

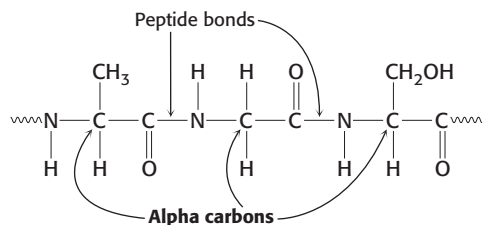
ANSWERS TO PROBLEMS

Chapter 1

- The hydrogen-bond donors are the NH and NH₂ groups. The hydrogen-bond acceptors are the carbonyl oxygen atoms and those ring nitrogen atoms that are not bonded to hydrogen or to deoxyribose.
- Interchange the positions of the single and double bonds in the six-membered ring.
- (a) Electrostatic interactions; (b) van der Waals interactions.
- Processes *a* and *b*
- $\Delta S_{\text{system}} = -661 \text{ J mol}^{-1} \text{ K}^{-1} (-158 \text{ kcal mol}^{-1} \text{ K}^{-1})$
- $\Delta S_{\text{surroundings}} = +842 \text{ J mol}^{-1} \text{ K}^{-1} (+201 \text{ cal mol}^{-1} \text{ K}^{-1})$
- (a) 1.0; (b) 13.0; (c) 1.3; (d) 12.7
- 2.88
- 1.96
- 11.83
- 447; 0.00050
- 0.00066 M
- 6.0
- 5.53
- 6.48
- 7.8
- 100
- (a) 1.6; (b) 0.51; (c) 0.16.
- 0.1 M sodium acetate solution: 6.34; 6.03; 5.70; 4.75.
0.01 M sodium acetate solution: 5.90; 4.75; 3.38; 1.40.
- 90 mM acetic acid; 160 mM sodium acetate, 0.18 moles acetic acid; 0.32 moles sodium acetate; 10.81 g acetic acid; 26.25 g sodium acetate.
- 0.50 moles of acetic acid; 0.32 moles of NaOH; 30.03 g of acetic acid; 12.80 g of NaOH.
- 250 mM; yes; no, it will also contain 90 mM NaCl.
- 8.63 g Na₂HPO₄; 4.71 g NaH₂PO₄
- 7.0; this buffer will not be very useful, because the pH value is far from the pK_a value.
- 1.45 kJ mol⁻¹ (0.35 kcal mol⁻¹); 57.9 kJ mol⁻¹ (13.8 kcal mol⁻¹)
- There will be approximately 15 million differences.

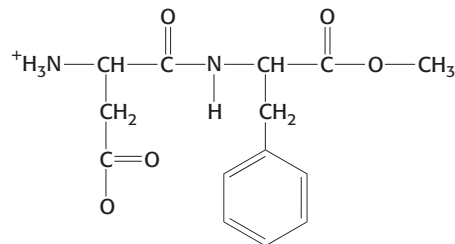
Chapter 2

- (A) Proline, Pro, P; (B) tyrosine, Tyr, Y; (C) leucine, Leu, L; (D) lysine, Lys, K.
- (a) C, B, A; (b) D; (c) D, B; (d) B, D; (e) B.
- (a) 6; (b) 2; (c) 3; (d) 1; (e) 4; (f) 5.
- (a) Ala; (b) Tyr; (c) Ser; (d) His.
- Ser, Glu, Tyr, Thr
- (a) Alanine-glycine-serine; (b) Alanine; (c) and (d):



- At pH 5.5, the net charge is +1. At pH 7.5, the net charge is 0.

- There are 20 choices for each of the 50 amino acids: 50^{20} , or 5×10^{21} .
- 9.



Aspartame at pH 7

- The (nitrogen- α carbon-carbonyl carbon) repeating unit.
- Side chain is the functional group attached to the α -carbon atom of an amino acid.
- Amino acid composition refers simply to the amino acids that make up the protein. The order is not specified. Amino acid sequence is the same as the primary structure—the sequence of amino acids from the amino terminal to the carboxyl terminal of the protein. Different proteins may have the same amino acid composition, but amino acid sequence identifies a unique protein.
- (a) Each strand is 35 kd and hence has about 318 residues (the mean residue mass is 110 daltons). Because the rise per residue in an α helix is 1.5 Å, the length is 477 Å. More precisely, for an α -helical coiled coil, the rise per residue is 1.46 Å; so the length is 464 Å.
- (b) Eighteen residues in each strand (40 minus 4 divided by 2) are in a β -sheet conformation. Because the rise per residue is 3.5 Å, the length is 63 Å.
- The methyl group attached to the β -carbon atom of isoleucine sterically interferes with α -helix formation. In leucine, this methyl group is attached to the γ -carbon atom, which is farther from the main chain and hence does not interfere.
- The first mutation destroys activity because valine occupies more space than alanine does, and so the protein must take a different shape, assuming that this residue lies in the closely packed interior. The second mutation restores activity because of a compensatory reduction of volume; glycine is smaller than isoleucine.
- The native conformation of insulin is not the thermodynamically most stable form, because it contains two separate chains linked by disulfide bonds. Insulin is formed from proinsulin, a single-chain precursor, that is cleaved to form insulin, a 51-residue molecule, after the disulfide bonds have formed.
- A segment of the main chain of the protease could hydrogen bond to the main chain of the substrate to form an extended parallel or antiparallel pair of β strands.
- Glycine has the smallest side chain of any amino acid. Its size is often critical in allowing polypeptide chains to make tight turns or to approach one another closely.
- Glutamate, aspartate, and the terminal carboxylate can form salt bridges with the guanidinium group of arginine. In addition, this group can be a hydrogen-bond donor to the side chains of glutamine, asparagine, serine, threonine, aspartate, tyrosine, and glutamate and to the main-chain carbonyl group. Histidine can form hydrogen bonds with arginine at pH7.
- Disulfide bonds in hair are broken by adding a thiol-containing reagent and applying gentle heat. The hair is curled, and an oxidizing agent is added to re-form disulfide bonds to stabilize the desired shape.
- Some proteins that span biological membranes are “the exceptions that prove the rule” because they have the reverse distribution of hydrophobic and hydrophilic amino acids. For example, consider

ANSWERS TO PROBLEMS

porins, proteins found in the outer membranes of many bacteria. Membranes are built largely of hydrophobic chains. Thus, porins are covered on the outside largely with hydrophobic residues that interact with the neighboring hydrophobic chains. In contrast, the center of the protein contains many charged and polar amino acids that surround a water-filled channel running through the middle of the protein. Thus, because porins function in hydrophobic environments, they are “inside out” relative to proteins that function in aqueous solution.

22. The amino acids would be hydrophobic in nature. An α helix is especially suited to crossing a membrane because all of the amide hydrogen atoms and carbonyl oxygen atoms of the peptide backbone take part in intrachain hydrogen bonds, thus stabilizing these polar atoms in a hydrophobic environment.

23. This example demonstrates that the pK_a values are affected by the environment. A given amino acid can have a variety of pK_a values, depending on the chemical environment inside the protein.

24. A possible explanation is that the severity of the symptoms corresponds to the degree of structural disruption. Hence, substitution of alanine for glycine might result in mild symptoms, but substitution of the much larger tryptophan might prevent little or no collagen triple-helix formation.

25. The energy barrier that must be crossed to go from the polymerized state to the hydrolyzed state is large even though the reaction is thermodynamically favorable.

26. Using the Henderson–Hasselbalch equation, we find the ratio of alanine-COOH to alanine-COO⁻ at pH 7 to be 10^{-4} . The ratio of alanine-NH₂ to alanine-NH₃⁺, determined in the same fashion, is 10^{-1} . Thus, the ratio of neutral alanine to the zwitterionic species is $10^{-4} \times 10^{-1} = 10^{-5}$.

27. The assignment of absolute configuration requires the assignment of priorities to the four groups connected to a tetrahedral carbon atom. For all amino acids except cysteine, the priorities are: (1) amino group; (2) carbonyl group; (3) side chain; (4) hydrogen. For cysteine, because of the sulfur atom in its side chain, the side chain has a greater priority than does the carbonyl group, leading to the assignment of an *R* rather than *S* configuration.

28. ELVISISLIVINGINLASVEGAS

29. No, Pro–X would have the characteristics of any other peptide bond. The steric hindrance in X–Pro arises because the R group of Pro is bonded to the amino group. Hence, in X–Pro, the proline R group is near the R group of X, which would not be the case in Pro–X.

30. A, c; B, e; C, d; D, a; E, b.

31. The reason is that the wrong disulfides formed pairs in urea. There are 105 different ways of pairing eight cysteine molecules to form four disulfides; only one of these combinations is enzymatically active. The 104 wrong pairings have been picturesquely termed “scrambled” ribonuclease.

Chapter 3

1. (a) Phenyl isothiocyanate; (b) urea; β -mercaptoethanol to reduce disulfides; (c) chymotrypsin; (d) CNBr; (e) trypsin.

2. Each amino acid residue, except the carboxyl-terminal residue, gives rise to a hydrazide on reacting with hydrazine. The carboxyl-terminal residue can be identified because it yields a free amino acid.

3. The *S*-aminoethylcysteine side chain resembles that of lysine. The only difference is a sulfur atom in place of a methylene group.

4. A 1 mg ml^{-1} solution of myoglobin (17.8 kd; Table 3.2) corresponds to $5.62 \times 10^{-5} \text{ M}$. The absorbance of a 1-cm path length is 0.84, which corresponds to an I_0/I ratio of 6.96. Hence 14.4% of the incident light is transmitted.

5. The sample was diluted 1000-fold. The concentration after dialysis is thus 0.001 M, or 1 mM. You could reduce the salt concentration by dialyzing your sample, now 1 mM, in more buffer free of $(\text{NH}_4)_2\text{SO}_4$.

6. If the salt concentration becomes too high, the salt ions interact with the water molecules. Eventually, there will not be enough water molecules to interact with the protein, and the protein will precipitate. If there is lack of salt in a protein solution, the proteins may interact with one another—the positive charges on one protein with the negative charges on another or several others. Such an aggregate becomes too large to be solubilized by water alone. If salt is added, the salt neutralizes the charges on the proteins, preventing protein–protein interactions.

7. Tropomyosin is rod shaped, whereas hemoglobin is approximately spherical.

8. The frictional coefficient, f , and the mass, m , determine s . Specifically, f is proportional to r (see equation 2 on p. 71). Hence, f is proportional to $m^{1/3}$, and so s is proportional to $m^{2/3}$ (see the equation on p. 76). An 80-kd spherical protein undergoes sedimentation 1.59 times as rapidly as a 40-kd spherical protein.

9. The long hydrophobic tail on the SDS molecule (see p. 72) disrupts the hydrophobic interactions in the interior of the protein. The protein unfolds, with the hydrophobic R groups now interacting with SDS rather than with one another.

10. 50 kd.

11. The protein may be modified. For instance, serine, threonine, and tyrosine may have phosphoryl groups attached.

12. A fluorescence-labeled derivative of a bacterial degradation product (e.g., a formylmethionyl peptide) would bind to cells containing the receptor of interest.

13. (a) Trypsin cleaves after arginine (R) and lysine (K), generating AVGWR, VK, and S. Because they differ in size, these products could be separated by molecular exclusion chromatography. (b) Chymotrypsin, which cleaves after large aliphatic or aromatic R groups, generates two peptides of equal size (AVGW) and (RVKS). Separation based on size would not be effective. The peptide RVKS has two positive charges (R and K), whereas the other peptide is neutral. Therefore, the two products could be separated by ion-exchange chromatography.

14. Antibody molecules bound to a solid support can be used for affinity purification of proteins for which a ligand molecule is not known or unavailable.

15. If the product of the enzyme-catalyzed reaction is highly antigenic, it may be possible to obtain antibodies to this particular molecule. These antibodies can be used to detect the presence of product by ELISA, providing an assay format suitable for the purification of this enzyme.

16. An inhibitor of the enzyme being purified might have been present and subsequently removed by a purification step. This removal would lead to an apparent increase in the total amount of enzyme present.

17. Many proteins have similar masses but different sequences and different patterns when digested with trypsin. The set of masses of tryptic peptides forms a detailed “fingerprint” of a protein that is very unlikely to appear at random in other proteins regardless of size. (A conceivable analogy is: “Just as similarly sized fingers will give different individual fingerprints, so also similarly sized proteins will give different digestion patterns with trypsin.”)

18. Isoleucine and leucine are isomers and, hence, have identical masses. Peptide sequencing by mass spectrometry as described in this chapter is incapable of distinguishing these residues. Further analytical techniques are required to differentiate these residues.

19. See the table at the top of the facing page.

Purification procedure	Total protein (mg)	Total activity (units)	Specific activity (units mg ⁻¹)	Purification level	Yield (%)
Crude extract	20,000	4,000,000	200	1	100
(NH ₄) ₂ SO ₄ precipitation	5,000	3,000,000	600	3	75
DEAE-cellulose chromatography	1,500	1,000,000	667	3.3	25
Gel-filtration chromatography	500	750,000	1,500	7.5	19
Affinity chromatography	45	675,000	15,000	75	17

20. Protein crystal formation requires the ordered arrangement of identically positioned molecules. Proteins with flexible linkers can introduce disorder into this arrangement and prevent the formation of suitable crystals. A ligand or binding partner may induce an ordered conformation to this linker and could be included in the solution to facilitate crystal growth. Alternatively, the individual domains separated by the linker may be expressed by recombinant methods and their crystal structures solved separately.

21. Treatment with urea will disrupt noncovalent bonds. Thus the original 60-kD protein must be made of two 30-kD subunits. When these subunits are treated with urea and β-mercaptoethanol, a single 15-kD species results, suggesting that disulfide bonds link the 30-kD subunits.

22. (a) Electrostatic repulsion between positively charged ε-amino groups hinders α-helix formation at pH 7. At pH 10, the side chains become deprotonated, allowing α-helix formation.

(b) Poly-L-glutamate is a random coil at pH 7 and becomes α helical below pH 4.5 because the γ-carboxylate groups become protonated.

23. The difference between the predicted and the observed masses for this fragment equals 28.0, exactly the mass shift that would be expected in a formylated peptide. This peptide is likely formylated at its amino terminus, and corresponds to the most N-terminal fragment of the protein.

24. Light was used to direct the synthesis of these peptides. Each amino acid added to the solid support contained a photolabile protecting group instead of a *t*-Boc protecting group at its α-amino group. Illumination of selected regions of the solid support led to the release of the protecting group, which exposed the amino groups in these sites to make them reactive. The pattern of masks used in these illuminations and the sequence of reactants define the ultimate products and their locations.

25. Mass spectrometry is highly sensitive and capable of detecting the mass difference between a protein and its deuterated counterpart. Fragmentation techniques can be used to identify the amino acids that retained the isotope label. Alternatively, NMR spectroscopy can be used to detect the isotopically labeled atoms because the deuteron and the proton have very different nuclear-spin properties.

26. First amino acid: A

Last amino acid: R (not cleaved by carboxypeptidase).

Sequence of N-terminal tryptic peptide: AVR (tryptic peptide ends in K)

Sequence of N-terminal chymotryptic peptide: AVRY (chymotryptic peptide ends in Y)

Sequence: AVRYSR

27. First amino acid: S

Last amino acid: L

Cyanogen bromide cleavage: M is 10th position,

C-terminal residues are: (2S,L,W)

Amino-terminal residues: (G,K,S,Y), tryptic peptide, ends in K

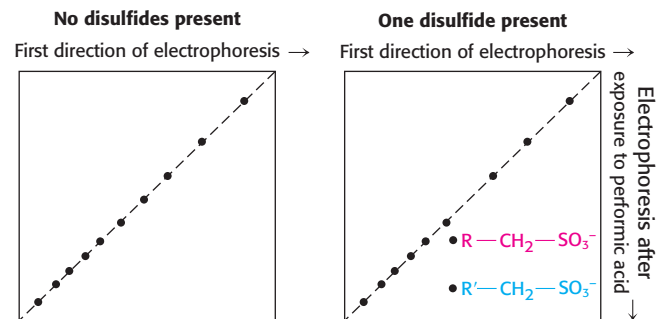
Amino-terminal sequence: SYGK

Chymotryptic peptide order: (S,Y), (G,K,L), (F,I,S),

(M,T), (S,W), (S,L)

Sequence: SYGKLSIFTMSWSL

28. If the protein did not contain any disulfide bonds, then the electrophoretic mobility of the trypsin fragments would be the same before and after performic acid treatment: all the fragments would lie along the diagonal of the paper. If one disulfide bond were present, the disulfide-linked trypsin fragments would run as a single peak in the first direction, then would run as two separate peaks after performic acid treatment. The result would be two peaks appearing off the diagonal:



These fragments could then be isolated from the chromatography paper and analyzed by mass spectrometry to determine their amino acid composition and thus identify the cysteines participating in the disulfide bond.

Chapter 4

1. A nucleoside is a base attached to a ribose sugar. A nucleotide is a nucleoside with one or more phosphoryl groups attached to the ribose.
2. Hydrogen-bond pairing between the base A and the base T as well as hydrogen-bond pairing between the base G and the base C in DNA.
3. T is always equal to A, and so these two nucleotides constitute 40% of the bases. G is always equal to C, and so the remaining 60% must be 30% G and 30% C.
4. Nothing, because the base-pair rules do not apply to single-stranded nucleic acids.
5. (a) TTGATC; (b) GTTCGA; (c) ACGCGT; (d) ATGGTA.
6. (a) [T] + [C] = 0.46. (b) [T] = 0.30, [C] = 0.24, and [A] + [G] = 0.46.
7. Stable hydrogen bonding occurs only between GC and AT pairs. Moreover, two purines are too large to fit inside the double helix, and two pyrimidines are too small to form base pairs with each other.
8. The thermal energy causes the chains to wiggle about, which disrupts the hydrogen bonds between base pairs and the stacking forces between bases and thereby causes the strands to separate.
9. The probability that any sequence will appear is 4ⁿ, where 4 is the number of nucleotides and *n* is the length of the sequence. The probability of any 15-base sequence appearing is 1/4¹⁵, or 1/1,073,741,824. Thus, a 15-nucleotide sequence would be likely to appear approximately three times (3 billion × probability of appearance). The probability of a 16-base sequence appearing is 1/4¹⁶, which is equal to 1/4,294,967,296. Such a sequence will be unlikely to appear more than once.

ANSWERS TO PROBLEMS

10. One end of a nucleic acid polymer ends with a free 5'-hydroxyl group (or a phosphoryl group esterified to the hydroxyl group), and the other end has a free 3'-hydroxyl group. Thus, the ends are different. Two chains of DNA can form a double helix only if the chains are running in different directions—that is, have opposite polarity.

11. Although the individual bonds are weak, the population of thousands to millions of such bonds provides much stability. There is strength in numbers.

12. There would be too much charge repulsion from the negative charges on the phosphoryl groups. These charges must be countered by the addition of cations.

13. The three forms are the A-DNA, the B-DNA and the Z-DNA, with B-DNA being the most common. There are many differences (see Table 4.2). Some key differences are: A-DNA and B-DNA are right-handed, whereas Z-DNA is left-handed. A-DNA forms in less-hydrated conditions than does B-DNA. The A form is shorter and wider than the B form.

14. 5.88×10^3 base pairs

15. In conservative replication, after 1.0 generation, half of the molecules would be $^{15}\text{N}-^{15}\text{N}$, the other half $^{14}\text{N}-^{14}\text{N}$. After 2.0 generations, one-quarter of the molecules would be $^{15}\text{N}-^{15}\text{N}$, the other three-quarters $^{14}\text{N}-^{14}\text{N}$. Hybrid $^{14}\text{N}-^{15}\text{N}$ molecules would not be observed in conservative replication.

16. (a) Tritiated thymine or tritiated thymidine.

(b) dATP, dGTP, dCTP, and TTP labeled with ^{32}P in the innermost (α) phosphorus atom.

17. Molecules in parts a and b would not lead to DNA synthesis, because they lack a 3'-OH group (a primer). The molecule in part d has a free 3'-OH group at one end of each strand but no template strand beyond. Only the molecule in part c would lead to DNA synthesis.

18. A retrovirus is a virus that has RNA as its genetic material. However, for the information to be expressed, it must first be converted into DNA, a reaction catalyzed by the enzyme reverse transcriptase. Thus, at least initially, information flow is opposite that of a normal cell: $\text{RNA} \rightarrow \text{DNA}$ rather than $\text{DNA} \rightarrow \text{RNA}$.

19. A thymidylate oligonucleotide should be used as the primer. The poly(A) template specifies the incorporation of T; hence, radioactive thymidine triphosphate (labeled in the α phosphoryl group) should be used in the assay.

20. The ribonuclease serves to degrade the RNA strand, a necessary step in forming duplex DNA from the RNA-DNA hybrid.

21. Treat one aliquot of the sample with ribonuclease and another with deoxyribonuclease. Test these nuclease-treated samples for infectivity.

22. Deamination changes the original G · C base pair into a G · U pair. After one round of replication, one daughter duplex will contain a G · C pair and the other duplex will contain an A · U pair. After two rounds of replication, there will be two G · C pairs, one A · U pair, and one A · T pair.

23. (a) $4^8 = 65,536$. In computer terminology, there are 64K 8-mers of DNA.

(b) A bit specifies two bases (say, A and C) and a second bit specifies the other two (G and T). Hence, two bits are needed to specify a single nucleotide (base pair) in DNA. For example, 00, 01, 10, and 11 could encode A, C, G, and T. An 8-mer stores 16 bits ($2^{16} = 65,536$), the *E. coli* genome (4.6×10^6 bp) stores 9.2×10^6 bits, and the human genome (3.0×10^9 bases) stores 6.0×10^9 bits of genetic information.

