Tripos Inc., www.tripos.com; Visual Molecular Dynamics, www.ks.uiuc.edu/Research/vmd/; or RasMol, rasmol.org.

CHAPTER 1 Figure 1–1a Dennis Kunkel Microscopy, Inc./Visuals Unlimited; **Figure 1–1b** W. Perry Conway/Corbis; **Figure 1–1c** Dave Pape/Wikipedia; **Figure 1–2** The Bridgeman Art Library; **Figure 1–4** Adapted from Woese, C.R. (1987) Bacterial evolution. *Microbiol. Rev.* 51, 221, Fig. 4; **Figure 1–6a** David S. Goodsell; **Figure 1–6b,c,d** Adapted from Albers, S.-V. & Meyer, B.H. (2011) The archaeal cell envelope. *Nat. Rev. Microbiol.* 9, 414, Fig. 2; **Figure 1–8** Adapted from Alberts, B., Bray, D., Lewis, J., Raff, M., Roberts, K., & Watson, J.D. (1989) *Molecular Biology of the Cell*, 2nd edn, Garland Publishing, Inc., New York, pp. 165–166; **Figure 1–9a** Courtesy of Invitrogen; **Figure 1–9b** Dr. Alexey Khodjakov, Wadsworth Center, New York State Department of Health; **Figure 1–11** Adapted from Becker, W.M. & Deamer, D.W. (1991) *The World of the Cell*, 2nd edn, Fig. 2–15, Benjamin/Cummings Publishing Company, Menlo Park, CA; **Figure 1–12** © David S. Goodsell 1999; **Figure 1–17** Acetyl-CoA extracted from PDB ID 1DM3, Modis, Y. & Wierenga, R.K. (2000) Crystallographic analysis of the reaction pathway of *Zoogloea ramigera* biosynthetic thiolase. *J. Mol. Biol.* 297, 1171; **Figure 1–21** Adapted from Carroll, F. (1998) *Perspectives on Structure and Mechanism in Organic Chemistry*, Brooks/Cole Publishing Co., Pacific Grove, CA, p. 63; **Box 1–2** (Pasteur) The Granger Collection; **Figure 1–23** PDB ID 3B8A, Kuser, P., Cupri, F., Bleicher, L., & Polikarpov, I. (2008) Crystal structure of yeast hexokinase PI in complex with glucose: a classical "induced fit" example revised. *Proteins* 72, 731; **p. 23** (Gibbs) Historical Pictures Service/Stock Montage; **Figure 1–30a** Erich Lessing/Art Resource, New York; **Figure 1–30b** Dr. Gopal Murti–CNRI/Phototake New York; **p. 32** Theodosius Dobzhansky (1973) Nothing in biology makes sense except in the light of evolution. *The American Biology Teacher* (March) 35, 125–129; **Figure 1–34b** Bettmann/Corbis; **Figure 1–35** P. Rona/OAR/National Undersea Research Program (NURP); NOAA; **p. 36** (Margulis) Ben Barnhart/UMass Magazine.