(c) A standard CD can hold about 700 megabytes, which is equal to 5.6×10^9 bits. A large number of 8-mer sequences could be stored on such a CD. The DNA sequence of *E. coli*, could be written on a single CD with room to spare for a lot of music. One CD would not be quite enough to record the entire human genome.

24. (a) Deoxyribonucleoside triphosphates versus ribonucleoside triphosphates.

(b) $5' \rightarrow 3'$ for both.

(c) Semiconserved for DNA polymerase I; conserved for RNA polymerase.

(d) DNA polymerase I needs a primer, whereas RNA polymerase does not.

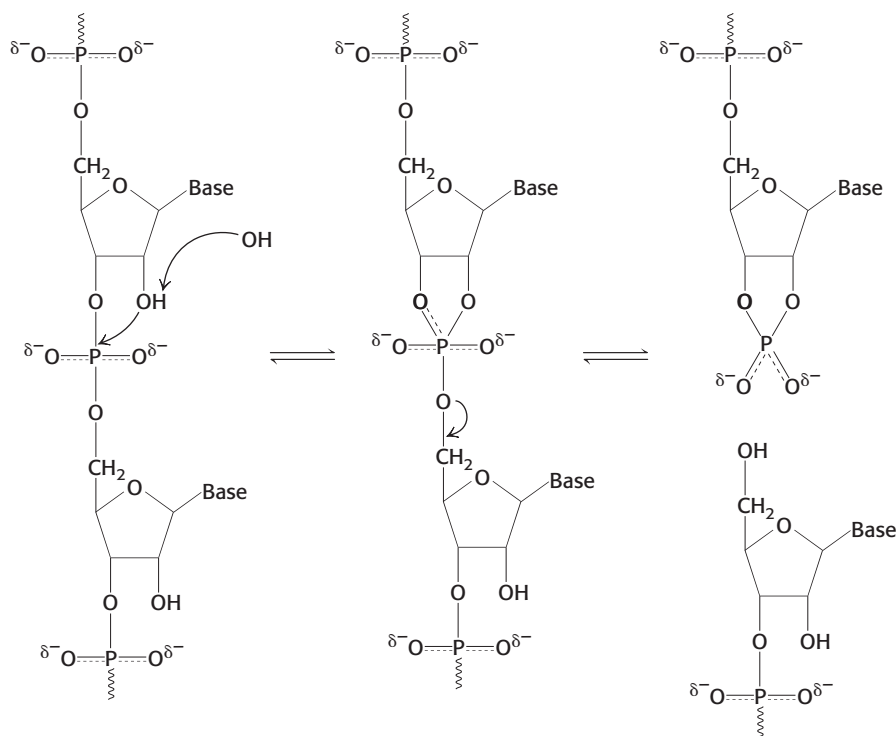
25. Messenger RNA encodes the information that, on translation, yields a protein. Ribosomal RNA is the catalytic component of ribosomes, the molecular complexes that synthesize proteins. Transfer RNA is an adaptor molecule, capable of binding a specific amino acid and recognizing a corresponding codon. Transfer RNAs with attached amino acids are substrates for the ribosome.

26. (a) 5'-UAACGGUACGAU-3'

(b) Leu-Pro-Ser-Asp-Trp-Met

(c) Poly(Leu-Leu-Thr-Tyr)

27. The 2'-OH group in RNA acts as an intramolecular nucleophile. In the alkaline hydrolysis of RNA, it forms a 2'-3' cyclic intermediate.



29. Gene expression is the process of expressing the information of a gene in its functional molecular form. For many genes, the functional information is a protein molecule. Thus, gene expression includes transcription and translation.

30. A nucleotide sequence whose bases represent the most-common, but not necessarily the only, members of the sequence. A consensus sequence can be thought of as the average of many similar sequences.

31. Cordycepin terminates RNA synthesis. An RNA chain containing cordycepin lacks a 3'-OH group.

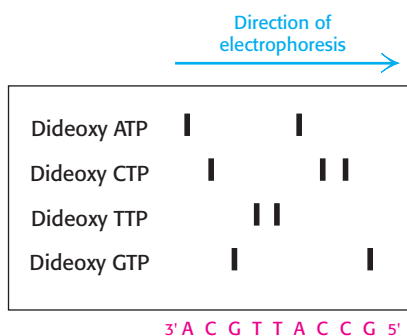
32. Only single-stranded RNA can serve as a template for protein synthesis.

33. Degeneracy of the code refers to the fact that most amino acids are encoded by more than one codon.

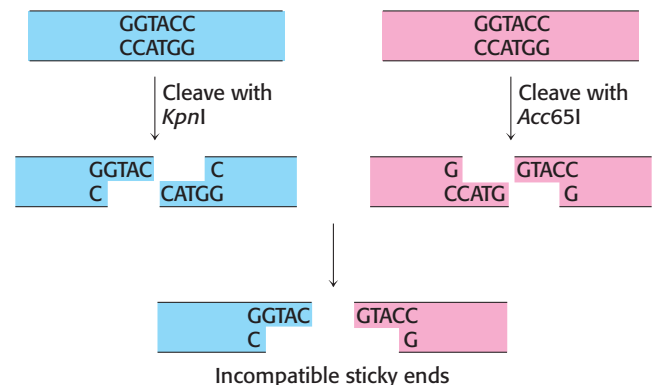
34. If only 20 of the 64 possible codons encoded amino acids, then a mutation that changed a codon would likely result in a nonsense codon, leading to termination of protein synthesis. With degeneracy, a nucleotide change might yield a synonym or a codon for an amino acid with similar chemical properties.
35. (a) 2, 4, 8; (b) 1, 6, 10; (c) 3, 5, 7, 9.
36. (a) 3; (b) 6; (c) 2; (d) 5; (e) 7; (f) 1; (g) 4.
37. Incubation with RNA polymerase and only UTP, ATP, and CTP led to the synthesis of only poly(UAC). Only poly(GUA) was formed when GTP was used in place of CTP.
38. A peptide terminating with Lys (UGA is a stop codon), another containing -Asn-Glu-, and a third containing -Met-Arg-.
39. Highly abundant amino acid residues have the most codons (e.g., Leu and Ser each have six), whereas the least-abundant amino acids have the fewest (Met and Trp each have only one). Degeneracy (1) allows variation in base composition and (2) decreases the likelihood that a substitution for a base will change the encoded amino acid. If the degeneracy were equally distributed, each of the 20 amino acids would have three codons. Both benefits (1 and 2) are maximized by the assignment of more codons to prevalent amino acids than to less frequently used ones.
40. Phe-Cys-His-Val-Ala-Ala
41. Exon shuffling is a molecular process that can lead to the generation of new proteins by the rearrangement of exons within genes. Because many exons encode functional protein domains, exon shuffling is a rapid and efficient means of generating new genes.
42. It shows that the genetic code and the biochemical means of interpreting the code are common to even very distantly related life forms. It also testifies to the unity of life; that all life arose from a common ancestor.
43. (a) A codon for lysine cannot be changed to one for aspartate by the mutation of a single nucleotide. (b) Arg, Asn, Gln, Glu, Ile, Met, or Thr.
44. The genetic code is degenerate. Of the 20 amino acids, 18 are specified by more than one codon. Hence, many nucleotide changes (especially in the third base of a codon) do not alter the nature of the encoded amino acid. Mutations leading to an altered amino acid are usually more deleterious than those that do not and hence are subject to more stringent selection.
45. GC base pairs have three hydrogen bonds compared with two for AT base pairs. Thus, the higher content of GC means more hydrogen bonds and greater helix stability.
46. C_0t value essentially corresponds to the complexity of the DNA sequence—in other words, how long it will take for a sequence of DNA to find its complementary strand to form a double helix. The more complex the DNA, the slower it reassociates to make the double-stranded form.

Chapter 5

1. (a) 5'-GGCATAC-3'
 (b) The Sanger dideoxy method of sequencing would give the gel pattern shown here.



2. Ovalbumin cDNA should be used. *E. coli* lacks the machinery to splice the primary transcript arising from genomic DNA.
3. Consistent with its planar, aromatic structure, ethidium bromide is a DNA intercalator: it aligns itself between the paired bases in a DNA duplex.
4. The presence of the *AluI* sequence would, on average, be $(1/4)^4$, or $1/256$, because the likelihood of any base being at any position is one-fourth and there are four positions. By the same reasoning, the presence of the *NotI* sequence would be $(1/4)^8$, or $1/65,536$. Thus, the average product of digestion by *AluI* would be 250 base pairs (0.25 kb) in length, whereas that by *NotI* would be 66,000 base pairs (66 kb) in length.
5. No, because most human genes are much longer than 4 kb. A fragment would contain only a small part of a complete gene.
6. Southern blotting of an *MstII* digest would distinguish between the normal and the mutant genes. The loss of a restriction site would lead to the replacement of two fragments on the Southern blot by a single longer fragment. Such a finding would not prove that GTG replaced GAG; other sequence changes at the restriction site could yield the same result.
7. Although the two enzymes cleave the same recognition site, they each break different bonds within the 6-bp sequence. Cleavage by *KpnI* yields an overhang on the 3' strand, whereas cleavage by *Acc65I* produces an overhang on the 5' strand. These sticky ends do not overlap.



8. A simple strategy for generating many mutants is to synthesize a degenerate set of cassettes by using a mixture of activated nucleosides in particular rounds of oligonucleotide synthesis. Suppose that the 30-bp coding region begins with GTT, which encodes valine. If a mixture of all four nucleotides is used in the first and second rounds of synthesis, the resulting oligonucleotides will begin with the sequence XYT (where X and Y denote A, C, G, or T). These 16 different versions of the cassette will encode proteins containing either Phe, Leu, Ile, Val, Ser, Pro, Thr, Ala, Tyr, His, Asn, Asp, Cys, Arg, or Gly at the first position. Likewise, degenerate cassettes can be made in which two or more codons are simultaneously varied.
9. Because PCR can amplify as little as one molecule of DNA, statements claiming the isolation of ancient DNA need to be greeted with some skepticism. The DNA would need to be sequenced. Is it similar to human, bacterial, or fungal DNA? If so, contamination is the likely source of the amplified DNA. Is it similar to that of birds or crocodiles? This sequence similarity would strengthen the case that it is dinosaur DNA because these species are evolutionarily close to dinosaurs.
10. PCR amplification is greatly hindered by the presence of G-C-rich regions within the template. Owing to their high melting temperatures, these templates do not denature easily, preventing the initiation of an amplification cycle. In addition, rigid secondary

structures prevent the progress of DNA polymerase along the template strand during elongation.

11. At high temperatures of hybridization, only very close matches between primer and target would be stable because all (or most) of the bases would need to find partners to stabilize the primer–target helix. As the temperature is lowered, more mismatches would be tolerated; so the amplification is likely to yield genes with less sequence similarity. In regard to the yeast gene, synthesize primers corresponding to the ends of the gene, and then use these primers and human DNA as the target. If nothing is amplified at 54°C, the human gene differs from the yeast gene, but a counterpart may still be present. Repeat the experiment at a lower temperature of hybridization.

12. Digest genomic DNA with a restriction enzyme, and select the fragment that contains the known sequence. Circularize this fragment. Then carry out PCR with the use of a pair of primers that serve as templates for the synthesis of DNA away from the known sequence.

13. The encoded protein contains four repeats of a specific sequence.

14. Use chemical synthesis or the polymerase chain reaction to prepare hybridization probes that are complementary to both ends of the known (previously isolated) DNA fragment. Challenge clones representing the library of DNA fragments with both of the hybridization probes. Select clones that hybridize to one of the probes but not the other; such clones are likely to represent DNA fragments that contain one end of the known fragment along with the adjacent region of the particular chromosome.

15. The codon(s) for each amino acid can be used to determine the number of possible nucleotide sequences that encode each peptide sequence (see Table 4.5):

Ala–Met–Ser–Leu–Pro–Trp:
 $4 \times 1 \times 6 \times 6 \times 4 \times 1 = 576$ total sequences

Gly–Trp–Asp–Met–His–Lys:
 $4 \times 1 \times 2 \times 1 \times 2 \times 2 = 32$ total sequences

Cys–Val–Trp–Asn–Lys–Ile:
 $2 \times 4 \times 1 \times 2 \times 2 \times 3 = 96$ total sequences

Arg–Ser–Met–Leu–Gln–Asn:
 $6 \times 6 \times 1 \times 6 \times 2 \times 2 = 864$ total sequences

The set of DNA sequences encoding the peptide Gly–Trp–Asp–Met–His–Lys would be most ideal for probe design because it encompasses only 32 total oligonucleotides.

16. Within a single species, individual dogs show enormous variation in body size and substantial diversity in other physical characteristics. Therefore, genomic analysis of individual dogs would provide valuable clues concerning the genes responsible for the diversity within the species.

17. On the basis of the comparative genome map shown in Figure 5.27, the region of greatest overlap with human chromosome 20 can be found on mouse chromosome 2.

18. T_m is the melting temperature of a double-stranded nucleic acid. If the melting temperatures of the primers are too different, the extent of hybridization with the target DNA will differ during the annealing phase, which would result in differential replications of the strands.

19. Careful comparison of the sequences reveals that there is a 7-bp region of complementarity at the 3' ends of these two primers:

5'-GGATCGATGCTCGCGA-3'
 |||||
 3'-GAGCGCTGGGCTAGGA-5'

In a PCR experiment, these primers would likely anneal to one another, preventing their interaction with the template DNA. During DNA synthesis by the polymerase, each primer would act as a template for the other primer, leading to the amplification of a 25-bp sequence corresponding to the overlapped primers.

20. A mutation in person B has altered one of the alleles for gene X, leaving the other intact. The fact that the mutated allele is smaller suggests that a deletion has occurred in one copy of the gene. The one functioning copy is transcribed and translated and apparently produces enough protein to render the person asymptomatic.

Person C has only the smaller version of the gene. This gene is neither transcribed (negative northern blot) nor translated (negative western blot).

Person D has a normal-size copy of the gene but no corresponding RNA or protein. There may be a mutation in the promoter region of the gene that prevents transcription.

Person E has a normal-size copy of the gene that is transcribed, but no protein is made, which suggests that a mutation prevents translation. There are a number of possible explanations, including a mutation that introduced a premature stop codon in the mRNA.

Person F has a normal amount of protein but still displays the metabolic problem. This finding suggests that the mutation affects the activity of the protein—for instance, a mutation that compromises the active site of enzyme Y.

21. Chongqing: residue 2, L → R, CTG → CGG

Karachi: residue 5, A → P, GCC → CCC

Swan River: residue 6, D → G, GAC → GGC

22. This particular person is heterozygous for this particular mutation: one allele is wild type, whereas the other carries a point mutation at this position. Both alleles are PCR amplified in this experiment, yielding the “dual peak” appearance on the sequencing chromatogram.

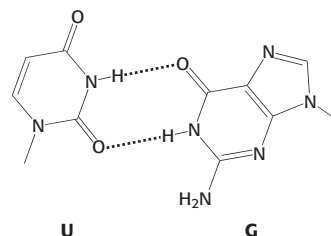
Chapter 6

1. There are 26 identities and two gaps for a score of 210. The two sequences are approximately 26% identical. This level of homology is likely to be statistically significant.

2. They are likely related by divergent evolution, because three-dimensional structure is more conserved than is sequence identity.

3. (a) Identity score = –25; Blosum score = 14; (b) identity score = 15; Blosum score = 3.

4. U



5. There are 4^{40} , or 1.2×10^{24} , different molecules. Each molecule has a mass of 2.2×10^{-20} , because 1 mol of polymer has a mass of $330 \text{ g mol}^{-1} \times 40$, and there are 6.02×10^{23} molecules per mole. Therefore, 26.4 kg of RNA would be required.

6. Because three-dimensional structure is much more closely associated with function than is sequence, tertiary structure is more evolutionarily conserved than is primary structure. In other words, protein function is the most important characteristic, and protein function is determined by structure. Thus, the structure must be conserved but not necessarily a specific amino acid sequence.

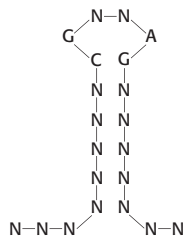
7. Alignment score of sequences (1) and (2) is $6 \times 10 = 60$. Many answers are possible, depending on the randomly reordered sequence. A possible result is

Shuffled sequence: (2) TKADKAGEYL

Alignment: (1) ASNFLDKAGK
(2) TKADKAGEYL

Alignment score is $4 \times 10 = 40$.

8. (a) Almost certainly diverged from a common ancestor. (b) Almost certainly diverged from a common ancestor. (c) May have diverged from a common ancestor, but the sequence alignment may not provide supporting evidence. (d) May have diverged from a common ancestor, but the sequence alignment is unlikely to provide supporting evidence.
9. Replacement of cysteine, glycine, and proline never yields a positive score. Each of these residues exhibits features unlike those of its other 19 counterparts: cysteine is the only amino acid capable of forming disulfide bonds, glycine is the only amino acid without a side-chain and is highly flexible, and proline is the only amino acid that is highly constrained through the bonding of its side chain to its amine nitrogen.
10. Protein A is clearly homologous to protein B, given 65% sequence identity, and so A and B are expected to have quite similar three-dimensional structures. Likewise, proteins B and C are clearly homologous, given 55% sequence identity, and so B and C are expected to have quite similar three-dimensional structures. Thus, proteins A and C are likely to have similar three-dimensional structures, even though they are only 15% identical in sequence.
11. The likely secondary structure is

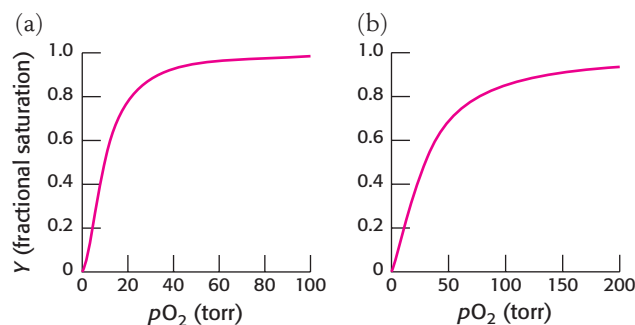


12. To detect pairs of residues with correlated mutations, there must be variability in these sequences. If the alignment is over-represented by closely related organisms, there may not be enough changes in their sequences to allow the identification of potential base-pairing patterns.
13. After RNA molecules have been selected and reverse transcribed, PCR is performed to introduce additional mutations into these strands. The use of this error-prone, thermostable polymerase in the amplification step would enhance the efficiency of this random mutagenesis.
14. The initial pool of RNA molecules used in a molecular-evolution experiment is typically much smaller than the total number of possible sequences. Hence, the best possible RNA sequences will likely not be represented in the initial set of oligonucleotides. Mutagenesis of the initial selected RNA molecules allows for the iterative improvement of these sequences for the desired property.
15. 107 or 108 identities (depending on which annotated human sequence is chosen).

Chapter 7

1. The whale swims long distances between breaths. A high concentration of myoglobin in the whale muscle maintains a ready supply of oxygen for the muscle between breathing episodes.

2. (a) 2.96×10^{-11} g
(b) 2.74×10^8 molecules
(c) No. There would be 3.17×10^8 hemoglobin molecules in a red cell if they were packed in a cubic crystalline array. Hence, the actual packing density is about 84% of the maximum possible.
3. 2.65 g (or 4.75×10^{-2} mol) of Fe
4. (a) In human beings, 1.44×10^{-2} g (4.49×10^{-4} mol) of O_2 per kilogram of muscle. In sperm whale, 0.144 g (4.49×10^{-3} mol) of O_2 per kilogram.
(b) 128
5. The pK_a is (a) lowered; (b) raised; and (c) raised.
6. Deoxy Hb A contains a complementary site, and so it can add on to a fiber of deoxy Hb S. The fiber cannot then grow further, because the terminal deoxy Hb A molecule lacks a sticky patch.
7. 62.7% oxygen-carrying capacity
8. A higher concentration of BPG would shift the oxygen-binding curve to the right, causing an increase in P_{50} . The larger value of P_{50} would promote dissociation of oxygen in the tissues and would thereby increase the percentage of oxygen delivered to the tissues.
9. Oxygen binding appears to cause the copper ions and their associated histidine ligands to move closer to one another, thereby also moving the helices to which the histidines are attached (in similar fashion to the conformational change in hemoglobin).
10. The modified hemoglobin should not show cooperativity. Although the imidazole in solution will bind to the heme iron (in place of histidine) and will facilitate oxygen binding, the imidazole lacks the crucial connection to the particular α helix that must move so as to transmit the change in conformation.
11. Inositol pentaphosphate (part c) is highly anionic, much like 2,3-bisphosphoglycerate.
- 12.



13. Release of acid will lower the pH. A lower pH promotes oxygen dissociation in the tissues. However, the enhanced release of oxygen in the tissues will increase the concentration of deoxy-Hb, thereby increasing the likelihood that the cells will sickle.
14. (a) $Y = 0.5$ when $pO_2 = 10$ torr. The plot of Y versus pO_2 appears to indicate little or no cooperativity.
(b) The Hill plot shows slight cooperativity with $n \cdot 1.3$ in the central region.
(c) Deoxy dimers of lamprey hemoglobin could have lower affinity for oxygen than do the monomers. If the binding of the first oxygen atom to a dimer causes dissociation of the dimer to give two monomers, then the process would be cooperative. In this mechanism, oxygen binding to each monomer would be easier than binding the first oxygen atom to a deoxy dimer.
15. (a) 2; (b) 4; (c) 2; (d) 1.
16. The electrostatic interactions between BPG and hemoglobin would be weakened by competition with water molecules. The T state would not be stabilized.