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CHAPTER 3 Figure 3–1a Runk/Schoenburger/Grant Heilman Photography; **Figure 3–1b** Bill Longcore/Photo Researchers; **Figure 3–1c** Jerry Cooke, Inc./Animals Animals; **p. 76** (Dayhoff) Courtesy of Ruth E. Dayhoff; **Figure 3–18b** Julia Cox, University of Wisconsin–Madison, Department of Biochemistry; **Figure 3–21** Courtesy of Axel Mogk, from Mogk, A., Tomoyasu, T., Goloubinoff, P., Rüdiger, S., Röder, D., Lanen, H., & Bukau, B. (1999) Identification of thermolabile *Escherichia coli* proteins: prevention and reversion of aggregation by DnaK and ClpB. *EMBO J.* 18, 6934, Fig. 7A; **Figure 3–23** PDB ID 1HGA, Liddington, R., Derewenda, Z., Dodson, E., Hubbard, R., & Dodson, G. (1992) High resolution crystal structures and comparisons of T-state deoxyhaemoglobin and two liganded T-state haemoglobins: T(α-oxy) haemoglobin and T(met) haemoglobin. *J. Mol. Biol.* 228, 551; **p. 98** (Sanger) UPI/Corbis-Bettmann; **Figures 3–30** Adapted from Mann, M. & Wilm, M. (1995) Electrospray mass spectrometry for protein characterization. *Trends Biochem. Sci.* 20, 219; **Figure 3–31a** Adapted from Keough, T., Youngquist, R.S., & Lacey, M.P. (1999) A method for high-sensitivity peptide sequencing using postsource decay matrix-assisted laser desorption ionization mass spectrometry. *Proc. Natl. Acad. Sci. USA* 96, 7131, Fig. 3; **p. 103** (Merrifield) Corbis/Bettmann; **Box 3–2 Figure 1** Sequence data for **(a)** from document ID PDOC00017 and for **(b)** from document ID PDOC00018, www.expasy.org/prosite, Hulo, N., Bairoch, A., Bulliard, V., Cerutti, L., De Castro, E., Langendijk-Genevaux, P.S., Pagni, M., & Sigrist, C.J.A. (2006) The PROSITE database. *Nucleic Acids Res.* 34, D227; WebLogo from http://weblogo.berkeley.edu, Crooks, G.E., Hon, G., Chandonia, J.M., & Brenner, S.E. (2004) WebLogo: a sequence logo generator. *Genome Res.* 14, 1188; **Figures 3–33, 3–34, 3–35** Adapted from Gupta, R.S. (1998) Protein phylogenies and signature sequences: a reappraisal of evolutionary relationships among archaebacteria, eubacteria, and eukaryotes. *Microbiol. Mol. Biol. Rev.* 62, 1435, Figs 2, 7, 11, respectively; **Figure 3–36** Adapted from Delsuc, F., Brinkmann, H., & Philippe, H. (2005) Phylogenomics and the reconstruction of the tree of life. *Nat. Rev. Genet.* 6, 366; **p. 113, problem 21**, see citation for Box 3–2 Figure 1, document ID PDOC00270; **p. 113, problem 22**, see citation for Box 3–2 Figure 1, document ID PDOC00017.

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CHAPTER 10 Figures 10–2a,b, 10–3 Coordinates from Sybyl; **Figure 10–4a** Dr. Alvin Telser/Visuals Unlimited, Inc.; **Figure 10–4b** Courtesy of Howard Goodman, Harvard Medical School, Department of Genetics; **Figure 10–6b** iStockphoto/Thinkstock; **p. 367** (Thudichum) From Drabkin, D.L. (1958) *Thudichum: Chemist of the Brain*, University of Pennsylvania Press, credited to Thudichum, J.L.W. (1898) *Briefe über öffentliche Gesundheitspflege: ihre bisherigen Leistungen und heutigen Aufgaben*, F. Pietzcker, Tübingen; **Box 10–1 Figure 2** Herbert A. Fischler, Isaac Albert Research Institute of the Kingsbrook Jewish Medical Center; **p. 371** (Vane, Bergström, and Samuelsson) Ira Wyman/Sygma/Corbis; **Figure 10–20b** Courtesy of Media Center, University of Wisconsin–Madison, Department of Biochemistry; **p. 375** (Dam) AP Photo/John Rooney; (Doisy) AP/Wide World Photos; **Figure 10–23** (cardinal) Dr. Dan Suda; (goldfinch) Richard Day/VIREO; **Figure 10–26** Christie, W.W. (1996) Beginners' guide to mass spectrometry of fatty acids: 2. general purpose derivatives. *Lipid Technol.* 8, 64.

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Index

Key: b = boxed material; f = figures; s = structural formulas; t = tables; **boldface** = boldfaced terms in text

B

C

D

E

F

G

H

M

N

O

P

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R

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V

W

X

Y

Z

Abbreviations for Amino Acids

A	Ala	Alanine	N	Asn	Asparagine
B	Asx	Asparagine or aspartate	P	Pro	Proline
			Q	Gln	Glutamine
C	Cys	Cysteine	R	Arg	Arginine
D	Asp	Aspartate	S	Ser	Serine
E	Glu	Glutamate	T	Thr	Threonine
F	Phe	Phenylalanine	V	Val	Valine
G	Gly	Glycine	W	Trp	Tryptophan
H	His	Histidine	X	—	Unknown or nonstandard amino acid
I	Ile	Isoleucine			
K	Lys	Lysine	Y	Tyr	Tyrosine
L	Leu	Leucine	Z	Glx	Glutamine or glutamate
M	Met	Methionine			

Asx and Glx are used in describing the results of amino acid analytical procedures in which Asp and Glu are not readily distinguished from their amide counterparts, Asn and Gln.

The Standard Genetic Code

UUU	Phe	UCU	Ser	UAU	Tyr	UGU	Cys
UUC	Phe	UCC	Ser	UAC	Tyr	UGC	Cys
UUA	Leu	UCA	Ser	UAA	Stop	UGA	Stop
UUG	Leu	UCG	Ser	UAG	Stop	UGG	Trp
CUU	Leu	CCU	Pro	CAU	His	CGU	Arg
CUC	Leu	CCC	Pro	CAC	His	CGC	Arg
CUA	Leu	CCA	Pro	CAA	Gln	CGA	Arg
CUG	Leu	CCG	Pro	CAG	Gln	CGG	Arg
AUU	Ile	ACU	Thr	AAU	Asn	AGU	Ser
AUC	Ile	ACC	Thr	AAC	Asn	AGC	Ser
AUA	Ile	ACA	Thr	AAA	Lys	AGA	Arg
AUG	Met*	ACG	Thr	AAG	Lys	AGG	Arg
GUU	Val	GCU	Ala	GAU	Asp	GGU	Gly
GUC	Val	GCC	Ala	GAC	Asp	GGC	Gly
GUA	Val	GCA	Ala	GAA	Glu	GGA	Gly
GUG	Val	GCG	Ala	GAG	Glu	GGG	Gly

*AUG also serves as the initiation codon in protein synthesis.

1 **H** 1.008																	2 **He** 4.003
3 **Li** 6.94	4 **Be** 9.01											5 **B** 10.81	6 **C** 12.011	7 **N** 14.01	8 **O** 16.00	9 **F** 19.00	10 **Ne** 20.18
11 **Na** 22.99	12 **Mg** 24.31											13 **Al** 26.98	14 **Si** 28.09	15 **P** 30.97	16 **S** 32.06	17 **Cl** 35.45	18 **Ar** 39.95
19 **K** 39.10	20 **Ca** 40.08		21 **Sc** 44.96	22 **Ti** 47.90	23 **V** 50.94	24 **Cr** 52.00	25 **Mn** 54.94	26 **Fe** 55.85	27 **Co** 58.93	28 **Ni** 58.71	29 **Cu** 63.55	30 **Zn** 65.37	31 **Ga** 69.72	32 **Ge** 72.59	33 **As** 74.92	34 **Se** 78.96	35 **Br** 79.90	36 **Kr** 83.30
37 **Rb** 85.47	38 **Sr** 87.62		39 **Y** 88.91	40 **Zr** 91.22	41 **Nb** 92.91	42 **Mo** 95.94	43 **Te** 98.91	44 **Ru** 101.07	45 **Rh** 102.91	46 **Pd** 106.4	47 **Ag** 107.87	48 **Cd** 112.40	49 **In** 114.82	50 **Sn** 118.69	51 **Sb** 121.75	52 **Te** 126.70	53 **I** 126.90	54 **Xe** 131.30
55 **Cs** 132.91	56 **Ba** 137.34	57–70 *	71 **Lu** 174.97	72 **Hf** 178.49	73 **Ta** 180.95	74 **W** 183.85	75 **Re** 186.2	76 **Os** 190.2	77 **Ir** 192.2	78 **Pt** 195.09	79 **Au** 196.97	80 **Hg** 200.59	81 **Tl** 204.37	82 **Pb** 207.19	83 **Bi** 208.98	84 **Po** (209)	85 **At** (210)	86 **Rn** (222)
87 **Fr** (223)	88 **Ra** 226.03	89–102 **	103 **Lr** 262.11	104 **Rf** 261.11	105 **Db** 262.11	106 **Sg** 263.12	107 **Bh** 264.12	108 **Hs** 265.13	109 **Mt** 268	110 **Uun** 269	111 **Uuu** 272	112 **Uub** 277		114 **Uuq** 289		116 **Uuh** 289		118 **Uuo** 293