Chapter 8

1. Rate enhancement and substrate specificity
2. A cofactor
3. Coenzymes and metals
4. Vitamins are converted into coenzymes.
5. Enzymes facilitate the formation of the transition state.
6. The intricate three-dimensional structure of proteins allows the construction of active sites that will recognize only specific substrates.
7. The energy required to reach the transition state (the activation energy) is returned when the transition state proceeds to product.
8. Protein hydrolysis has a large activation energy. Protein synthesis must require energy to proceed.
9. The enzymes help protect the fluid that surrounds eyes from bacterial infection.
10. Transition states are very unstable. Consequently, molecules that resemble transition states are themselves likely to be unstable and, hence, difficult to synthesize.
11. (a) 0; (b) 28.53; (c) -22.84; (d) -11.42; (e) 5.69.
12. (a) $\Delta G^{\circ'} = -RT \ln K'_{\text{eq}}$

$$+1.8 = -(1.98 \times 10^{-3} \text{ kcal}^{-1} \text{ K}^{-1} \text{ mol}^{-1}) (298 \text{ K}) (\ln[\text{G1P}]/[\text{G6P}])$$

$$-3.05 = \ln [\text{G1P}]/[\text{G6P}]$$

$$+3.05 = \ln [\text{G6P}]/[\text{G1P}]$$

$$K'_{\text{eq}}^{-1} = 21 \quad \text{or} \quad K'_{\text{eq}} = 4.8 \times 10^{-2}$$

Because $[\text{G6P}]/[\text{G1P}] = 21$, there is 1 molecule of G1P for every 21 molecules of G6P. Because we started with 0.1 M, the $[\text{G1P}]$ is $1/22(0.1 \text{ M}) = 0.0045 \text{ M}$ and $[\text{G6P}]$ must be $21/22(0.1 \text{ M})$ or 0.096 M. Consequently, the reaction does not proceed as written to a significant extent.

(b) Supply G6P at a high rate and remove G1P at a high rate by other reactions. In other words, make sure that the $[\text{G6P}]/[\text{G1P}]$ is large.

$$13. K'_{\text{eq}} = 19, \Delta G^{\circ'} = -7.41 \text{ kJ mol}^{-1} (-1.77 \text{ kcal mol}^{-1})$$

14. The three-dimensional structure of an enzyme is stabilized by interactions with the substrate, reaction intermediates, and products. This stabilization minimizes thermal denaturation.

15. At substrate concentrations near the K_M , the enzyme displays significant catalysis yet is sensitive to changes in substrate concentration.

$$16. A + S = 10 K_M, V_0 = 0.91 V_{\text{max}}. I + S = 20 K_M, V_0 = 0.91 V_{\text{max}}.$$

So any Michaelis–Menten curves showing that the enzyme actually attains V_{max} are pernicious lies.

17. (a) 31.1 μmol ; (b) 0.05 μmol ; (c) 622 s^{-1} , a midrange value for enzymes (see Table 8.5).

18. (a) Yes, $K_M = 5.2 \times 10^{-6} \text{ M}$; (b) $V_{\text{max}} = 6.8 \times 10^{-10} \text{ mol minute}^{-1}$; (c) 337 s^{-1} .

19. Penicillinase, like glycopeptide transpeptidase, forms an acyl-enzyme intermediate with its substrate but transfers the intermediate to water rather than to the terminal glycine residue of the pentaglycine bridge.

20. (a) V_{max} is 9.5 $\mu\text{mol minute}^{-1}$. K_M is $1.1 \times 10^{-5} \text{ M}$, the same as without inhibitor.

(b) Noncompetitive

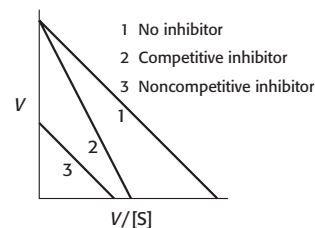
(c) $2.5 \times 10^{-5} \text{ M}$

(d) $f_{\text{ES}} = 0.73$, in the presence or absence of this noncompetitive inhibitor.

21. (a) $V = V_{\text{max}} - (V/[S]) K_M$.

(b) Slope = $-K_M$, y-intercept = V_{max} , x-intercept = V_{max}/K_M .

(c) An Eadie–Hofstee plot



22. The rates of utilization of substrates A and B are given by

$$V_A = \left(\frac{k_{\text{cat}}}{K_M} \right)_A [E][A]$$

and

$$V_B = \left(\frac{k_{\text{cat}}}{K_M} \right)_B [E][B]$$

Hence, the ratio of these rates is

$$V_A/V_B = \left(\frac{k_{\text{cat}}}{K_M} \right)_B [A] / \left(\frac{k_{\text{cat}}}{K_M} \right)_A [B]$$

Thus, an enzyme discriminates between competing substrates on the basis of their values of k_{cat}/K_M rather than of K_M alone.

23. The mutation slows the reaction by a factor of 100 because the activation free energy is increased by 53.22 kJ mol^{-1} (12.72 kcal mol^{-1}). Strong binding of the substrate relative to the transition state slows catalysis.

24. 1.1 $\mu\text{mol minute}^{-1}$

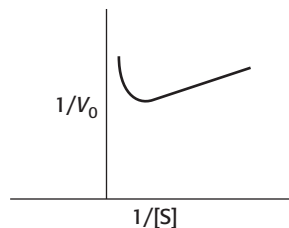
25. (a) This piece of information is necessary for determining the correct dosage of succinylcholine to administer.

(b) The duration of the paralysis depends on the ability of the serum cholinesterase to clear the drug. If there were one-eighth the amount of enzyme activity, paralysis could last eight times as long, which is undesirable for two reasons. First, the respirator might break from extended use, which would not be good for the patient on the respirator; second, the doctors might miss their golf game.

(c) K_M is the concentration needed by the enzyme to reach $1/2 V_{\text{max}}$. Consequently, for a given concentration of substrate, the reaction catalyzed by the enzyme with the lower K_M will have the higher rate. The mutant patient with the higher K_M will clear the drug at a much lower rate.

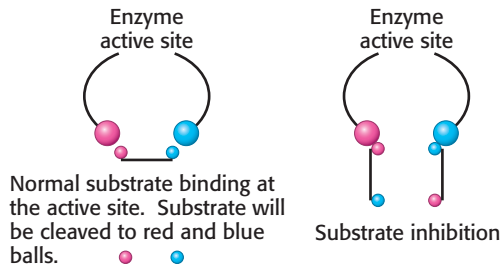
26. If the total amount of enzyme (E_T) is increased, V_{max} will increase, because $V_{\text{max}} = k_2[E_T]$. But $K_M = (k_{-1} + k_2)/k_1$; that is, it is independent of substrate concentration. The middle graph describes this situation.

27. (a)



(b) This behavior is substrate inhibition: at high concentrations, the substrate forms unproductive complexes at the active site. The adjoining drawing shows what might happen. Substrate normally binds in a defined orientation, shown in the drawing

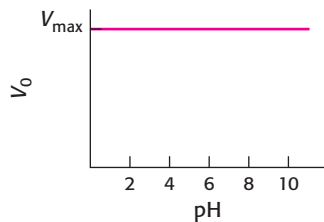
as red to red and blue to blue. At high concentrations, the substrate may bind at the active site such that the proper orientation is met for each end of the molecule, but two different substrate molecules are binding.



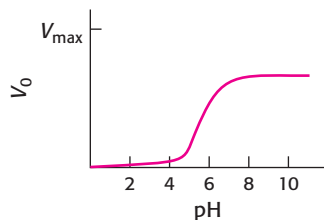
28. The first step will be the rate-limiting step. Enzymes E_B and E_C are operating at $\frac{1}{2} V_{\max}$, whereas the K_M for enzyme E_A is greater than the substrate concentration. E_A would be operating at approximately $10^{-2} V_{\max}$.

29. The fluorescence spectroscopy reveals the existence of an enzyme-serine complex and of an enzyme-serine-indole complex.

30. (a) When $[S^+]$ is much greater than the value of K_M , pH will have a negligible effect on the enzyme because S^+ will interact with E^- as soon as the enzyme becomes available.



(b) When $[S^+]$ is much less than the value of K_M , the plot of V_0 versus pH becomes essentially a titration curve for the ionizable groups, with enzyme activity being the titration marker. At low pH, the high concentration of H^+ will keep the enzyme in the EH form and inactive. As the pH rises, more and more of the enzyme will be in the E^- form and active. At high pH (low H^+), all of the enzyme is E^- .



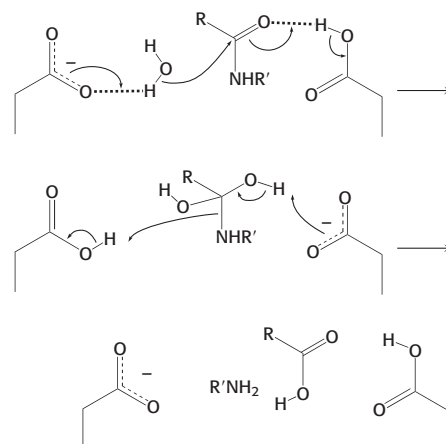
(c) The midpoint on this curve will be the pK_a of the ionizable group, which is stated to be pH 6.

31. (a) Incubating the enzyme at $37^\circ C$ leads to a denaturation of enzyme structure and a loss of activity. For this reason, most enzymes must be kept cool if they are not actively catalyzing their reactions.

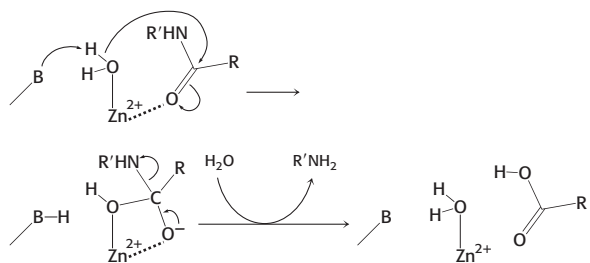
(b) The coenzyme apparently helps to stabilize enzyme structure, because enzyme from PLP-deficient cells denatures faster. Cofactors often help stabilize enzyme structure.

Chapter 9

- For the amide substrate, the formation of the acyl-enzyme intermediate is slower than the hydrolysis of the acyl-enzyme intermediate, and so no burst is observed. A burst is observed for ester substrates; the formation of the acyl-enzyme intermediate is faster, leading to the observed burst.
- The histidine residue in the substrate can substitute to some extent for the missing histidine residue of the catalytic triad of the mutant enzyme.
- No. The catalytic triad works as a unit. After this unit has been made ineffective by the mutation of histidine to alanine, the further mutation of serine to alanine should have only a small effect.
- The substitution corresponds to one of the key differences between trypsin and chymotrypsin, and so trypsinlike specificity (cleavage after lysine and arginine) might be predicted. In fact, additional changes are required to effect this specificity change.
- Imidazole is apparently small enough to reach the active site of carbonic anhydrase. Buffers with large molecular components cannot do so, and the effects of the mutation are more evident.
- No. The odds of such a sequence being present are approximately 1 in $4^{10} = 1,048,576$. Because a typical viral genome has only 50,000 bp, the target sequence would be unlikely to be present.
- No, because the enzyme would destroy the host DNA before protective methylation could take place.
- No. The bacteria receiving the enzyme would have their own DNA destroyed because they would likely lack the appropriate protective methylase.
- EDTA will bind to Zn^{2+} and remove the ion, which is required for enzyme activity, from the enzyme.
- (a) The aldehyde reacts with the active-site serine. (b) A hemiacetal is formed.
- Trypsin
- The reaction is expected to be slower by a factor of 10 because the rate depends on the pK_a of the zinc-bound water. $k_{\text{cat}} = 60,000 \text{ s}^{-1}$.
- EDTA binds the magnesium necessary for the reaction.
- ATP hydrolysis is reversible within the active site. ATP hydrolysis takes place within the active site with the incorporation of ^{18}O , ATP is re-formed, and the ATP is released back into solution.
- If the aspartate is mutated, the protease is inactive and the virus will not be viable.
- Water substitutes for the hydroxyl group of serine 236 in mediating proton transfer from the attacking water and the γ -phosphoryl group.
- (a) Cysteine protease: The same as Figure 9.8, except that cysteine replaces serine in the active site and no aspartate is present. (b) Aspartyl protease:



(c) Metalloprotease:



Chapter 10

1. The enzyme catalyzes the first step in the synthesis of pyrimidines. It facilitates the condensation of carbamoyl phosphate and aspartate to form *N*-carbamoylaspartate and inorganic phosphate.

2. The protonated form of histidine probably stabilizes the negatively charged carbonyl oxygen atom of the scissile bond in the transition state. Deprotonation would lead to a loss of activity. Hence, the rate is expected to be half maximal at a pH of about 6.5 (the pK of an unperturbed histidine side chain in a protein) and to decrease as the pH is raised.

3. The inhibition of an allosteric enzyme by the end product of the pathway controlled by the enzyme. It prevents the production of too much end product and the consumption of substrates when product is not required.

4. High concentrations of ATP might signal two overlapping situations. The high levels of ATP might suggest that some *nucleotides* are available for nucleic acid synthesis, and consequently, CTP should be synthesized. The high levels of ATP indicate that *energy* is available for nucleic acid synthesis, and so CTP should be produced.

5. All of the enzyme would be in the R form all of the time. There would be no cooperativity. The kinetics would look like that of a Michaelis–Menten enzyme.

6. The enzyme would show simple Michaelis–Menten kinetics because it is essentially always in the R state.

7. CTP is formed by the addition of an amino group to UTP. Evidence indicates the UTP is also capable of inhibiting ATCase.

8. Homotropic effectors are the substrates of allosteric enzymes. Heterotropic effectors are the regulators of allosteric enzymes.

Homotropic effectors account for the sigmoidal nature of the velocity versus substrate concentration curve, whereas heterotropic effectors alter the midpoint of K_M of the curve. Ultimately, both types of effectors work by altering the T/R ratio.

9. The reconstitution shows that the complex quaternary structure and the resulting catalytic and regulatory properties are ultimately encoded in the primary structure of individual components.

10. If substrates had been used, the enzyme would catalyze the reaction. Intermediates would not accumulate on the enzyme. Consequently, any enzyme that crystallized would have been free of substrates or products.

11. (a) 100. The change in the $[R]/[T]$ ratio on binding one substrate molecule must be the same as the ratio of the substrate affinities of the two forms.

(b) 10. The binding of four substrate molecules changes the $[R]/[T]$ by a factor of $100^4 = 10^8$. The ratio in the absence of substrate is 10^{-7} . Hence, the ratio in the fully liganded molecule is $10^8 \times 10^{-7} = 10$.

12. The fraction of molecules in the R form is 10^{-5} , 0.004, 0.615, 0.998, and 1 when 0, 1, 2, 3, and 4 ligands, respectively, are bound.

13. The sequential model can account for negative cooperativity, whereas the concerted model cannot.

14. The binding of PALA switches ATCase from the T to the R state because PALA acts as a substrate analog. An enzyme

molecule containing bound PALA has fewer free catalytic sites than does an unoccupied enzyme molecule. However, the PALA-containing enzyme will be in the R state and, hence, have a higher affinity for the substrates. The dependence of the degree of activation on the concentration of PALA is a complex function of the allosteric constant L_0 and of the binding affinities of the R and T states for the analog and substrates.

15. The net outcome of the two reactions is the hydrolysis of ATP to ADP and P_i , which has a ΔG of -50 kJ mol^{-1} ($-12 \text{ kcal mol}^{-1}$) under cellular conditions.

16. Isozymes are homologous enzymes that catalyze the same reaction but have different kinetic or regulatory properties.

17. Although the same reaction may be required in a variety of different tissues, the biochemical properties of tissues will differ according to their biological function. Isozymes allow the fine-tuning of catalytic and regulatory properties to meet the specific needs of the tissue.

18. (a) 7; (b) 8; (c) 11; (d) 6; (e) 1; (f) 12; (g) 3; (h) 4; (i) 5; (j) 2; (k) 10; (l) 9.

19. When phosphorylation takes place at the expense of ATP, sufficient energy is expended to dramatically alter the structure and hence activity of a protein. Moreover, because ATP is the cellular energy currency, protein modification is linked to the energy status of the cell.

20. Covalent modification is reversible, whereas proteolytic cleavage is irreversible.

21. Activation is independent of zymogen concentration because the reaction is intramolecular.

22. Although quite rare, cases of enteropeptidase deficiency have been reported. The affected person has diarrhea and fails to thrive because digestion is inadequate. In particular, protein digestion is impaired.

23. Add blood from the second patient to a sample from the first. If the mixture clots, the second patient has a defect different from that of the first. This type of assay is called a complementation test.

24. Activated factor X remains bound to blood-platelet membranes, which accelerates its activation of prothrombin.

25. Antithrombin III is a very slowly hydrolyzed substrate of thrombin. Hence, its interaction with thrombin requires a fully formed active site on the enzyme.

26. Residues *a* and *d* are located in the interior of an α -helical coiled coil, near the axis of the superhelix. Hydrophobic interactions between these side chains contribute to the stability of the coiled coil.

27. Leucine would be a good choice. It is resistant to oxidation and has nearly the same volume and degree of hydrophobicity as methionine has.

28. Inappropriate clot formation could block arteries in the brain, causing a stroke, or the heart, causing a heart attack.

29. Tissue-type plasminogen activator, or TPA, is a serine protease that leads to the dissolution of blood clots. TPA activates plasminogen that is bound to a fibrin clot, converting it into active plasmin, which then hydrolyzes the fibrin of the clot.

30. A mature clot is stabilized by amide linkages between the side chains of lysine and glutamine that are absent in a soft clot. The linkages are formed by transglutaminase.

31. The simple sequential model predicts that the fraction of catalytic chains in the R state, f_R , is equal to the fraction containing bound substrate, Y . The concerted model, in contrast, predicts that f_R increases more rapidly than Y as the substrate concentration is increased. The change in f_R leads to the change in Y on addition of substrate, as predicted by the concerted model.

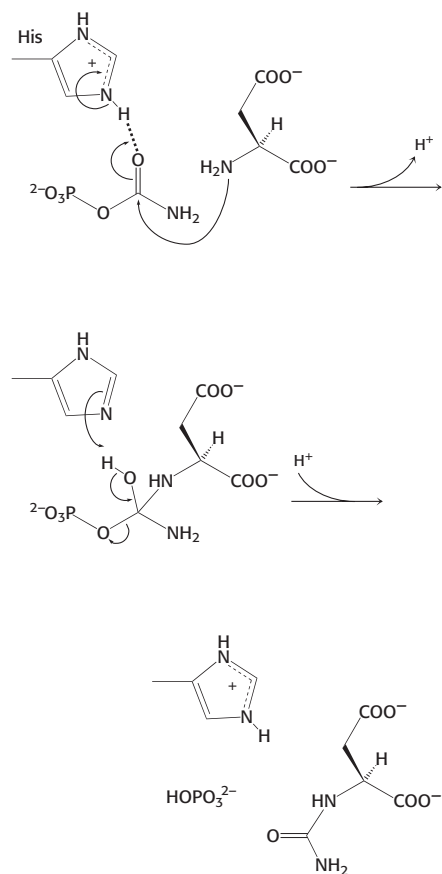
32. The binding of succinate to the functional catalytic sites of the native c_3 moiety changed the visible absorption spectrum of nitrotyrosine residues in the *other* c_3 moiety of the hybrid enzyme. Thus, the binding of substrate analog to the active sites of one trimer altered the structure of the other trimer.

33. According to the concerted model, an allosteric activator shifts the conformational equilibrium of all subunits toward the R state, whereas an allosteric inhibitor shifts it toward the T state. Thus, ATP (an allosteric activator) shifted the equilibrium to the R form, resulting in an absorption change similar to that obtained when substrate is bound. CTP had a different effect. Hence, this allosteric inhibitor shifted the equilibrium to the T form. Thus, the concerted model accounts for the ATP-induced and CTP-induced (heterotropic), as well as for the substrate-induced (homotropic), allosteric interactions of ATCase.

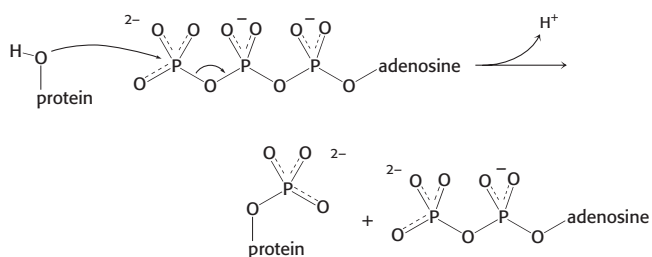
34. In the R state, ATCase expands and becomes less dense. This decrease in density results in a decrease in the sedimentation value (see the formula on p. 76).

35. The interaction between trypsin and the inhibitor is so stable that the transition state is rarely formed. Recall that maximal binding energy is released when an enzyme binds to the transition state. If the substrate-enzyme interaction is too stable, the transition state rarely forms.

36.



37.



Chapter 11

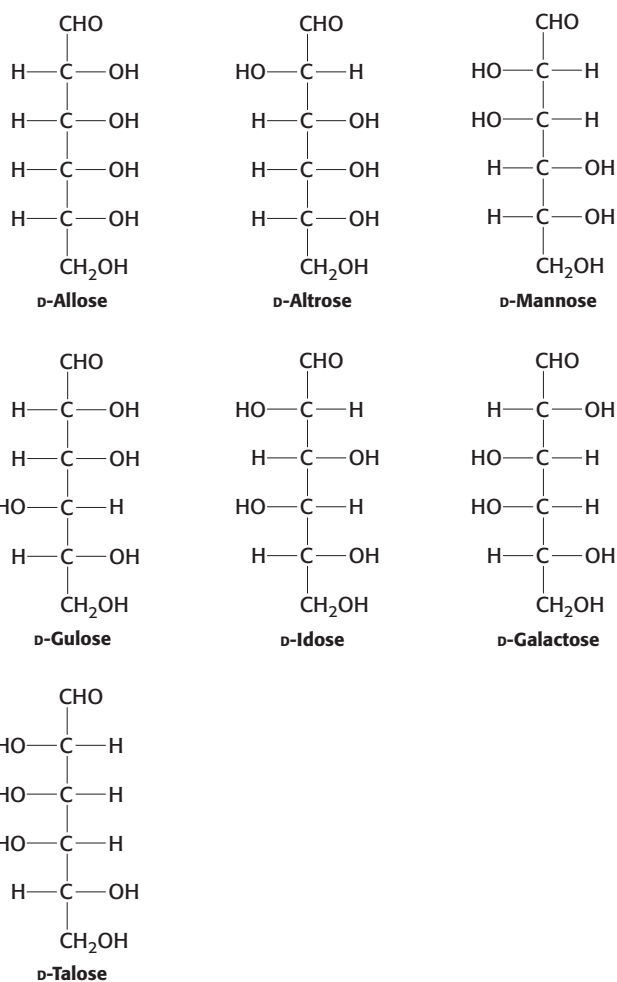
1. Carbohydrates were originally regarded as *hydrates of carbon* because the empirical formula of many of them is (CH₂O)_n.

2. Three amino acids can be linked by peptide bonds in only six different ways. However, three different monosaccharides can be linked in a plethora of ways. The monosaccharides can be linked in a linear or branched manner, with α or β linkages, with bonds between C-1 and C-3, between C-1 and C-4, between C-1 and C-6, and so forth. In fact, the three monosaccharides can form 12,288 different trisaccharides.

3. (a) aldose-ketose; (b) epimers; (c) aldose-ketose (d) anomers; (e) aldose-ketose; (f) epimers.

4. Erythrose: tetrose aldose; Ribose: pentose aldose; Glyceraldehyde: triose aldose; Dihydroxyacetone: triose ketose; Erythrulose: tetrose ketose; Ribulose: pentose ketose; Fructose: hexose ketose.

5.



6. The proportion of the α anomer is 0.36, and that of the β anomer is 0.64.

7. Glucose is reactive because of the presence of an aldehyde group in its open-chain form. The aldehyde group slowly condenses with amino groups to form aldimine products of a type called Schiff-base adducts.

8. A pyranoside reacts with two molecules of periodate; formate is one of the products. A furanoside reacts with only one molecule of periodate; formate is not formed.

9. From methanol

10 (a) β-D-Mannose; (b) β-D-galactose; (c) β-D-fructose; (d) β-D-glucosamine.

ANSWERS TO PROBLEMS

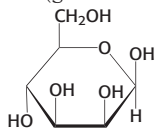
11. The trisaccharide itself should be a competitive inhibitor of cell adhesion if the trisaccharide unit of the glycoprotein is critical for the interaction.

12. Reducing ends would form 1,2,3,6-tetramethylglucose. The branch points would yield 2,3-dimethylglucose. The remainder of the molecule would yield 2,3,6-trimethylglucose.

13. (a) not a reducing sugar; no open-chain forms are possible.

(b) D-Galactose, D-glucose, D-fructose. (c) D-Galactose and sucrose (glucose + fructose).

14. The hemiketal linkage of the α anomer is broken to form the open form. Rotation about the C-1 and C-2 bonds allows the formation of the β anomer, and a mixture of isomers results.



β -D-Mannose

15. Heating converts the very sweet pyranose form into the more-stable but less-sweet

furanose form. Consequently, the sweetness of the preparation is difficult to accurately control, which also accounts for why honey loses sweetness with time. See Figure 11.5 for structures.

16. (a) Each glycogen molecule has one reducing end, whereas the number of nonreducing ends is determined by the number of branches, or α -1,6 linkages. (b) Because the number of nonreducing ends greatly exceeds the number of reducing ends in a collection of glycogen molecules, all of the degradation and synthesis of glycogen takes place at the nonreducing ends, thus maximizing the rate of degradation and synthesis.

17. No, sucrose is not a reducing sugar. The anomeric carbon atom acts as the reducing agent in both glucose and fructose but, in sucrose, the anomeric carbon atoms of fructose and glucose are joined by a covalent bond and are thus not available to react.

18. Glycogen is polymer of glucose linked by α -1,4-glycosidic bonds with branches formed approximately every 10 glucose units by α -1,6-glycosidic bonds. Starch consists of two polymers of glucose. Amylose is a straight-chain polymer formed by α -1,4-glycosidic bonds. Amylopectin is similar to glycogen but amylopectin has fewer branches, one branch per 30 or so glucose units.

19. Cellulose is a linear polymer of glucose joined by β -1,4 linkages. Glycogen is a branched polymer with the main chain being formed by α -1,4-glycosidic bonds. The β -1,4 linkages allow the formation of a linear polymer ideal for structural roles. The α -1,4 linkages of glycogen form a helical structure, which allows the storage of many glucose moieties in a small space.

20. Simple glycoproteins are often secreted proteins and thus play a variety of roles. For example, the hormone EPO is a glycoprotein. Usually, the protein component constitutes the bulk of the glycoprotein by mass. In contrast, proteoglycans and mucoproteins are predominantly carbohydrates. Proteoglycans have glycosaminoglycans attached, and play structural roles as in cartilage and the extracellular matrix. Mucoproteins often serve as lubricants and have multiple carbohydrates attached through an *N*-acetylgalactosamine moiety.

21. The attachment of the carbohydrate allows the EPO to stay in circulation longer and thus to function for longer periods of time than would a carbohydrate-free EPO.

22. The glycosaminoglycan, because it is heavily charged, binds many water molecules. When cartilage is stressed, such as when your heel hits the ground, the water is released, thus cushioning the impact. When you lift your heel, the water rebinds.

23. The lectin that binds the mannose 6-phosphate might be defective and not recognize a correctly addressed protein.

24. Different molecular forms of a glycoprotein that differ in the amount of carbohydrate attached or the location of attachment or both.

25. The total collection of carbohydrates synthesized by a cell at particular times and under particular environmental conditions.

26. The genome comprises all of the genes present in an organism. The proteome includes all of the possible protein products and modified proteins that a cell expresses under any particular set of circumstances. The glycome consists of all of the carbohydrates synthesized by the cell under any particular set of circumstances. Because the genome is static, but any given protein can be variously expressed and modified, the proteome is more complex than the genome. The glycome, which includes not only glycoforms of proteins, but also many possible carbohydrate structures, must be even more complex.

27. It suggests that carbohydrates are on the cell surfaces of all organisms for the purpose of recognition by other organisms or the environment.

28. A glycoprotein is a protein that is decorated with carbohydrates. A lectin is a protein that specifically recognizes carbohydrates. A lectin can also be a glycoprotein.

29. Each site either is or is not glycosylated, and so there are $2^6 = 64$ possible proteins.

30. As discussed in Chapter 9, many enzymes display stereochemical specificity. Clearly, the enzymes of sucrose synthesis are able to distinguish between the isomers of the substrates and link only the correct pair.

31. If the carbohydrate specificity of the lectin is known, an affinity column with the appropriate carbohydrate attached could be prepared. The protein preparation containing the lectin of interest could be passed over the column. The use of this method was indeed how the glucose-binding lectin concanavalin A was purified.

32. (a) Aggrecan is heavily decorated with glycosaminoglycans. If glycosaminoglycans are released into the media, aggrecan must be undergoing degradation.

(b) Another enzyme might be present that cleaves glycosaminoglycans from aggrecan without degrading aggrecan. Other experiments not shown established that glycosaminoglycan release is an accurate measure of aggrecan destruction.

(c) The control provides a baseline of “background” degradation inherent in the assay.

(d) Aggrecan degradation is greatly enhanced.

(e) Aggrecan degradation is reduced to the background system.

(f) It is an *in vitro* system in which not all the factors contributing to cartilage stabilization *in vivo* are present.

Chapter 12

1. 2.86×10^6 molecules, because each leaflet of the bilayer contains 1.43×10^6 molecules.

2. Essentially an “inside-out” membrane. The hydrophilic groups would come together on the interior of the structure, away from the solvent, whereas the hydrocarbon chains would interact with the solvent.

3. 2×10^{-7} cm, 6×10^{-6} cm, and 2×10^{-4} cm.

4. The radius of this molecule is 3.1×10^{-7} cm, and its diffusion coefficient is 7.4×10^{-9} cm² s⁻¹. The average distances traversed are 1.7×10^{-7} cm in 1 μ s, 5.4×10^{-6} cm in 1 ms, and 1.7×10^{-4} cm in 1 s.

5. The membrane underwent a phase transition from a highly fluid to a nearly frozen state when the temperature was lowered. A carrier can shuttle ions across a membrane only when the bilayer is highly fluid. A channel, in contrast, allows ions to traverse its pore even when the bilayer is quite rigid.

6. The presence of a *cis* double bond introduces a kink in the fatty acid chain that prevents tight packing and reduces the number of atoms in van der Waals contact. The kink lowers the melting point compared with that of a saturated fatty acid. *Trans* fatty acids do not have the kink, and so their melting temperatures are higher, more similar to those of saturated fatty acids.

Because trans fatty acids have no structural effect, they are rarely observed.

7. Palmitic acid is shorter than stearic acid. Thus, when the chains pack together, there is less opportunity for van der Waals interaction and the melting point is thus lower than that of the longer stearic acid.

8. Hibernators selectively feed on plants that have a high proportion of polyunsaturated fatty acids with lower melting temperature.

9. The initial decrease in fluorescence with the first addition of sodium dithionite results from the quenching of NBD-PS molecules in the outer leaflet of the bilayer. Sodium dithionite does not traverse the membrane under these experimental conditions; hence, it does not quench the labeled phospholipids in the inner leaflet. A second addition of sodium dithionite has no effect, as the NBD-PS molecules in the outer leaflet remain quenched. However, after a 6.5 hour incubation, about half the NBD-PS has flipped over to the outer leaflet of the bilayer, resulting in the 50% decrease in fluorescence when sodium dithionite is added.

10. The addition of the carbohydrate introduces a significant energy barrier to the flip-flop because a hydrophilic carbohydrate moiety would need to be moved through a hydrophobic environment. This energetic barrier enhances membrane asymmetry.

11. The C_{16} alkyl chain is attached by an ether linkage. The C-2 carbon atom of glycerol has only an acetyl group attached by an ester linkage instead of a fatty acid, as is the case with most phospholipids.

12. In a hydrophobic environment, the formation of intrachain hydrogen bonds stabilizes the amide hydrogen atoms and carbonyl oxygen atoms of the polypeptide chain, and so an α helix forms. In an aqueous environment, these groups are stabilized by interaction with water, and so there is no energetic reason to form an α helix. Thus, the α helix would be more likely to form in a hydrophobic environment.

13. The protein may contain an α helix that passes through the hydrophobic core of the protein. This helix is likely to feature a stretch of hydrophobic amino acids similar to those observed in transmembrane helices.

14. The shift to the lower temperature would decrease fluidity by enhancing the packing of the hydrophobic chains by van der Waals interactions. To prevent this packing, new phospholipids having shorter chains and a greater number of cis double bonds would be synthesized. The shorter chains would reduce the number of van der Waals interactions, and the cis double bonds, which cause the kink in structure, would prevent the packing of the fatty acid tails of the phospholipids.

15. Each of the 21 v-SNARE proteins could interact with each of 7 t-SNARE partners. Multiplication gives the total number of different interacting pairs: $7 \times 21 = 147$ different v-SNARE-t-SNARE pairs.

16. (a) The graph shows that, as temperature increases, the phospholipid bilayer becomes more fluid. T_m is the temperature of the transition from the predominantly less fluid state to the predominantly more fluid state. Cholesterol broadens the transition from the less-fluid to the more-fluid state. In essence, cholesterol makes membrane fluidity less sensitive to temperature changes.

(b) This effect is important because the presence of cholesterol tends to stabilize membrane fluidity by preventing sharp transitions. Because protein function depends on the proper fluidity of the membrane, cholesterol maintains the proper environment for membrane-protein function.

17. The protein plotted in part c is a transmembrane protein from *C. elegans*. It spans the membrane with four α helices that are prominently displayed as hydrophobic peaks in the hydrophathy

plot. Interestingly, the protein plotted in part a also is a membrane protein, a porin. This protein is made primarily of β strands, which lack the prominent hydrophobic window of membrane helices.

This example shows that, although hydrophathy plots are useful, they are not infallible.

18. To purify any protein, the protein must first be solubilized. For a membrane protein, solubilization usually requires a detergent—hydrophobic molecules that bind to the protein and thus replace the lipid environment of the membrane. If the detergent is removed, the protein aggregates and precipitates from solution. Often, the steps in purification, such as ion-exchange chromatography, are difficult to perform in the presence of sufficient detergent to solubilize the protein. Crystals of appropriate protein-detergent complexes must be generated.

Chapter 13

1. In simple diffusion, the substance in question can diffuse down its concentration gradient through the membrane. In facilitated diffusion, the substance is not lipophilic and cannot directly diffuse through the membrane. A channel or carrier is required to facilitate movement down the gradient.

2. The two forms are (1) ATP hydrolysis and (2) the movement of one molecule down its concentration gradient coupled with the movement of another molecule up its concentration gradient.

3. The three types of carriers are symporters, antiporters, and uniporters. Symporters and antiporters can mediate secondary active transport.

4. The free-energy cost is 32 kJ mol^{-1} ($7.6 \text{ kcal mol}^{-1}$). The chemical work performed is 20.4 kJ mol^{-1} ($4.9 \text{ kcal mol}^{-1}$), and the electrical work performed is 11.5 kJ mol^{-1} ($2.8 \text{ kcal mol}^{-1}$).

5. For chloride, $z = -1$; for calcium $z = +2$. At the concentrations given, the equilibrium potential for chloride is -97 mV and the equilibrium potential for calcium is $+122 \text{ mV}$.

6. The concentration of glucose inside the cell is 66 times as great as that outside the cell [$(c_2/c_1) = 66$] when the free-energy input is 10.8 kJ mol^{-1} ($2.6 \text{ kcal mol}^{-1}$).

7. By analogy with the Ca^{2+} ATPase, with three Na^+ ions binding from inside the cell to the E_1 conformation and with two K^+ ions binding from outside the cell to the E_2 conformation, a plausible mechanism is as follows:

(i) A catalytic cycle could begin with the enzyme in its unphosphorylated state (E_1) with three sodium ions bound.

(ii) The E_1 conformation binds ATP. A conformational change traps sodium ions inside the enzyme.

(iii) The phosphoryl group is transferred from ATP to an aspartyl residue.

(iv) On ADP release, the enzyme changes its overall conformation, including the membrane domain. This new conformation (E_2) releases the sodium ions to the side of the membrane opposite that at which they entered and binds two potassium ions from the side where sodium ions are released.

(v) The phosphorylaspartate residue is hydrolyzed to release inorganic phosphate. With the release of phosphate, the interactions stabilizing E_2 are lost, and the enzyme everts to the E_1 conformation. Potassium ions are released to the cytoplasmic side of the membrane. The binding of three sodium ions from the cytoplasmic side of the membrane completes the cycle.

8. Establish a lactose gradient across vesicle membranes that contain properly oriented lactose permease. Initially, the pH should be the same on both sides of the membrane and the lactose concentration should be higher on the “exit” side of lactose

ANSWERS TO PROBLEMS

permease. As the lactose flows “in reverse” through the permease, down its concentration gradient, it can be tested whether or not a pH gradient becomes established as the lactose gradient is dissipated.

9. Ligand-gated channels open in response to the binding of a molecule by the channel, whereas voltage-gated channels open in response to changes in the membrane potential.

10. An ion channel must transport ions in either direction at the same rate. The net flow of ions is determined only by the composition of the solutions on either side of the membrane.

11. Uniporters act as enzymes do; their transport cycles include large conformational changes, and only a few molecules interact with the protein per transport cycle. In contrast, channels, after having opened, provide a pore in the membrane through which many ions may pass. As such, channels mediate transport at a much higher rate than do uniporters.

12. FCCP effectively creates a pore in the bacterial membrane through which protons can pass rapidly. Protons that are pumped out of the bacteria will pass through this pore preferentially (the “path of least resistance”), rather than participate in H^+ /lactose symport.

13. Cardiac muscle must contract in a highly coordinated manner in order to pump blood effectively. Gap junctions mediate the orderly cell-to-cell propagation of the action potential through the heart during each beat.

14. The positively charged guanidinium group resembles Na^+ and binds to negatively charged carboxylate groups in the mouth of the channel.

15. SERCA, a P-type ATPase, uses a mechanism by which a covalent phosphorylated intermediate (at an aspartate residue) is formed. At steady state, a subset of the SERCA molecules are trapped in the E_2 -P state and, as a result, radiolabeled.

The MDR protein is an ABC transporter and does not operate through a phosphorylated intermediate. Hence, a radiolabeled band would not be observed for MDR.

16. The blockage of ion channels inhibits action potentials, leading to loss of nervous function. Like tetrodotoxin, these toxin molecules are useful for isolating and specifically inhibiting particular ion channels.

17. After repolarization, the ball domains of the ion channels engage the channel pore, rendering them inactive for a short period of time. During this time, the channels cannot be reopened until the ball domains disengage and the channel returns to the “closed” state.

18. Because sodium ions are charged and because sodium channels carry only sodium ions (but not anions), the accumulation of excess positive charge on one side of the membrane dominates the chemical gradients.

19. A mutation that impairs the ability of the sodium channel to inactivate would prolong the duration of the depolarizing sodium current, thus lengthening the cardiac action potential.

20. No. Channels will likely open or close in response to an external stimulus, but the unit conductance of the open channel will be influenced very little.

21. The ratio of closed to open forms of the channel is 10^5 , 5000, 250, 12.5, and 0.625 when zero, one, two, three, and four ligands, respectively, are bound. Hence, the fraction of open channels is 1.0×10^{-5} , 2.0×10^{-4} , 4.0×10^{-3} , 7.4×10^{-2} , and 0.62.

22. These organic phosphates inhibit acetylcholinesterase by reacting with the active-site serine residue to form a stable phosphorylated derivative. They cause respiratory paralysis by blocking synaptic transmission at cholinergic synapses.

23. (a) The binding of the first acetylcholine molecule increases the open-to-closed ratio by a factor of 240, and the binding of

the second increases it by a factor of 11,700. (b) The free-energy contributions are 14 kJ mol^{-1} ($3.3 \text{ kcal mol}^{-1}$) and 23 kJ mol^{-1} ($5.6 \text{ kcal mol}^{-1}$), respectively. (c) No; the MWC model predicts that the binding of each ligand will have the same effect on the open-to-closed ratio.

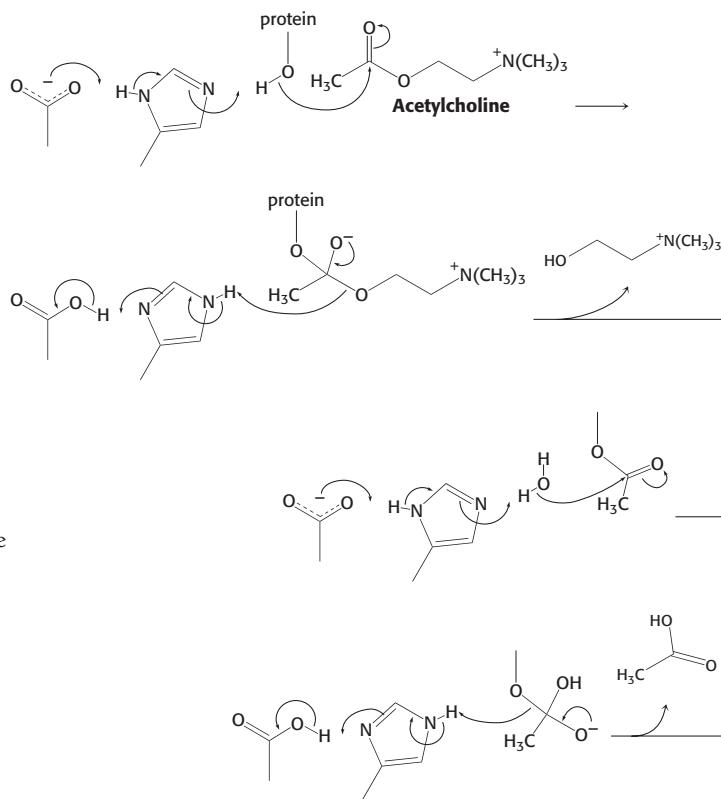
24. Batrachotoxin blocks the transition from the open to the closed state.

25. (a) Chloride ions flow into the cell. (b) Chloride flux is inhibitory because it hyperpolarizes the membrane. (c) The channel consists of five subunits.

26. After the addition of ATP and calcium, SERCA will pump Ca^{2+} ions into the vesicle. However, the accumulation of Ca^{2+} ions inside the vesicle will rapidly lead to the formation of an electrical gradient that cannot be overcome by ATP hydrolysis. The addition of calcimycin will allow the pumped Ca^{2+} ions to flow back out of the vesicle, dissipating the charge buildup, and enabling the pump to operate continuously.

27. The catalytic prowess of acetylcholinesterase ensures that the duration of the nerve stimulus will be short.

28. See reaction below.



29. (a) Only ASIC1a is inhibited by the toxin. (b) Yes; when the toxin was removed, the activity of the acid-sensing channel began to be restored. (c) 0.9 nM.