*Lanthanides	57 **La** 138.91	58 **Ce** 140.12	59 **Pr** 140.91	60 **Nd** 144.24	61 **Pm** 144.91	62 **Sm** 150.36	63 **Eu** 151.96	64 **Gd** 157.25	65 **Tb** 158.93	66 **Dy** 162.50	67 **Ho** 164.93	68 **Er** 167.26	69 **Tm** 168.93	70 **Yb** 173.04
**Actinides	89 **Ac** 227.03	90 **Th** 232.04	91 **Pa** 231.04	92 **U** 238.03	93 **Np** 237.05	94 **Pu** 244.06	95 **Am** 243.06	96 **Cm** 247.07	97 **Bk** 247.07	98 **Cf** 251.08	99 **Es** 252.08	100 **Fm** 257.10	101 **Md** 258.10	102 **No** 259.10

Some Conversion Factors

Length	1 cm = 10 mm = 10^4 μm = 10^7 nm = 10^8 Å = 0.394 in 1 in = 2.54 cm 1 yard = 0.9144 meters 1 mile = 1.609 kilometers
Mass	1 g = 10^{-3} kg = 10^3 mg = 10^6 μg = 3.53×10^{-2} oz 1 oz = 28.3 g
Temperature	°C = 5/9(°F − 32) K = °C + 273
Energy	1 J = 10^7 erg = 0.239 cal 1 cal = 4.184 J
Pressure	1 torr = 1 mm Hg = 1.32×10^{-3} atm = 1.333×10^2 Pa 1 atm = 758 torr = 1.01×10^5 Pa
Radioactivity	1 Ci = 3.7×10^{10} dps = 37 GBq 1,000 dpm = 16.7 Bq

Some Physical Constants, With Symbols and Values

Atomic mass unit (dalton)	amu	1.661×10^{-24} g
Avogadro's number	N	6.022×10^{23}/mol
Becquerel	Bq	1 dps
Boltzmann constant	**k**	1.381×10^{-23} J/K; 3.298×10^{-24} cal/K
Curie	Ci	3.70×10^{10} dps
Electron volt	eV	1.602×10^{-19} J; 3.828×10^{-20} cal
Faraday constant	$\mathcal{F}$	96,480 J/V • mol
Gas constant	R	1.987 cal/mol • K; 8.315 J/mol • K
Planck's constant	h	1.584×10^{-34} cal • s; 6.626×10^{-34} J • s
Speed of light (in vacuum)	c	2.998×10^{10} cm/s

Unit Abbreviations

A	ampere
Å	angstrom
atm	atmosphere
Bq	becquerel
C	coulomb
°C	degree Celsius
cal	calorie
Ci	curie
cm	centimeter
cpm	counts per minute
Da	dalton
dm	decimeter
dpm	disintegrations per minute
dps	disintegrations per second
$\mathcal{F}$	faraday
G	gauss
g	gram
GBq	gigabecquerel
h	hour
J	joule
K	kelvin
kcal	kilocalorie
kDa	kilodalton
kJ	kilojoule
kPa	kilopascal
L	liter
M	molar (concentration)
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury (pressure)
mol	mole
mV	millivolt
μm	micrometer
μmol	micromole
N	normal (concentration)
nm	nanometer
Pa	pascal
r	revolution
S	Svedberg unit
s	second
V	volt
yr	year

Some Prefixes Used in the International System of Units

10^{9}	giga	G	10^{-3}	milli	m
10^{6}	mega	M	10^{-6}	micro	μ
10^{3}	kilo	k	10^{-9}	nano	n
10^{-1}	deci	d	10^{-12}	pico	p
10^{-2}	centi	c	10^{-15}	femto	f

Mathematical Constants

π	3.1416
e	2.718
$\ln x$	$2.303 \log_{10} x$

On the front cover

The network of interactions in an animal mitochondrion. Each dot represents a compound, and each line, an enzyme that interconverts the two compounds. The major nodes include ADP, ATP, NAD^+, and NADH.

The image was constructed with Cytoscape software by Anthony Smith in the laboratory of Alan Robinson, Medical Research Council Mitochondrial Biology Unit, Cambridge, UK, using data from MitoMiner (Smith, A.C., Blackshaw, J.A., & Robinson, A.J. (2012) MitoMiner: a data warehouse for mitochondrial proteomics data. *Nucleic Acids Res.* 40, D1160–D1167).

Background image: Transmission electron micrograph of interscapular brown adipose cell from a bat. Don W. Fawcett/Science Source/Photo Researchers

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