30. This mutation is one of a class of mutations that result in slow-channel syndrome (SCS). The results suggest a defect in channel closing; so the channel remains open for prolonged periods. Alternatively, the channel may have a higher affinity for acetylcholine than does the control channel.

31. The mutation reduces the affinity of acetylcholine for the receptor. The recordings would show the channel opening only infrequently.

32. Glucose displays a transport curve that suggests the participation of a carrier because the initial rate is high but then levels off

at higher concentrations, consistent with saturation of the carrier, which is reminiscent of Michaelis–Menten enzymes (Section 8.4). Indole shows no such saturation phenomenon, which implies that the molecule is lipophilic and simply diffuses across the membrane. Ouabain is a specific inhibitor the $\text{Na}^+ - \text{K}^+$ pump. If ouabain were to inhibit glucose transport, then a Na^+ -glucose cotransporter would be assisting in transport.

Chapter 14

- The negatively charged glutamate residues mimic the negatively charged phosphoserine or phosphothreonine residues and stabilize the active conformation of the enzyme.
- No. Phosphoserine and phosphothreonine are considerably shorter than phosphotyrosine.
- The GTPase activity terminates the signal. Without such activity, after a pathway has been activated, it remains activated and is unresponsive to changes in the initial signal. If the GTPase activity were more efficient, the lifetime of the GTP-bound G_{α} subunit would be too short to achieve downstream signaling.
- Two identical receptor molecules must recognize different aspects of the same signal molecule.
- Growth-factor receptors can be activated by dimerization. If an antibody causes a receptor to dimerize, the signal-transduction pathway in a cell will be activated.
- The mutated α subunit will always be in the GTP form and, hence, in the active form, which would stimulate its signaling pathway.
- A G protein is a component of the signal-transduction pathway. GTP γ S is not hydrolyzed by the G_{α} subunit, leading to prolonged activation.
- Calcium ions diffuse slowly because they bind to many protein surfaces within a cell, impeding their free motion. Cyclic AMP does not bind as frequently, and so it diffuses more rapidly.
- Fura-2 is a highly negatively charged molecule, with five carboxylate groups. Its charge prevents it from effectively crossing the hydrophobic region of the plasma membrane.
- $G_{\alpha s}$ stimulates adenylate cyclase, leading to the generation of cAMP. This signal then leads to glucose mobilization (see Chapter 21). If cAMP phosphodiesterase were inhibited, then cAMP levels would remain high even after the termination of the epinephrine signal, and glucose mobilization would continue.
- If the two kinase domains are forced to be within close proximity of each other, the activation loop of one kinase, in its inactivating conformation, can be displaced by the activation loop of the neighboring kinase, which acts as a substrate for phosphorylation.
- The full network of pathways initiated by insulin includes a large number of proteins and is substantially more elaborate than indicated in Figure 14.25. Furthermore, many additional proteins take part in the termination of insulin signaling. A defect in any of the proteins in the insulin signaling pathways or in the subsequent termination of the insulin response could potentially cause problems. Therefore, it is not surprising that many different gene defects can cause type 2 diabetes.
- The binding of growth hormone causes its monomeric receptor to dimerize. The dimeric receptor can then activate a separate tyrosine kinase to which the receptor binds. The signaling pathway can then continue in similar fashion to the pathways that are activated by the insulin receptor or other mammalian EGF receptors.
- The truncated receptor will dimerize with the full-length monomers on EGF-binding, but cross-phosphorylation cannot take place, because the truncated receptor possesses neither the substrate for the neighboring kinase domain nor its own kinase domain to

phosphorylate the C-terminal tail of the other monomer. Hence, these mutant receptors will block normal EGF signaling.

- Insulin would elicit the response that is normally caused by EGF. Insulin binding will likely stimulate dimerization and phosphorylation of the chimeric receptor and thereby signal the downstream events that are normally triggered by EGF binding. Exposure of these cells to EGF would have no effect.
- 10^5
- The formation of diacylglycerol implies the participation of phospholipase C. A simple pathway would entail receptor activation by cross-phosphorylation, followed by the binding of phospholipase C γ (through its SH2 domains). The participation of phospholipase C indicates that IP₃ would be formed and, hence, calcium concentrations would increase.
- Other potential drug targets within the EGF signaling cascade include, but are not limited to, the kinase active sites of the EGF receptor, Raf, MEK, or ERK.
- In the reaction catalyzed by adenylate cyclase, the 3'-OH group nucleophilically attacks the α -phosphorus atom attached to the 5'-OH group, leading to displacement of pyrophosphate. The reaction catalyzed by DNA polymerase is similar except that the 3'-OH group is on a different nucleotide.
- ATP-competitive inhibitors are likely to act on multiple kinases because every kinase domain contains an ATP-binding site. Hence, these drugs may not be selective for the desired kinase target.
- (a) $X \approx 10^{-7}$ M; $Y \approx 5 \times 10^{-6}$ M; $Z \approx 10^{-3}$ M. (b) Because much less X is required to fill half of the sites, X displays the highest affinity. (c) The binding affinity almost perfectly matches the ability to stimulate adenylate cyclase, suggesting that the hormone–receptor complex leads to the stimulation of adenylate cyclase. (d) Try performing the experiment in the presence of antibodies to $G_{\alpha s}$.
- (a) The total binding does not distinguish binding to a specific receptor from binding to different receptors or from nonspecific binding to the membrane. (b) The rationale is that the receptor will have a high affinity for the ligand. Thus, in the presence of excess nonradioactive ligand, the receptor will bind to nonradioactive ligand. Therefore, any binding of the radioactive ligand must be nonspecific. (c) The plateau suggests that the number of receptor-binding sites in the cell membrane is limited.
- Number of receptors per cell =

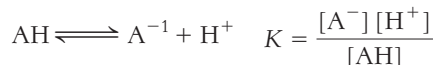
$$\frac{10^4 \text{ cpm}}{\text{mg of membrane protein}} \times \frac{\text{mg of membrane protein}}{10^{10} \text{ cells}} \times \frac{\text{mmol}}{10^{12} \text{ cpm}} \times \frac{6.023 \times 10^{20} \text{ molecules}}{\text{mmol}} = 600$$

Chapter 15

- The highly integrated biochemical reactions that take place inside the cell.
- Anabolism is the set of biochemical reactions that use energy to build new molecules and ultimately new cells. Catabolism is the set of biochemical reactions that extract energy from fuel sources or breakdown biomolecules.
- Cellular movements and the performance of mechanical work; active transport; biosynthetic reactions.
1. f; 2. h; 3. i; 4. a; 5. g; 6. b; 7. c; 8. e; 9. j; 10. d.
- Charge repulsion, resonance stabilization, and stabilization by hydration.
- Trick question. The answer is not known. Adenine appears to form more readily under prebiotic conditions; so ATP may have predominated initially.

ANSWERS TO PROBLEMS

7. Having only one nucleotide represent the available energy allows the cell to better monitor its energy status.
8. Increasing the concentration of ATP or decreasing the concentration cellular ADP or P_i (by rapid removal by other reactions, for instance) would make the reaction more exergonic. Likewise, altering the Mg^{2+} concentration could raise or lower the ΔG of the reaction.
9. The free-energy changes of the individual steps in a pathway are summed to determine the overall free-energy change of the entire pathway. Consequently, a reaction with a positive free-energy value can be powered to take place if coupled to a sufficiently exergonic reaction.
10. Reactions in parts *a* and *c*, to the left; reactions in parts *b* and *d*, to the right.
11. None whatsoever
12. (a) $\Delta G^{\circ'} = 31.4 \text{ kJ mol}^{-1}$ (7.5 kcal mol⁻¹) and $K'_{\text{eq}} = 3.06 \times 10^{-6}$; (b) 3.28×10^4 .
13. $\Delta G^{\circ'} = 7.1 \text{ kJ mol}^{-1}$ (1.7 kcal mol⁻¹). The equilibrium ratio is 17.8.
14. (a) Acetate + CoA + H^+ goes to acetyl CoA + H_2O , $\Delta G^{\circ'} = -31.4 \text{ kJ mol}^{-1}$ (-7.5 kcal mol⁻¹). ATP hydrolysis to AMP and P_i , $\Delta G^{\circ'} = -45.6 \text{ kJ mol}^{-1}$ (-10.9 kcal mol⁻¹). Overall reaction, $\Delta G^{\circ'} = -14.2 \text{ kJ mol}^{-1}$ (-3.4 kcal mol⁻¹).
(b) With pyrophosphate hydrolysis, $\Delta G^{\circ'} = -33.4 \text{ kJ mol}^{-1}$ (-7.98 kcal mol⁻¹). Pyrophosphate hydrolysis makes the overall reaction even more exergonic.
15. (a) For an acid AH,



- The pK is defined as $pK = -\log_{10} K$. $\Delta G^{\circ'}$ is the standard free-energy change at pH 7. Thus, $\Delta G^{\circ'} = -RT \ln K = -2.303 RT \log_{10} K = +2.303 RT pK$.
- (b) $\Delta G^{\circ'} = 27.32 \text{ kJ mol}^{-1}$ (6.53 kcal mol⁻¹).
16. Arginine phosphate in invertebrate muscle, like creatine phosphate in vertebrate muscle, serves as a reservoir of high-potential phosphoryl groups. Arginine phosphate maintains a high level of ATP in muscular exertion.
17. An ADP unit
18. (a) The rationale behind creatine supplementation is that it would be converted into creatine phosphate and thus serve as a rapid means of replenishing ATP after muscle contraction. (b) If creatine supplementation is beneficial, it would affect activities that depend on short bursts of activity; any sustained activity would require ATP generation by fuel metabolism, which, as Figure 15.7 shows, requires more time.
19. Under standard conditions, $\Delta G^{\circ'} = -RT \ln [\text{products}]/[\text{reactants}]$. Substituting 23.8 kJ mol^{-1} (5.7 kcal mol⁻¹) for $\Delta G^{\circ'}$ and solving for $[\text{products}]/[\text{reactants}]$ yields 7×10^{-5} . In other words, the forward reaction does not take place to a significant extent. Under intracellular conditions, ΔG is -1.3 kJ mol^{-1} (-0.3 kcal mol⁻¹). Using the equation $\Delta G = \Delta G^{\circ'} + RT \ln [\text{products}]/[\text{reactants}]$ and solving for $[\text{products}]/[\text{reactants}]$ gives a ratio of 3.7×10^{-5} . Thus, a reaction that is endergonic under standard conditions can be converted into an exergonic reaction by maintaining the $[\text{products}]/[\text{reactants}]$ ratio below the equilibrium value. This conversion is usually attained by using the products in another coupled reaction as soon as they are formed.
20. Under standard conditions,

$$K'_{\text{eq}} = \frac{[B]_{\text{eq}}}{[A]_{\text{eq}}} \times \frac{[ADP]_{\text{eq}}[P_i]_{\text{eq}}}{[ATP]_{\text{eq}}} = 10^{3.3/1.36} = 2.67 \times 10^2$$

At equilibrium, the ratio of [B] to [A] is given by

$$\frac{[B]_{\text{eq}}}{[A]_{\text{eq}}} = K'_{\text{eq}} \frac{[ATP]_{\text{eq}}}{[ADP]_{\text{eq}}[P_i]_{\text{eq}}}$$

The ATP-generating system of cells maintains the $[ATP]/[ADP][P_i]$ ratio at a high level, typically about 500 M^{-1} . For this ratio,

$$\frac{[B]_{\text{eq}}}{[A]_{\text{eq}}} = 2.67 \times 10^2 \times 500 = 1.34 \times 10^5$$

This equilibrium ratio is strikingly different from the value of 1.15×10^{-3} for the reaction $A \rightarrow B$ in the absence of ATP hydrolysis. In other words, coupling the hydrolysis of ATP with the conversion of A into B has changed the equilibrium ratio of B to A by a factor of about 10^8 .

21. Liver: $-45.2 \text{ kJ mol}^{-1}$ (-10.8 kcal mol⁻¹); muscle: $-48.1 \text{ kJ mol}^{-1}$ (-11.5 kcal mol⁻¹); brain: $-48.5 \text{ kJ mol}^{-1}$ (-11.6 kcal mol⁻¹). The ΔG is most negative in brain cells.
22. (a) Ethanol; (b) lactate; (c) succinate; (d) isocitrate; (e) malate; (f) 2-phosphoglycerate.
23. Recall that $\Delta G = \Delta G^{\circ'} + RT \ln [\text{products}]/[\text{reactants}]$. Altering the ratio of products to reactants will cause ΔG to vary. In glycolysis, the concentrations of the components of the pathway result in a value of ΔG greater than that of $\Delta G^{\circ'}$.
24. Unless the ingested food is converted into molecules capable of being absorbed by the intestine, no energy can ever be extracted by the body.
25. NADH and $FADH_2$ are electron carriers for catabolism; NADPH is the carrier for anabolism.
26. The electrons of the C–O bond cannot form resonance structures with the C–S bond that are as stable as those that they can form with the C–O bond. Thus, the thioester is not stabilized by resonance to the same degree as an oxygen ester is stabilized.
27. Oxidation–reduction reactions; ligation reactions; isomerization reactions; group-transfer reactions; hydrolytic reactions; the addition of functional groups to double bonds to form single bonds or the removal of functional groups to form double bonds.
28. Controlling the amount of enzymes; controlling enzyme activity; controlling the availability of substrates.
29. Although the reaction is thermodynamically favorable, the reactants are kinetically stable because of the large activation energy. Enzymes lower the activation energy so that reactions take place on time scales required by the cell.
30. The activated form of sulfate in most organisms is 3'-phosphoadenosine-5'-phosphosulfate.
31. (a) As the Mg^{2+} concentration falls, the ΔG of hydrolysis rises. Note that pMg is a logarithmic plot, and so each number on the *x*-axis represents a 10-fold change in $[Mg^{2+}]$.
(b) Mg^{2+} would bind to the phosphates of ATP and help to mitigate charge repulsion. As the $[Mg^{2+}]$ falls, charge stabilization of ATP would be less, leading to greater charge repulsion and an increase in ΔG on hydrolysis.

Chapter 16

1. Two molecules of ATP are produced per molecule of glyceraldehyde 3-phosphate and, because two molecules of GAP are produced per molecule of glucose, the total ATP yield is four. However, two molecules of ATP are required to convert glucose into fructose 1,6-bisphosphate. Thus, the net yield is only two molecules of ATP.

2. In both cases, the electron donor is glyceraldehyde 3-phosphate. In lactic acid fermentation, the electron acceptor is pyruvate, converting it into lactate. In alcoholic fermentation, acetaldehyde is the electron acceptor, forming ethanol.

3. (a) 3 ATP; (b) 2 ATP; (c) 2 ATP; (d) 2 ATP; (e) 4 ATP.

4. Glucokinase enables the liver to remove glucose from the blood when hexokinase is saturated, ensuring that glucose is captured for later use.

5. Glycolysis is a component of alcoholic fermentation, the pathway that produces alcohol for beer and wine. The belief was that understanding the biochemical basis of alcohol production might lead to a more-efficient means of producing beer.

6. The conversion of glyceraldehyde 3-phosphate into 1,3-bisphosphoglycerate would be impaired. Glycolysis would be less effective.

7. Glucose 6-phosphate must have other fates. Indeed, it can be converted into glycogen (Chapter 21) or be processed to yield reducing power for biosynthesis (Chapter 20).

8. The energy needs of a muscle cell vary widely, from rest to intense exercise. Consequently, the regulation of phosphofructokinase by energy charge is vital. In other tissues, such as the liver, ATP concentration is less likely to fluctuate and will not be a key regulator of phosphofructokinase.

9. The ΔG° for the reverse of glycolysis is $+96 \text{ kJ mol}^{-1}$ ($+23 \text{ kcal mol}^{-1}$), far too endergonic to take place.

10. The conversion of glucose into glucose 6-phosphate by hexokinase; the conversion of fructose 6-phosphate into fructose 1,6-bisphosphate by phosphofructokinase; the formation of pyruvate from phosphoenolpyruvate by pyruvate kinase.

11. Lactic acid is a strong acid. If it remained in the cell, the pH of the cell would fall, which could lead to the denaturation of muscle protein and result in muscle damage.

12. GLUT2 transports glucose only when the blood concentration of glucose is high, which is precisely the condition in which the β cells of the pancreas secrete insulin.

13. Fructose + ATP \longrightarrow fructose 1-phosphate + ADP:
Fructokinase

Fructose 1-phosphate \longrightarrow dihydroxyacetone phosphate +
glyceraldehyde: Fructose 1-phosphate aldolase

Glyceraldehyde + ATP \longrightarrow glyceraldehyde 3-phosphate +
ADP: Triose kinase

The primary controlling step of glycolysis catalyzed by phosphofructokinase is bypassed by the preceding reactions. Glycolysis will proceed in an unregulated fashion.

14. Without triose isomerase, only one of the two three-carbon molecules generated by aldolase could be used to generate ATP. Only two molecules of ATP would result from the metabolism of each glucose. But two molecules of ATP would still be required to form fructose 1,6-bisphosphate, the substrate for aldolase. The net yield of ATP would be zero, a yield incompatible with life.

15. Glucose is reactive because its open-chain form contains an aldehyde group.

16. (a) The label is in the methyl carbon atom of pyruvate.

(b) 5 mCi mM^{-1} . The specific activity is halved because the number of moles of product (pyruvate) is twice that of the labeled substrate (glucose).

17. (a) $\text{Glucose} + 2 \text{ P}_i + 2 \text{ ADP} \longrightarrow 2 \text{ lactate} + 2 \text{ ATP}$.

(b) $\Delta G = -114 \text{ kJ mol}^{-1}$ ($-27.2 \text{ kcal mol}^{-1}$).

18. 3.06×10^{-5}

19. The equilibrium concentrations of fructose 1,6-bisphosphate, dihydroxyacetone phosphate, and glyceraldehyde 3-phosphate

are $7.8 \times 10^{-4} \text{ M}$, $2.2 \times 10^{-4} \text{ M}$, and $2.2 \times 10^{-4} \text{ M}$, respectively.

20. All three carbon atoms of 2,3-BPG are ^{14}C labeled. The phosphorus atom attached to the C-2 hydroxyl group is ^{32}P labeled.

21. Hexokinase has a low ATPase activity in the absence of a sugar because it is in a catalytically inactive conformation. The addition of xylose closes the cleft between the two lobes of the enzyme. However, xylose lacks a hydroxymethyl group, and so it cannot be phosphorylated. Instead, a water molecule at the site normally occupied by the C-6 hydroxymethyl group acts as the acceptor of the phosphoryl group from ATP.

22. (a) The fructose 1-phosphate pathway forms glyceraldehyde 3-phosphate.

(b) Phosphofructokinase, a key control enzyme, is bypassed. Furthermore, fructose 1-phosphate stimulates pyruvate kinase.

23. The reverse of glycolysis is highly endergonic under cellular conditions. The expenditure of six NTP molecules in gluconeogenesis renders gluconeogenesis exergonic.

24. Lactic acid is capable of being further oxidized and is thus useful energy. The conversion of this acid into glucose saves the carbon atoms for future combustion.

25. In glycolysis, the formation of pyruvate and ATP by pyruvate kinase is irreversible. This step is bypassed by two reactions in gluconeogenesis: (1) the formation of oxaloacetate from pyruvate and CO_2 by pyruvate carboxylase and (2) the formation of phosphoenolpyruvate from oxaloacetate and GTP by phosphoenolpyruvate carboxykinase. The formation of fructose 1,6-bisphosphate by phosphofructokinase is bypassed by fructose 1,6-bisphosphatase in gluconeogenesis, which catalyzes the conversion of fructose 1,6-bisphosphate into fructose 6-phosphate. Finally, the hexokinase-catalyzed formation of glucose 6-phosphate in glycolysis is bypassed by glucose 6-phosphatase, but only in the liver.

26. Reciprocal regulation at the key allosteric enzymes in the two pathways. For instance, PFK is stimulated by fructose 2,6-bisphosphate and AMP. The effect of these signals is opposite that of fructose 1,6-bisphosphatase. If both pathways were operating simultaneously, a futile cycle would result. ATP would be hydrolyzed, yielding only heat.

27. Muscle is likely to produce lactic acid during contraction. Lactic acid is a strong acid and cannot accumulate in muscle or blood. Liver removes the lactic acid from the blood and converts it into glucose. The glucose can be released into the blood or stored as glycogen for later use.

28. Glucose produced by the liver could not be released into the blood. Tissues that rely on glucose as an energy source would not function as well unless glucose was provided in the diet.

29. Glucose is an important energy source for both tissues and is essentially the only energy source for the brain. Consequently, these tissues should never release glucose. Glucose release is prevented by the absence of glucose 6-phosphatase.

30. 6 NTP (4 ATP and 2 GTP); 2 NADH.

31. (a) None; (b) none; (c) 4 (2 ATP and 2 GTP); (d) none.

32. If the amino groups are removed from alanine and aspartate, the ketoacids pyruvate and oxaloacetate are formed. Both of these molecules are components of the gluconeogenic pathway.

33. (a) Increased; (b) increased; (c) increased; (d) decreased.

34. Fructose 2,6-bisphosphate, present at high concentration when glucose is abundant, normally inhibits gluconeogenesis by blocking fructose 1,6-bisphosphatase. In this genetic disorder, the phosphatase is active irrespective of the glucose level. Hence, substrate cycling is increased. The level of fructose 1,6-bisphosphate is

ANSWERS TO PROBLEMS

consequently lower than normal. Less pyruvate is formed and thus less ATP is generated.

35. Reactions in parts *b* and *e* would be blocked.

36. There will be no labeled carbons. The CO₂ added to pyruvate (formed from the lactate) to form oxaloacetate is lost with the conversion of oxaloacetate into phosphoenolpyruvate.

37. The net reaction in the presence of arsenate is



Glycolysis proceeds in the presence of arsenate, but the ATP normally formed in the conversion of 1,3-bisphosphoglycerate into 3-phosphoglycerate is lost. Thus, arsenate uncouples oxidation and phosphorylation by forming a highly labile acyl arsenate.

38. This example illustrates the difference between the *stoichiometric* and the *catalytic* use of a molecule. If cells used NAD⁺ stoichiometrically, a new molecule of NAD⁺ would be required each time a molecule of lactate was produced. As we will see, the synthesis of NAD⁺ requires ATP. On the other hand, if the NAD⁺ that is converted into NADH could be recycled and reused, a small amount of the molecule could regenerate a vast amount of lactate, which is the case in the cell. NAD⁺ is regenerated by the oxidation of NADH and reused. NAD⁺ is thus used catalytically.

39. Consider the equilibrium equation of adenylate kinase:

$$K_{\text{eq}} = [\text{ATP}] [\text{AMP}] / [\text{ADP}]^2 \quad (1)$$

or

$$\text{AMP} = K_{\text{eq}} [\text{ADP}]^2 / [\text{ATP}] \quad (2)$$

Recall that $[\text{ATP}] > [\text{ADP}] > [\text{AMP}]$ in the cell. As ATP is utilized, a small decrease in its concentration will result in a larger percentage increase in [ADP] because its concentration is greater than that of ADP. This larger percentage increase in [ADP] will result in an even greater percentage increase in [AMP] because the concentration of AMP is related to the square of [ADP]. In essence, equation 2 shows that monitoring the energy status with AMP magnifies small changes in [ATP], leading to tighter control.

40. The synthesis of glucose during intense exercise provides a good example of interorgan cooperation in higher organisms. When muscle is actively contracting, lactate is produced from glucose by glycolysis. The lactate is released into the blood and absorbed by the liver, where it is converted by gluconeogenesis into glucose. The newly synthesized glucose is then released and taken up by the muscle for energy generation.

41. The input of four additional high-phosphoryl-transfer-potential molecules in gluconeogenesis changes the equilibrium constant by a factor of 10³², which makes the conversion of pyruvate into glucose thermodynamically feasible. Without this energetic input, gluconeogenesis would not take place.

42. The mechanism is analogous to that for triose phosphate isomerase (Figure 16.5). It proceeds through an enediol intermediate. The active site would be expected to have a general base (analogous to Glu 165 in TPI) and a general acid (analogous to His 95 in TPI).

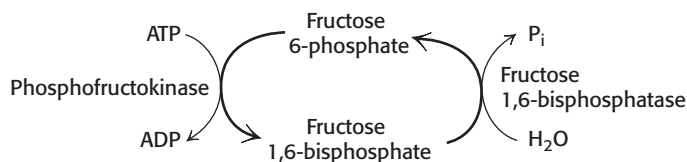
43. Galactose is a component of glycoproteins. Possibly, the absence of galactose leads to the improper formation or function of glycoproteins required in the central nervous system. More generally, the fact that the symptoms arise in the absence of galactose suggests that galactose is required in some fashion.

44. Fructose 2,6-bisphosphate stabilizes the R state of the enzyme.

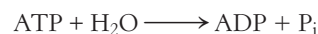
45. (a) Curiously, the enzyme uses ADP as the phosphoryl donor rather than ATP.

(b) Both AMP and ATP behave as competitive inhibitors of ADP, the phosphoryl donor. Apparently, the *P. furiosus* enzyme is not allosterically inhibited by ATP.

46. (a) If both enzymes operated simultaneously, the following reactions would take place:



The net result would be simply:



The energy of ATP hydrolysis would be released as heat.

(b) Not really. For the cycle to generate heat, both enzymes must be functional at the same time in the same cell.

(c) The species *B. terrestris* and *B. rufocinctus* might show some futile cycling because both enzymes are active to a substantial degree.

(d) No. These results simply suggest that simultaneous activity of phosphofructokinase and fructose 1,6-bisphosphatase is unlikely to be employed to generate heat in the species shown.

Chapter 17

1. Pyruvate dehydrogenase catalyzes the decarboxylation of pyruvate and the formation of acetyl lipoamide. Dihydrolipoyl transacetylase catalyzes the formation of acetyl CoA. Dihydrolipoyl dehydrogenase catalyzes the reduction of the oxidized lipoic acid. The kinase associated with the complex phosphorylates and inactivates the complex, whereas the phosphatase dephosphorylates and activates the complex.

2. Thiamine pyrophosphate plays a role in the decarboxylation of pyruvate. Lipoic acid (as lipoamide) transfers the acetyl group. Coenzyme A accepts the acetyl group from lipoic acid to form acetyl CoA. FAD accepts the electrons and hydrogen ions when reduced lipoic acid is oxidized. NAD⁺ accepts electrons from FADH₂.

3. Catalytic coenzymes (TPP, lipoic acid, and FAD) are modified but regenerated in each reaction cycle. Thus, they can play a role in the processing of many molecules of pyruvate. Stoichiometric coenzymes (coenzyme A and NAD⁺) are used in only one reaction because they are the components of products of the reaction.

4. The advantages are as follows:

The reaction is facilitated by having the active sites in proximity. The reactants do not leave the enzyme until the final product is formed.

Constraining the reactants minimizes loss due to diffusion and minimizes side reactions.

All of the enzymes are present in the correct amounts.

Regulation is more efficient because the regulatory enzymes—the kinase and phosphatase—are part of the complex.

5. (a) After one round of the citric acid cycle, the label emerges in C-2 and C-3 of oxaloacetate. (b) The label emerges in CO₂ in the formation of acetyl CoA from pyruvate. (c) After one round of the citric acid cycle, the label emerges in C-1 and C-4 of oxaloacetate. (d) and (e) Same fate as that in part *a*.

6. (a) Isocitrate lyase and malate synthase are required in addition to the enzymes of the citric acid cycle.

(b) $2 \text{ Acetyl CoA} + 2 \text{ NAD}^+ + \text{FAD} + 3 \text{ H}_2\text{O} \longrightarrow \text{oxaloacetate} + 2 \text{ CoA} + 2 \text{ NADH} + \text{FADH}_2 + 3 \text{ H}^+$.

(c) No. Hence, mammals cannot carry out the net synthesis of oxaloacetate from acetyl CoA.

7. $-41.0 \text{ kJ mol}^{-1}$ ($-9.8 \text{ kcal mol}^{-1}$)

8. Enzymes or enzyme complexes are biological catalysts. Recall that a catalyst facilitates a chemical reaction without the catalyst itself being permanently altered. Oxaloacetate can be thought of as a catalyst because it binds to an acetyl group, leads to the oxidative decarboxylation of the two carbon atoms, and is regenerated at the completion of a cycle. In essence, oxaloacetate (and any cycle intermediate) acts as a catalyst.

9. Thiamine thiazolone pyrophosphate is a transition-state analog. The sulfur-containing ring of this analog is uncharged, and so it closely resembles the transition state of the normal coenzyme in thiamine-catalyzed reactions (e.g., the uncharged resonance form of hydroxyethyl-TPP).

10. A decrease in the amount of O_2 will necessitate an increase in anaerobic glycolysis for energy production, leading to the generation of a large amount of lactic acid. Under conditions of shock, the kinase inhibitor is administered to ensure that pyruvate dehydrogenase is operating maximally.

11. Acetylipoamide and acetyl CoA

12. In muscle, the acetyl CoA generated by the complex is used for energy generation. Consequently, signals that indicate an energy-rich state (high ratios of ATP/ADP and NADH/NAD⁺) inhibit the complex, whereas the reverse conditions stimulate the enzyme. Calcium as the signal for muscle contraction (and, hence, energy need) also stimulates the enzyme. In liver, acetyl CoA derived from pyruvate is used for biosynthetic purposes, such as fatty acid synthesis. Insulin, the hormone denoting the fed state, stimulates the complex.

13. (a) Enhanced kinase activity will result in a decrease in the activity of the PDH complex because phosphorylation by the kinase inhibits the complex.

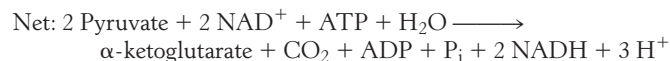
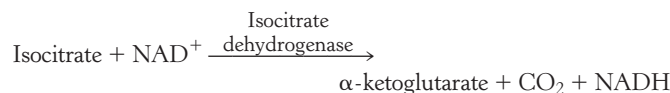
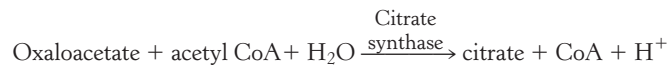
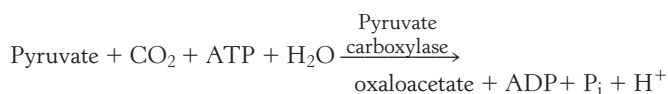
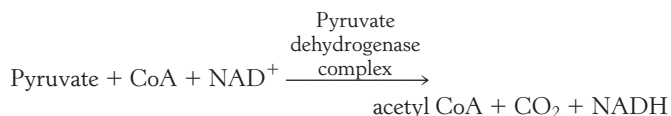
(b) Phosphatase activates the complex by removing a phosphate. If the phosphatase activity is diminished, the activity of the PDH complex also will decrease.

14. She might have been ingesting, in some fashion, the arsenite from the peeling paint or the wallpaper. Also, she might have been breathing arsine gas from the wallpaper, which would be oxidized to arsenite in her body. In any of these circumstances, the arsenite inhibited enzymes that require lipoic acid—notably, the PDH complex.

15. The TCA cycle depends on a steady supply of NAD⁺, which is typically generated from NADH by reaction of the NADH with oxygen. If there is no oxygen to accept the electrons, the citric acid cycle will cease to operate.

16. (a) The steady-state concentrations of the products are low compared with those of the substrates. (b) The ratio of malate to oxaloacetate must be greater than 1.57×10^4 for oxaloacetate to be formed.

17.



18. Succinate will increase in concentration, followed by α -ketoglutarate and the other intermediates “upstream” of the site of inhibition. Succinate has two methylene groups that are required for the dehydrogenation, whereas malonate has but one.

19. Pyruvate carboxylase should be active only when the acetyl CoA concentration is high. Acetyl CoA might accumulate if the energy needs of the cell are not being met, because of a deficiency of oxaloacetate. Under these conditions the pyruvate carboxylase catalyzes an anapleurotic reaction. Alternatively, acetyl CoA might accumulate because the energy needs of the cell have been met. In this circumstance, pyruvate will be converted back into glucose, and the first step in this conversion is the formation of oxaloacetate.

20. The energy released when succinate is reduced to fumarate is not sufficient to power the synthesis of NADH but is sufficient to reduce FAD.

21. Citrate is a tertiary alcohol that cannot be oxidized, because oxidation requires a hydrogen atom to be removed from the alcohol and a hydrogen atom to be removed from the carbon atom bonded to the alcohol. No such hydrogen exists in citrate. The isomerization converts the tertiary alcohol into isocitrate, which is a secondary alcohol that can be oxidized.

22. Because the enzyme nucleoside diphosphokinase transfers a phosphoryl group from GTP (or any nucleoside triphosphate) to ADP according to the reversible reaction:



23. The reaction is powered by the hydrolysis of a thioester. Acetyl CoA provides the thioester that is converted into citryl CoA. When this thioester is hydrolyzed, citrate is formed in an irreversible reaction.

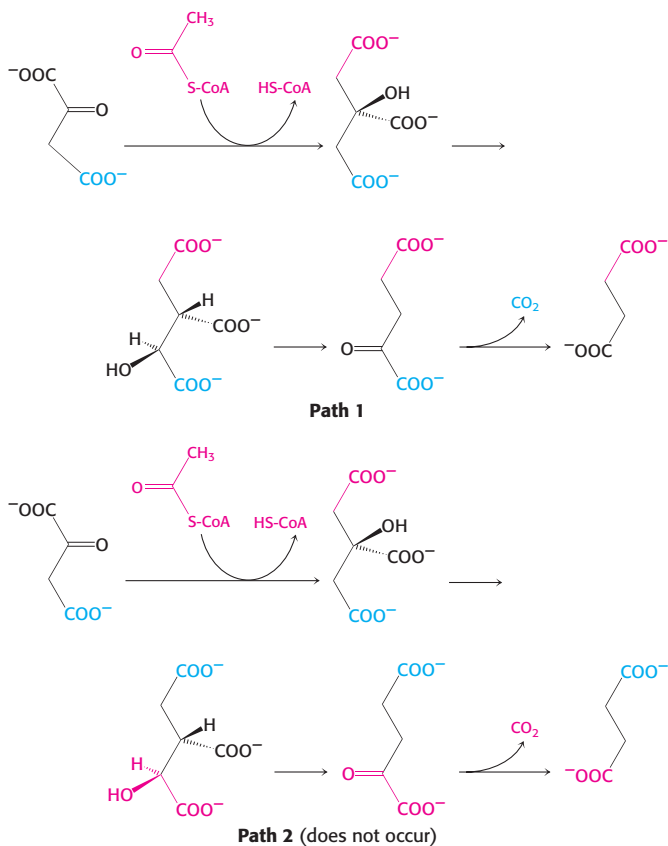
24. We cannot get the net conversion of fats into glucose, because the only means to get the carbon atoms from fats into oxaloacetate, the precursor of glucose, is through the citric acid cycle. However, although two carbon atoms enter the cycle as acetyl CoA, two carbon atoms are lost as CO_2 before oxaloacetate is formed. Thus, although some carbon atoms from fats may end up as carbon atoms in glucose, we cannot obtain a net synthesis of glucose from fats.

25. Acetyl CoA will inhibit the complex. Glucose metabolism to pyruvate will be slowed because acetyl CoA is being derived from an alternative source.

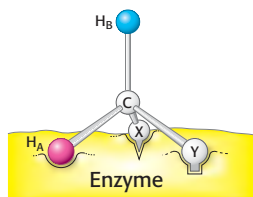
26. The enol intermediate of acetyl CoA attacks the carbonyl carbon atom of glyoxylate to form a C–C bond. This reaction is like the condensation of oxaloacetate with the enol intermediate of acetyl CoA in the reaction catalyzed by citrate synthase. Glyoxylate contains a hydrogen atom in place of the $-\text{CH}_2\text{COO}^-$ group of oxaloacetate; the reactions are otherwise nearly identical.

27. Citrate is a symmetric molecule. Consequently, the investigators assumed that the two $-\text{CH}_2\text{COO}^-$ groups in it would react identically. Thus, for every citrate molecule undergoing the reactions shown in path 1, they thought that another citrate

molecule would react as shown in path 2. If so, then only *half* the label should have emerged in the CO_2 .

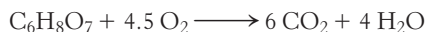


28. Call one hydrogen atom A and the other B. Now suppose that an enzyme binds three groups of this substrate—X, Y, and H—at three complementary sites. The adjoining diagram shows X, Y, and H_A bound to three points on the enzyme. In contrast, X, Y, and H_B cannot be bound to this active site; two of these three groups can be bound, but not all three. Thus, H_A and H_B will have different fates.



Sterically nonequivalent groups such as H_A and H_B will almost always be distinguished in enzymatic reactions. The essence of the differentiation of these groups is that the enzyme holds the substrate in a specific orientation. Attachment at three points, as depicted in the diagram, is a readily visualized way of achieving a particular orientation of the substrate, but it is not the only means of doing so.

29. (a) The complete oxidation of citrate requires $4.5 \mu\text{mol}$ of O_2 for every micromole of citrate.



Thus, $13.5 \mu\text{mol}$ of O_2 would be consumed by $3 \mu\text{mol}$ of citrate.

(b) Citrate led to the consumption of far more O_2 than can be accounted for simply by the oxidation of citrate itself. Citrate thus facilitated O_2 consumption.

30. (a) In the absence of arsenite, the amount of citrate remained constant. In its presence, the concentration of citrate fell, suggesting that it was being metabolized.

(b) The action of arsenite is not altered. Citrate still disappears.

(c) Arsenite is preventing the regeneration of citrate. Recall (pp. 517–518) that arsenite inhibits the pyruvate dehydrogenase complex.

31. (a) The initial infection is unaffected by the absence of isocitrate lyase, but the absence of this enzyme inhibits the latent phase of the infection.

(b) Yes

(c) A critic could say that, in the process of deleting the isocitrate lyase gene, some other gene was damaged, and it is the absence of this other gene that prevents latent infection. Reinserting the isocitrate lyase gene into the bacteria from which it had been removed renders the criticism less valid.

(d) Isocitrate lyase enables the bacteria to synthesize carbohydrates that are necessary for survival, including carbohydrate components of the cell membrane.

Chapter 18

1. In fermentations, organic compounds are both the donors and the acceptors of electrons. In respiration, the electron donor is usually an organic compound, whereas the electron acceptor is an inorganic molecule, such as oxygen.

2. Biochemists use E'_0 , the value at pH 7, whereas chemists use E_0 , the value in 1 M H^+ . The prime denotes that pH 7 is the standard state.

3. The reduction potential of FADH_2 is less than that of NADH (see Table 18.1). Consequently, when those electrons are passed along to oxygen, less energy is released. The consequence of the difference is that electron flow from FADH_2 to O_2 pumps fewer protons than do the electrons from NADH .

4. The $\Delta G^{\circ'}$ for the reduction of oxygen by FADH_2 is -200 kJ mol^{-1} ($-48 \text{ kcal mol}^{-1}$).

5. $\Delta G^{\circ'}$ is $+67 \text{ kJ mol}^{-1}$ ($+16.1 \text{ kcal mol}^{-1}$) for oxidation by NAD^+ and -3.8 kJ mol^{-1} ($-0.92 \text{ kcal mol}^{-1}$) for oxidation by FAD . The oxidation of succinate by NAD^+ is not thermodynamically feasible.

6. Pyruvate accepts electrons and is thus the oxidant. NADH gives up electrons and is the reductant.

7. $\Delta G^{\circ'} = -nF\Delta E'_0$

8. The $\Delta E'_0$ value of iron can be altered by changing the environment of the ion.

9. c, e, b, a, d.

10. (a) 4; (b) 3; (c) 1; (d) 5; (e) 2.

11. The 10 isoprene units render coenzyme Q soluble in the hydrophobic environment of the inner mitochondrial membrane. The two oxygen atoms can reversibly bind two electrons and two protons as the molecule transitions between the quinone form and quinol form.

12. Rotenone: NADH , NADH-Q oxidoreductase will be reduced. The remainder will be oxidized. Antimycin A: NADH , NADH-Q oxidoreductase and coenzyme Q will be reduced. The remainder will be oxidized. Cyanide: All will be reduced.

13. Complex I would be reduced, whereas Complexes II, III, and IV would be oxidized. The citric acid cycle would become reduced because it has no way to oxidize NADH .

14. The respirasome is another example of the use of supra-molecular complexes in biochemistry. Having the three complexes that are proton pumps associated with one another will enhance the efficiency of electron flow from complex to complex, which in turn will cause more-efficient proton pumping.

15. Hydroxyl radical ($\text{OH}\cdot$), hydrogen peroxide (H_2O_2), superoxide ion ($\text{O}_2^{\cdot-}$), and peroxide (O_2^{2-}). These small molecules react

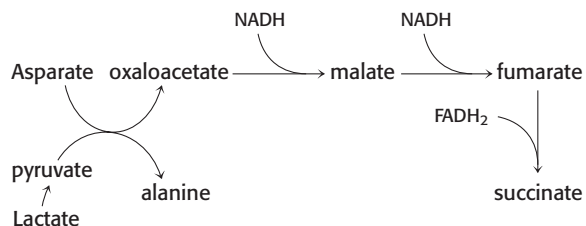
with a host of macromolecules—including proteins, nucleotides, and membranes—to disrupt cell structure and function.

16. The ATP is recycled by ATP-generating processes, most notably oxidative phosphorylation.
17. (a) 12.5; (b) 14; (c) 32; (d) 13.5; (e) 30; (f) 16.
18. (a) It blocks electron transport and proton pumping at Complex IV. (b) It blocks electron transport and ATP synthesis by inhibiting the exchange of ATP and ADP across the inner mitochondrial membrane. (c) It blocks electron transport and proton pumping at Complex I. (d) It blocks ATP synthesis without inhibiting electron transport by dissipating the proton gradient. (e) It blocks electron transport and proton pumping at Complex IV. (f) It blocks electron transport and proton pumping at Complex III.
19. If the proton gradient is not dissipated by the influx of protons into a mitochondrion with the generation of ATP, eventually the outside of the mitochondrion develops such a large positive charge that the electron-transport chain can no longer pump protons against the gradient.
20. The subunits are jostled by background thermal energy (Brownian motion). The proton gradient makes clockwise rotation more likely because that direction results in protons flowing down their concentration gradient.
21. In the presence of poorly functioning mitochondria, the only means of generating ATP is by anaerobic glycolysis, which will lead to an accumulation of lactic acid in blood.
22. If ADP cannot get into mitochondria, the electron-transport chain will cease to function because there will be no acceptor for the energy. NADH will build up in the matrix. Recall that NADH inhibits some citric acid cycle enzymes and that NAD^+ is required by several citric acid cycle enzymes. Glycolysis will stop functioning aerobically but will switch to anaerobic glycolysis so that the NADH can be reoxidized to NAD^+ by lactate dehydrogenase.
23. (a) No effect; mitochondria cannot metabolize glucose.
 (b) No effect; no fuel is present to power the synthesis of ATP.
 (c) The $[\text{O}_2]$ falls because citrate is a fuel and ATP can be formed from ADP and P_i .
 (d) Oxygen consumption stops because oligomycin inhibits ATP synthesis, which is coupled to the activity of the electron-transport chain.
 (e) No effect, for the reasons given in part *d*.
 (f) $[\text{O}_2]$ falls rapidly because the system is uncoupled and does not require ATP synthesis to lower the proton-motive force.
 (g) $[\text{O}_2]$ falls, though at a lower rate. Rotenone inhibits Complex I, but the presence of succinate will enable electrons to enter at Complex II.
 (h) Oxygen consumption ceases because Complex IV is inhibited and the entire chain backs up.
24. (a) The P : O ratio is equal to the product of $(\text{H}^+/2 \text{e}^-)$ and (P/H^+) . Note that the P : O ratio is identical with the P : 2e^- ratio.
 (b) 2.5 and 1.5, respectively.
25. Cyanide can be lethal because it binds to the ferric form of cytochrome oxidase and thereby inhibits oxidative phosphorylation. Nitrite converts ferrihemoglobin into ferrihemoglobin, which also binds cyanide. Thus, ferrihemoglobin competes with cytochrome oxidase for cyanide. This competition is therapeutically effective because the amount of ferrihemoglobin that can be formed without impairing oxygen transport is much greater than the amount of cytochrome oxidase.
26. Such a defect (called Luft syndrome) was found in a 38-year-old woman who was incapable of performing prolonged physical work. Her basal metabolic rate was more than twice normal, but her thyroid function was normal. A muscle biopsy showed that her mitochondria were highly variable and atypical in structure. Biochemical studies then revealed that oxidation and phosphorylation were not tightly coupled in these mitochondria. In this patient, much of the energy of fuel molecules was converted into heat rather than ATP.
27. Triose phosphate isomerase converts dihydroxyacetone phosphate (a potential dead end) into glyceraldehyde 3-phosphate (a mainstream glycolytic intermediate).
28. This inhibitor (like antimycin A) blocks the reduction of cytochrome c_1 by QH_2 , the crossover point.
29. If oxidative phosphorylation were uncoupled, no ATP could be produced. In a futile attempt to generate ATP, much fuel would be consumed. The danger lies in the dose. Too much uncoupling would lead to tissue damage in highly aerobic organs such as the brain and heart, which would have severe consequences for the organism as a whole. The energy that is normally transformed into ATP would be released as heat. To maintain body temperature, sweating might increase, although the very process of sweating itself depends on ATP.
30. If ATP and ADP cannot exchange between the matrix and the mitochondria, ATP synthase will cease to function because its substrate ADP is absent. The proton gradient will eventually become so large that the energy released by the electron-transport chain will not be great enough to pump protons against the larger-than-normal gradient.
31. Add the inhibitor with and without an uncoupler, and monitor the rate of O_2 consumption. If the O_2 consumption increases again in the presence of inhibitor and uncoupler, the inhibitor must be inhibiting ATP synthase. If the uncoupler has no effect on the inhibition, the inhibitor is inhibiting the electron-transport chain.
32. Presumably, because the muscle has greater energy needs, especially during exercise, it will require more ATP. This requirement means that more sites of oxidative phosphorylation are called for, and these sites can be provided by an increase in the amount of cristae.
33. The arginine residue, with its positive charge, will facilitate proton release from aspartic acid by stabilizing the negatively charged aspartate.
34. 4; 4.7
35. The ATP synthase would pump protons at the expense of ATP hydrolysis, thus maintaining the proton-motive force. The synthase would function as an ATPase. There is some evidence that damaged mitochondria use this tactic to maintain, at least temporarily, the proton-motive force.
36. It suggests that malfunctioning mitochondria may play a role in the development of Parkinson disease. Specifically, it implicates Complex I.
37. The extra negative charge on ATP relative to that on ADP accounts for ATP's more-rapid translocation out of the mitochondrial matrix. If the charge differences between ATP and ADP were lessened by the binding of Mg^{2+} , ADP might more readily compete with ATP for transport to the cytoplasm.
38. When all of the available ADP has been converted into ATP, ATP synthase can no longer function. The proton gradient becomes large enough that the energy of the electron-transport chain is not enough to pump against the gradient, and electron transport and, hence, oxygen consumption falls.
39. The effect on the proton gradient is the same in each case.
40. ATP export from the matrix. Phosphate import into the matrix.
41. Recall from the discussion of enzyme-catalyzed reactions that the direction of a reaction is determined by the ΔG difference between substrate and products. An enzyme speeds up the rate of both the forward and the backward reactions. The hydrolysis of ATP is exergonic, and so ATP synthase will enhance the hydrolytic reaction.

ANSWERS TO PROBLEMS

42. The cytoplasmic kinases thereby obtaining preferential access to the exported ATP.

43. The organic acids in the blood are indications that the mice are deriving a large part of their energy needs through anaerobic glycolysis. Lactate is the end product of anaerobic glycolysis. Alanine is an aminated transport form of lactate. Alanine formation plays a role in succinate formation, which is caused by the reduced state of the mitochondria.



The electron-transport chain is slowed because the inner mitochondrial membrane is hyperpolarized. Without ADP to accept the energy of the proton-motive force, the membrane becomes polarized to such an extent that protons can no longer be pumped. The excess H_2O_2 is probably due to the fact that the superoxide radical is present in higher concentration because the oxygen can no longer be effectively reduced.



Indeed, these mice display evidence of such oxidative damage.

44. (a) Vitamins C and E.

(b) Exercise induces superoxide dismutase, which converts ROS in hydrogen peroxide and oxygen.

(c) The answer to this question is not fully established. Two possibilities are (1) the suppression of ROS by vitamins prevents the expression of more superoxide dismutase and (2) some ROS may be signal molecules required to stimulate insulin-sensitivity pathways.

45. (a) Succinate is oxidized by Complex II, and the electrons are used to establish a proton-motive force that powers ATP synthesis.

(b) The ability to synthesize ATP is greatly reduced.

(c) Because the goal was to measure ATP hydrolysis. If succinate had been added in the presence of ATP, no reaction would have taken place, because of respiratory control.

(d) The mutation has little effect on the ability of the enzyme to catalyze the hydrolysis of ATP.

(e) They suggest two things: (1) the mutation did not affect the catalytic site on the enzyme, because ATP synthase is still capable of catalyzing the reverse reaction, and (2) the mutation did not affect the amount of enzyme present, given that the controls and patients had similar amounts of activity.

46. The absolute configuration of thiophosphate indicates that inversion at phosphorus has taken place in the reaction catalyzed by ATP synthase. This result is consistent with an in-line phosphoryl-transfer reaction taking place in a single step. The retention of configuration in the Ca^{2+} -ATPase reaction points to two phosphoryl-transfer reactions—inversion by the first and a return to the starting configuration by the second. The Ca^{2+} -ATPase reaction proceeds by a phosphorylated enzyme intermediate.

Chapter 19

1. Photosystem I generates ferredoxin, which reduces NADP^+ to NADPH, a biosynthetic reducing power. Photosystem II activates the manganese complex, an oxidant capable of oxidizing water, generating electrons for photosynthesis, and generating protons to form a proton gradient and to reduce NADP^+ and O_2 .

2. The light reactions take place on thylakoid membranes.

Increasing the membrane surface increases the number of ATP- and NADH-generating sites.

3. These complexes absorb more light than can a reaction center alone. The light-harvesting complexes funnel light to the reaction centers.

4. NADP^+ is the acceptor. H_2O is the donor. Light energy.

5. The charge gradient, a component of the proton-motive force in mitochondria, is neutralized by the influx of Mg^{2+} into the lumen of the thylakoid membranes.

6. Chlorophyll is readily inserted into the hydrophobic interior of the thylakoid membranes.

7. Protons released by the oxidation of water; protons pumped into the lumen by the cytochrome *bf* complex; protons removed from the stroma by the reduction of NADP^+ and plastoquinone.

8. 700-nm photons have an energy content of 172 kJ mol^{-1} . The absorption of light by photosystem I results in a $\Delta E_0'$ of -1.0 V . Recall that $\Delta G_0' = -nF \Delta E_0'$, where $F = 96.48 \text{ kJ mol}^{-1} \text{ V}^{-1}$. Under standard conditions, the energy change for the electrons is 96.5 kJ . Thus, the efficiency is $96.5/172 = 56\%$.

9. The electron flow from PS II to PS I is uphill, or exergonic. For this uphill flow, ATP would need to be consumed, defeating the purpose of photosynthesis.

10. $\Delta E_0' = 10.11 \text{ V}$, and $\Delta G^{\circ'} = -21.3 \text{ kJ mol}^{-1} (-5.1 \text{ kcal mol}^{-1})$.

11. (a) All ecosystems require an energy source from outside the system, because the chemical-energy sources will ultimately be limited. The photosynthetic conversion of sunlight is one example of such a conversion.

(b) Not at all. Spock would point out that chemicals other than water can donate electrons and protons.

12. DCMU inhibits electron transfer in the link between photosystems II and I. O_2 can evolve in the presence of DCMU if an artificial electron acceptor such as ferricyanide can accept electrons from Q.

13. DCMU will have no effect, because it blocks photosystem II, and cyclic photophosphorylation uses photosystem I and the cytochrome *bf* complex.

14. (a) $120 \text{ kJ einstein}^{-1} (28.7 \text{ kcal einstein}^{-1})$

(b) 1.24 V

(c) One 1000-nm photon has the free energy content of 2.4 molecules of ATP. A minimum of 0.42 photon is needed to drive the synthesis of a molecule of ATP.

15. At this distance, the expected rate is one electron per second.

16. The distance doubles, and so the rate should decrease by a factor of 64 to 640 ps.

17. The cristae.

18. In eukaryotes, both processes take place in specialized organelles. Both depend on high-energy electrons to generate ATP. In oxidative phosphorylation, the high-energy electrons originate in fuels and are extracted as reducing power in the form of NADH.

In photosynthesis, the high-energy electrons are generated by light and are captured as reducing power in the form of NADPH. Both processes use redox reactions to generate a proton gradient, and the enzymes that convert the proton gradient into ATP are very similar in both processes. In both systems, electron transport takes place in membranes inside organelles.

19. We need to factor in the NADPH because it is an energy-rich molecule. Recall from Chapter 18, that NADH is worth 2.5 ATP if oxidized by the electron-transport chain. $12 \text{ NADPH} = 30 \text{ ATP}$. Eighteen molecules of ATP are used directly, and so the equivalent of 48 molecules of ATP is required for the synthesis of glucose.

20. Both photosynthesis and cellular respiration are powered by high-energy electrons flowing toward a more-stable state. In cellular respiration, the high-energy electrons are derived from the

oxidation of carbon fuels as NADH and FADH₂. They release their energy as they reduce oxygen. In photosynthesis, high-energy electrons are generated by absorbing light energy, and they find stability in photosystem I and ferridoxin.

21. The electrons flow through photosystem II directly to ferricyanide. No other steps are required.

22. (a) Thioredoxin

(b) The control enzyme is unaffected, but the mitochondrial enzyme with part of the chloroplast γ subunit increases activity as the concentration of DTT increases.

(c) The increase was even larger when thioredoxin was present. Thioredoxin is the natural reductant for the chloroplast enzyme, and so it presumably operates more efficiently than would DTT, which probably functions to keep the thioredoxin reduced.

(d) They seem to have done so.

(e) The enzyme is susceptible to control by the redox state. In plant cells, reduced thioredoxin is generated by photosystem I. Thus, the enzyme is active when photosynthesis is taking place.

(f) Cysteine

(g) Group-specific modification or site-specific mutagenesis.

Chapter 20

1. The Calvin cycle is the primary means of converting gaseous CO₂ into organic matter—that is, biomolecules. Essentially, every carbon atom in your body passed through rubisco and the Calvin cycle at some time in the past.

2.

Calvin cycle	Krebs cycle
Stroma	Matrix
Carbon chemistry for photosynthesis	Carbon chemistry for oxidative phosphorylation
Fixes CO ₂	Releases CO ₂
Requires high-energy electrons (NADPH)	Generates high-energy electrons (NADPH)
Regenerates starting compound (ribulose 1,5-bisphosphate)	Regenerates starting compound (oxaloacetate)
Requires ATP	Generates ATP or GTP
Complex stoichiometry	Simple stoichiometry

3. (a) 3-Phosphoglycerate. (b) The other members of the Calvin cycle.

4. Stage 1 is the fixation of CO₂ with ribulose 1,5-bisphosphate and the subsequent formation of 3-phosphoglycerate. Stage 2 is the conversion of some of the 3-phosphoglycerate into hexose. Stage 3 is the regeneration of ribulose 1,5-bisphosphate.

5. It catalyzes a crucial reaction, but it is highly inefficient. Consequently, it is required in large amounts to overcome its slow catalysis.

6. Because carbamate forms only in the presence of CO₂, this property prevents rubisco from catalyzing the oxygenase reaction exclusively when CO₂ is absent.

7. Because NADPH is generated in the chloroplasts by the light reactions.

8. The concentration of 3-phosphoglycerate would increase, whereas that of ribulose 1,5-bisphosphate would decrease.

9. The concentration of 3-phosphoglycerate would decrease, whereas that of ribulose 1,5-bisphosphate would increase.

10. Aspartate + glyoxylate \longrightarrow oxaloacetate + glycine

11. The oxygenase activity of rubisco increases with temperature.

Crabgrass is a C₄ plant, whereas most grasses lack this capability. Consequently, the crabgrass will thrive at the hottest part of the summer because the C₄ pathway provides an ample supply of CO₂.

12. The C₄ pathway allows the CO₂ concentration to increase at the site of carbon fixation. High concentrations of CO₂ inhibit the oxygenase reaction of rubisco. This inhibition is important for tropical plants because the oxygenase activity increases more rapidly with temperature than does the carboxylase activity.

13. ATP is required to form phosphoenolpyruvate (PEP) from pyruvate. The PEP combines with CO₂ to form oxaloacetate and, subsequently, malate. Two ATP molecules are required because a second ATP molecule is required to phosphorylate AMP to ADP.

14. Photorespiration is the consumption of oxygen by plants with the production of CO₂, but it does not generate energy. Photorespiration is due to the oxygenase activity of rubisco. It is wasteful because, instead of fixing CO₂ for conversion into hexoses, rubisco is generating CO₂.

15. As global warming progresses, C₄ plants will invade the higher latitudes, and C₃ plants will retreat to cooler regions.

16. The light reactions lead to an increase in the stromal concentrations of NADPH, reduced ferredoxin, and Mg²⁺, as well as an increase in pH.

17. The enzymes catalyze the transformation of the five-carbon sugar formed by the oxidative phase of the pentose phosphate pathway into fructose 6-phosphate and glyceraldehyde 3-phosphate, intermediates in glycolysis (and gluconeogenesis).

18. The label emerges at C-5 of ribulose 5-phosphate.

19. Oxidative decarboxylation of isocitrate to α -ketoglutarate. A β -ketoacid intermediate is formed in both reactions.

20. (a) 5 Glucose 6-phosphate + ATP \longrightarrow 6 ribose 5-phosphate + ADP + H⁺.

(b) Glucose 6-phosphate + 12 NADP⁺ + 7 H₂O \longrightarrow 6 CO₂ + 12 NADPH + 12 H⁺ + P_i.

21. The nonoxidative phase of the pentose phosphate pathway can be used to convert three molecules of ribose 5-phosphate into two molecules of fructose 6-phosphate and one molecule of glyceraldehyde 3-phosphate. These molecules are components of the glycolytic pathway.

22. The conversion of fructose 6-phosphate into fructose 1,6-bisphosphate by phosphofructokinase requires ATP.

23. When much NADPH is required. The oxidative phase of the pentose phosphate pathway is followed by the nonoxidative phase. The resulting fructose 6-phosphate and glyceraldehyde 3-phosphate are used to generate glucose 6-phosphate through gluconeogenesis, and the cycle is repeated until the equivalent of one glucose molecule is oxidized to CO₂.

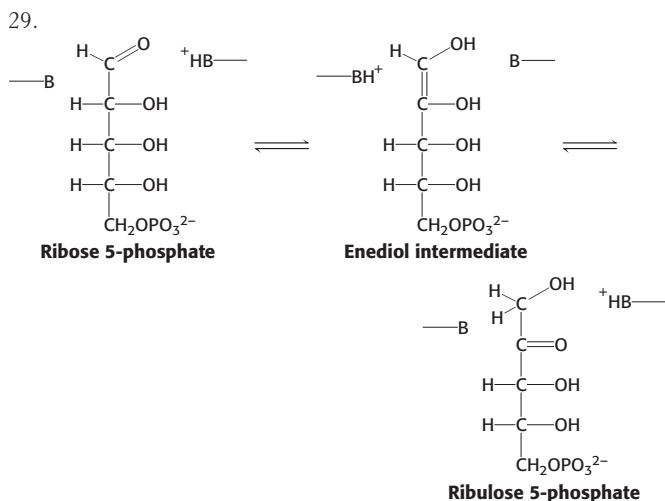
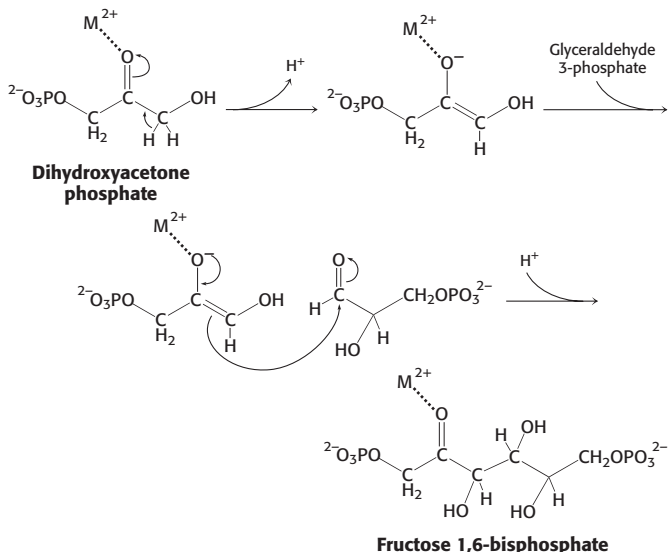
24. Fava beans contain pamaquine, a purine glycoside that can lead to the generation of peroxides—reactive oxygen species that can damage membranes as well as other biomolecules. Glutathione is used to detoxify the ROS. The regeneration of glutathione depends on an adequate supply of NADPH, which is synthesized by the oxidative phase of the pentose phosphate pathway. People with low levels of the dehydrogenase are especially susceptible to pamaquine toxicity.

25. Because red blood cells do not have mitochondria and the only means to obtain NADPH is through the pentose phosphate pathway. There are biochemical means to convert mitochondrial NADH into cytoplasmic NADPH.

26. Reactive peroxides are a type of reactive oxygen species. The enzyme glutathione peroxidase uses reduced glutathione to neutralize peroxides by converting them into alcohols while generating oxidized glutathione. Reduced glutathione is regenerated by glutathione reductase with the use of NADPH, the product of the oxidative phase of the pentose phosphate pathway.

ANSWERS TO PROBLEMS

27. $\Delta E'_0$ for the reduction of glutathione by NADPH is +0.09 V. Hence, $\Delta G'^{\circ}$ is $-17.4 \text{ kJ mol}^{-1}$ ($-4.2 \text{ kcal mol}^{-1}$), which corresponds to an equilibrium constant of 1126. The required $[\text{NADPH}]/[\text{NADP}^+]$ ratio is 8.9×10^{-5} .



30. Incubate an aliquot of a tissue homogenate with glucose labeled with ^{14}C at C-1, and incubate another with glucose labeled with ^{14}C at C-6. Compare the radioactivity of the CO_2 produced by the two samples. The rationale of this experiment is that only C-1 is decarboxylated by the pentose phosphate pathway, whereas C-1 and C-6 are decarboxylated equally when glucose is metabolized by the glycolytic pathway, the pyruvate dehydrogenase complex, and the citric acid cycle. The reason for the equivalence of C-1 and C-6 in the latter set of reactions is that glyceraldehyde 3-phosphate and dihydroxyacetone phosphate are rapidly interconverted by triose phosphate isomerase.

31. The reduction of each mole of CO_2 to the level of a hexose requires two moles of NADPH. The reduction of NADP^+ is a two-electron process. Hence, the formation of two moles of NADPH requires the pumping of four moles of electrons by photosystem I. The electrons given up by photosystem I are replenished by photosystem II, which needs to absorb an equal number of photons. Hence, eight photons are needed to generate the

required NADPH. The energy input of eight moles of photons is 1594 kJ (381 kcal). Thus, the overall efficiency of photosynthesis under standard conditions is at least $477/1594$, or 30%.

32. It is neither a violation nor a miracle. The equation on page 580 requires not only 18 ATP, but also 12 NADPH. These electrons, if transferred to NAD^+ and used in the electron-transport chain, would yield 30 ATP. Thus, the synthesis of glucose requires the equivalent of 48 ATP.

33. (a) The curve on the right in graph A was generated by the C_4 plant. Recall that the oxygenase activity of rubisco increases with temperature more rapidly than does the carboxylase activity. Consequently, at higher temperatures, the C_3 plants would fix less carbon. Because C_4 plants can maintain a higher CO_2 concentration, the rise in temperature is less deleterious.

(b) The oxygenase activity will predominate. Additionally, when the temperature rise is very high, the evaporation of water might become a problem. The higher temperatures can begin to damage protein structures as well.

(c) The C_4 pathway is a very effective active-transport system for concentrating CO_2 , even when environmental concentrations are very low.

(d) With the assumption that the plants have approximately the same capability to fix CO_2 , the C_4 pathway is apparently the rate-limiting step in C_4 plants.

Chapter 21

1. Glycogen is an important fuel reserve for several reasons. The controlled breakdown of glycogen and release of glucose increase the amount of glucose that is available between meals. Hence, glycogen serves as a buffer to maintain blood-glucose levels. Glycogen's role in maintaining blood-glucose levels is especially important because glucose is virtually the only fuel used by the brain, except during prolonged starvation. Moreover, the glucose from glycogen is readily mobilized and is therefore a good source of energy for sudden, strenuous activity. Unlike fatty acids, the released glucose can provide energy in the absence of oxygen and can thus supply energy for anaerobic activity.

2. As an unbranched polymer, α -amylose has only one nonreducing end. Therefore, only one glycogen phosphorylase molecule could degrade each α -amylose molecule. Because glycogen is highly branched, there are many nonreducing ends per molecule. Consequently, many phosphorylase molecules can release many glucose molecules per glycogen molecule.

3. The patient has a deficiency of the branching enzyme.

4. In muscle, the *b* form of phosphorylase is activated by AMP. In the liver, the *a* form is inhibited by glucose. The difference corresponds to the difference in the metabolic role of glycogen in each tissue. Muscle uses glycogen as a fuel for contraction, whereas the liver uses glycogen to maintain blood-glucose levels.

5. Cells maintain the $[\text{P}_i]/[\text{glucose 1-phosphate}]$ ratio at greater than 100, substantially favoring phosphorolysis. We see here an example of how the cell can alter the free-energy change to favor a reaction taking place by altering the ratio of substrate and product.

6. The high level of glucose 6-phosphate in von Gierke disease, resulting from the absence of glucose 6-phosphatase or the transporter, shifts the allosteric equilibrium of phosphorylated glycogen synthase toward the active form.

7. The phosphoryl donor is glucose 1,6-bisphosphate, which is formed from glucose 1-phosphate and ATP in a reaction catalyzed by phosphoglucokinase.

8. The different manifestations correspond to the different roles of the liver and muscle. Liver glycogen phosphorylase plays a crucial role in the maintenance of blood-glucose levels. Recall that glucose

is the primary fuel for the brain. Muscle glycogen phosphorylase provides glucose only for the muscle and, even then, only when the energy needs of the muscle are high, as during exercise. The fact that there are two different diseases suggests that there are two different isozymic forms of the glycogen phosphorylase—a liver-specific isozyme and a muscle-specific isozyme.

9. Water is excluded from the active site to prevent hydrolysis. The entry of water could lead to the formation of glucose rather than glucose 1-phosphate. A site-specific mutagenesis experiment is revealing in this regard. In phosphorylase, Tyr 573 is hydrogen bonded to the 2'-OH group of a glucose residue. The ratio of glucose 1-phosphate to glucose product is 9000 : 1 for the wild-type enzyme, and 500 : 1 for the Phe 573 mutant. Model building suggests that a water molecule occupies the site normally filled by the phenolic OH group of tyrosine and occasionally attacks the oxocarbenium ion intermediate to form glucose.

10. The amylase activity was necessary to remove all of the glycogen from the glycogenin. Recall that glycogenin synthesizes oligosaccharides of about eight glucose units, and then activity stops. Consequently, if the glucose residues are not removed by extensive amylase treatment, glycogenin will not function.

11. The substrate can be handed directly from the transferase site to the debranching site.

12. During exercise, [ATP] falls and [AMP] rises. Recall that AMP is an allosteric activator of glycogen phosphorylase *b*. Thus, even in the absence of covalent modification by phosphorylase kinase, glycogen is degraded.

13. Although glucose 1-phosphate is the actual product of the phosphorylase reaction, glucose 6-phosphate is a more versatile molecule with respect to metabolism. Among other fates, glucose-6-phosphate can be processed to yield energy or building blocks. In the liver, glucose 6-phosphate can be converted into glucose and released into the blood.

14. Epinephrine binds to its G-protein-coupled receptor. The resulting structural changes activate a G_{α} protein, which in turn activates adenylyl cyclase. Adenylyl cyclase synthesizes cAMP, which activates protein kinase A. Protein kinase A partly activates phosphorylase kinase, which phosphorylates and activates glycogen phosphorylase. The calcium released during muscle contraction further activates the phosphorylase kinase, leading to further stimulation of glycogen phosphorylase.

15. First, the signal-transduction pathway is shut down when the initiating hormone is no longer present. Second, the inherent GTPase activity of the G protein converts the bound GTP into inactive GDP. Third, phosphodiesterases convert cyclic AMP into AMP. Fourth, PP1 removes the phosphoryl group from glycogen phosphorylase, converting the enzyme into the usually inactive *b* form.

16. It prevents both from operating simultaneously, which would lead to a useless expenditure of energy. See the answer to Problem 24.

17. All these symptoms suggest central nervous system problems. If exercise is exhaustive enough or the athlete has not prepared well enough or both, liver glycogen also can be depleted. The brain depends on glucose derived from liver glycogen. The symptoms suggest that the brain is not getting enough fuel.

18. Liver phosphorylase *a* is inhibited by glucose, which facilitates the R \rightarrow T transition. This transition releases PP1, which inactivates glycogen breakdown and stimulates glycogen synthesis. Muscle phosphorylase is insensitive to glucose.

19. The presence of high concentrations of glucose 6-phosphate indicates that glucose is abundant and that it is not being used by glycolysis. Therefore, this valuable resource is saved by incorporation into glycogen.

20. Free glucose must be phosphorylated at the expense of a molecule of ATP. Glucose 6-phosphate derived from glycogen is formed by phosphorolytic cleavage, thus sparing one molecule of ATP. Thus, the net yield of ATP when glycogen-derived glucose is processed to pyruvate is three molecules of ATP compared with two molecules of ATP from free glucose.

21. Breakdown: Phosphoglucomutase converts glucose 1-phosphate, liberated from glycogen breakdown, into glucose 6-phosphate, which can be released as free glucose (liver) or processed in glycolysis (muscle and liver). Synthesis: Converts glucose 6-phosphate into glucose 1-phosphate, which reacts with UTP to form UDP-glucose, the substrate for glycogen synthase.

22. $\text{Glycogen}_n + \text{P}_i \longrightarrow \text{glycogen}_{n-1} + \text{glucose 6-phosphate}$

$\text{Glucose 6-phosphate} \longrightarrow \text{glucose 1-phosphate}$

$\text{UTP} + \text{glucose 1-phosphate} \longrightarrow \text{UDP-glucose} + 2 \text{P}_i$

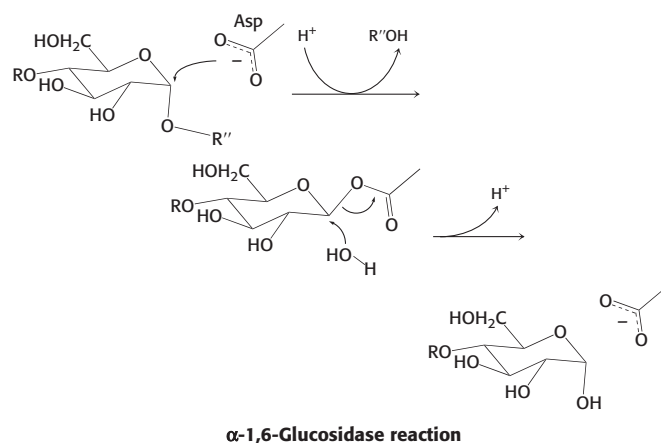
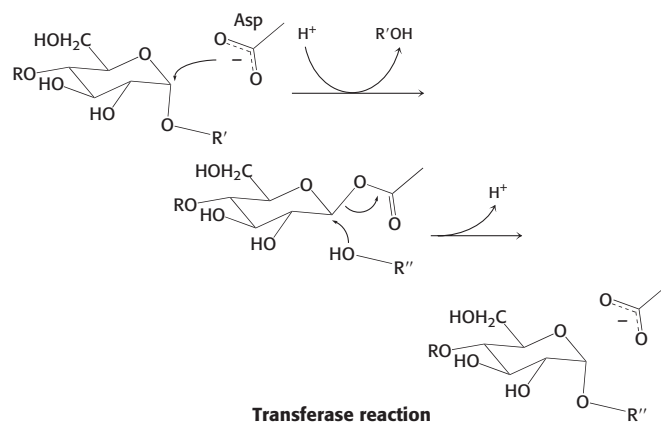
$\text{Glycogen}_{n-1} + \text{UDP-glucose} \longrightarrow \text{glycogen}_n + \text{UDP}$

Sum: $\text{Glycogen}_n + \text{UTP} \longrightarrow \text{glycogen}_n + \text{UDP} + \text{P}_i$

23. In principle, having glycogen be the only primer for the further synthesis of glycogen should be a successful strategy. However, if the glycogen granules were not evenly divided between daughter cells, glycogen stores for future generations of cells might be compromised. Glycogenin synthesizes the primer for glycogen synthase.

24. Insulin binds to its receptor and activates the tyrosine kinase activity of the receptor, which in turn triggers a pathway that activates protein kinases. The kinases phosphorylate and inactivate glycogen synthase kinase. Protein phosphatase 1 then removes the phosphate from glycogen synthase and thereby activates the synthase.

25.



ANSWERS TO PROBLEMS

26. Galactose + ATP + UTP + H₂O + glycogen_n → glycogen_{n+1} + ADP + UDP + 2 P_i + H⁺.

27. Phosphorylase, transferase, glucosidase, phosphoglucomutase, and glucose 6-phosphatase.

28. Glucose is an allosteric inhibitor of phosphorylase *a*. Hence, crystals grown in its presence are in the T state. The addition of glucose 1-phosphate, a substrate, shifts the R-to-T equilibrium toward the R state. The conformational differences between these states are sufficiently large that the crystal shatters unless it is stabilized by chemical cross-links.

29. Galactose is converted into UDP-galactose to eventually form glucose 6-phosphate.

30. This disease can also be produced by a mutation in the gene that encodes the glucose 6-phosphate transporter. Recall that glucose 6-phosphate must be transported into the lumen of the endoplasmic reticulum to be hydrolyzed by phosphatase. Mutations in the other three essential proteins of this system can likewise lead to von Gierke disease.

31. (a) Glycogen was too large to enter the gel and, because analysis was by western blot with the use of an antibody specific to glycogenin, we would not expect to see background proteins.

(b) α-Amylase degrades glycogen, releasing the protein glycogenin, which can be visualized by a western blot.

(c) Glycogen phosphorylase, glycogen synthase, and protein phosphatase 1. These proteins might be visible if the gel were stained for protein, but a western analysis reveals the presence of glycogenin only.

32. (a) The smear was due to molecules of glycogenin with increasingly large amounts of glycogen attached to them.

(b) In the absence of glucose in the medium, glycogen is metabolized, resulting in a loss of the high-molecular-weight material.

(c) Glycogen could have been resynthesized and added to the glycogenin when the cells were fed glucose again.

(d) No difference between lanes 3 and 4 suggests that, by 1 hour, the glycogen molecules had attained maximum size in this cell line. Prolonged incubation does not apparently increase the amount of glycogen.

(e) α-Amylase removes essentially all of the glycogen, and so only the glycogenin remains.

Chapter 22

1. Glycerol + 2 NAD⁺ + P_i + ADP → pyruvate + ATP + H₂O + 2 NADH + H⁺

Glycerol kinase and glycerol phosphate dehydrogenase

2. The ready reversibility is due to the high-energy nature of the thioester in the acyl CoA.

3. To return the AMP to a form that can be phosphorylated by oxidative phosphorylation or substrate-level phosphorylation, another molecule of ATP must be expended in the reaction:



4. b, c, a, g, h, d, e, f.

5. The citric acid cycle. The reactions that take succinate to oxaloacetate, or the reverse, are similar to those of fatty acid metabolism (Section 17.2).

6. The next-to-last degradation product, acetoacetyl CoA, yields two molecules of acetyl CoA with the thiolysis by only one molecule of CoA.

7. Palmitic acid yields 106 molecules of ATP. Palmitoleic acid has a double bond between carbons C-9 and C-10. When palmitoleic acid is processed in β oxidation, one of the oxidation steps

(to introduce a double bond before the addition of water) will not take place, because a double bond already exists. Thus, FADH₂ will not be generated, and palmitoleic acid will yield 1.5 fewer molecules of ATP than palmitic acid, for a total of 104.5 molecules of ATP.

8.

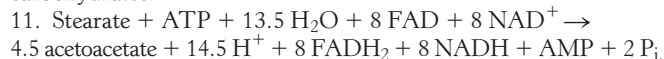
Activation fee to form the acyl CoA	-2 ATP
Seven rounds of yield:	
7 acetyl CoA at 10 ATP/acetyl CoA	+ 70 ATP
7 NADH at 2.5 ATP/NADH	+ 17.5 ATP
7 FADH ₂ at 1.5 ATP/FADH ₂	+ 10.5 ATP
Propionyl CoA, which requires an ATP to be converted into succinyl CoA	- 1 ATP
Succinyl CoA → succinate	+ 1 ATP (GTP)
Succinate → fumarate + FADH ₂	+ 1.5 ATP
FADH ₂ at 1.5 ATP/FADH ₂	
Fumarate → malate	
Malate → oxaloacetate + NADH	+ 2.5 ATP
NADH at 2.5 ATP/NADH	
Total	120 ATP

9. You might hate yourself in the morning, but at least you won't have to worry about energy. To form stearoyl CoA requires the equivalent of 2 molecules of ATP.

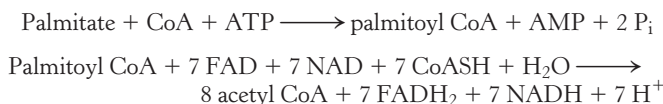


9 acetyl CoA at 10 ATP/acetyl CoA	+ 90 ATP
8 NADH at 2.5 ATP/NADH	+ 20 ATP
8 FADH ₂ at 1.5 ATP/FADH ₂	+ 12 ATP
Activation fee	-2.0
Total	122 ATP

10. Keep in mind that, in the citric acid cycle, 1 molecule of FADH₂ yields 1.5 ATP, 1 molecule of NADH yields 2.5 ATP, and 1 molecule of acetyl CoA yields 10 ATP. Two molecules of ATP are produced when glucose is degraded to 2 molecules of pyruvate. Two molecules of NADH also are produced, but the electrons are transferred to FADH₂ to enter the mitochondria. Each molecule of FADH₂ can generate 1.5 ATP. Each molecule of pyruvate will produce 1 molecule of NADH. Each molecule of acetyl CoA generates 3 molecules of NADH, 1 molecule of FADH₂, and 1 molecule of ATP. So, we have a total of 10 ATP per acetyl CoA, or 20 for the 2 molecules of acetyl CoA. The total for glucose is 30 ATP. Now, what about hexanoic acid? Caproic acid is activated to caproic CoA at the expense of 2 ATP, and so we are 2 ATP in the hole. The first cycle of β oxidation generates 1 FADH₂, 1 NADH, and 1 acetyl CoA. After the acetyl CoA has been run through the citric acid cycle, this step will have generated a total of 14 ATP. The second cycle of β oxidation generates 1 FADH₂ and 1 NADH but 2 acetyl CoA. After the acetyl CoA has been run through the citric acid cycle, this step will have generated a total of 24 ATP. The total is 36 ATP. Thus, the foul-smelling caproic acid has a net yield of 36 ATP. So on a per carbon basis, this fat yields 20% more ATP than does glucose, a manifestation of the fact that fats are more reduced than carbohydrates.



12. Palmitate is activated and then processed by β oxidation according to the following reactions.



The eight molecules of acetyl CoA combine to form four molecules of acetoacetate for release into the blood, and so they do not contribute to the energy yield in the liver. However, the FADH₂ and NADH generated in the preparation of acetyl CoA can be processed by oxidative phosphorylation to yield ATP.

$$1.5 \text{ ATP/FADH}_2 \times 7 = 10.5 \text{ ATP}$$

$$2.5 \text{ ATP/NADH} \times 7 = 17.5 \text{ ATP}$$

The equivalent of 2 ATP were used to form palmitoyl CoA. Thus, 26 ATP were generated for use by the liver.

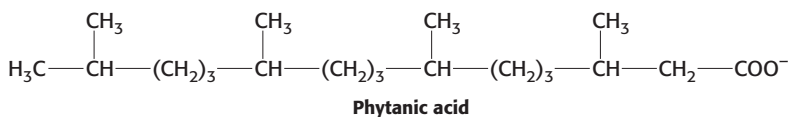
13. NADH produced with the oxidation to acetoacetate = 2.5 ATP. Acetoacetate is converted into acetoacetyl CoA.

Two molecules of acetyl CoA result from the hydrolysis of acetoacetyl CoA, each worth 10 ATP when processed by the citric acid cycle. Total ATP yield is 22.5.

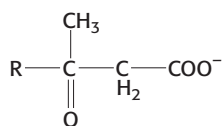
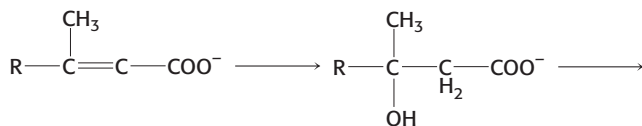
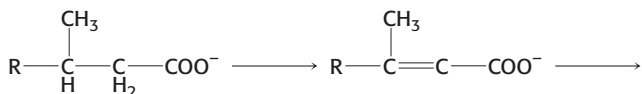
14. Because a molecule of succinyl CoA is used to form acetoacetyl CoA. Succinyl CoA could be used to generate one molecule of ATP (GTP), and so someone could argue that the yield is 21.5.

15. For fats to be combusted, not only must they be converted into acetyl CoA, but the acetyl CoA must be processed by the citric acid cycle. In order for acetyl CoA to enter the citric acid cycle, there must be a supply of oxaloacetate. Oxaloacetate can be formed by the metabolism of glucose to pyruvate and the subsequent carboxylation of pyruvate to form oxaloacetate.

16. (a)

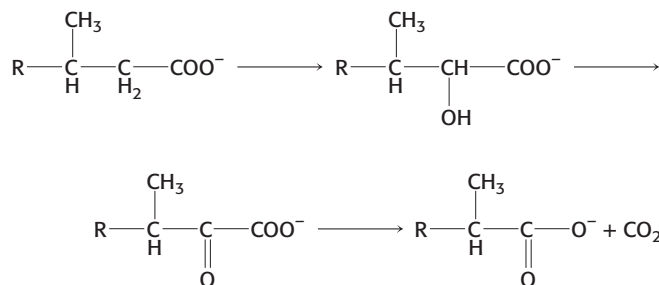


The problem with phytanic acid is that, as it undergoes β oxidation, we encounter the dreaded pentavalent carbon atom. Because the pentavalent carbon atom doesn't exist, β oxidation cannot take place and phytanic acid accumulates.



The dreaded pentavalent carbon atom

(b) Removing methyl groups, though theoretically possible, would be time consuming and, lacking in elegance. What would we do with the methyl groups? Our livers solve the problem by inventing α oxidation.

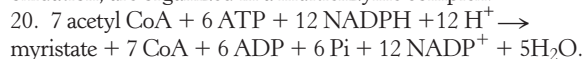


One round of α oxidation rather than β oxidation converts phytanic acid into a β-oxidation substrate.

17. The first oxidation removes two tritium atoms. The hydration adds nonradioactive H and OH. The second oxidation removes another tritium atom from the β-carbon atom. Thiolysis removes an acetyl CoA with only one tritium atom; so the tritium-to-carbon ratio is 1/2. This ratio will be the same for two of the acetates. The last one, however, does not undergo oxidation, and so all tritium remains. The ratio for this acetate is 3/2. The ratio for the entire molecule is then 5/6.

18. In the absence of insulin, lipid mobilization will take place to an extent that it overwhelms the ability of the liver to convert the lipids into ketone bodies.

19. (a) Oxidation in mitochondria; synthesis in the cytoplasm. (b) Coenzyme A in oxidation; acyl carrier protein for synthesis. (c) FAD and NAD⁺ in oxidation; NADPH for synthesis. (d) the L isomer of 3-hydroxyacyl CoA in oxidation; the D isomer in synthesis. (e) From carboxyl to methyl in oxidation; from methyl to carboxyl in synthesis. (f) The enzymes of fatty acid synthesis, but not those of oxidation, are organized in a multienzyme complex.



21. We will need six acetyl CoA units. One acetyl CoA unit will be used directly to become the two carbon atoms farthest from the acid end. The other five units must be converted into malonyl CoA. The synthesis of each malonyl CoA molecule costs a molecule of ATP; so 5 molecules of ATP will be required. Each round of elongation requires 2 molecules of NADPH, 1 molecule to reduce the keto group to an alcohol and 1 molecule to reduce the double bond. As a result, 10 molecules of NADPH will be required. Therefore, 5 molecules of ATP and 10 molecules of NADPH are required to synthesize lauric acid.

22. e, b, d, a, c.

23. Such a mutation would inhibit fatty acid synthesis because the enzyme cleaves cytoplasmic citrate to yield acetyl CoA for fatty acid synthesis.

24. (a) False. Biotin is required for acetyl CoA carboxylase activity.

(b) True.

(c) False. ATP is required to synthesize malonyl CoA.

(d) True.

(e) True.

(f) False. Fatty acid synthase is a dimer.

(g) True.

(h) False. Acetyl CoA carboxylase is stimulated by citrate, which is cleaved to yield its substrate acetyl CoA.

25. Fatty acids with odd numbers of carbon atoms are synthesized starting with propionyl ACP (instead of acetyl ACP), which is formed from propionyl CoA by acetyl transacetylase.

26. All of the labeled carbon atoms will be retained. Because we need 8 acetyl CoA molecules and only 1 carbon atom is labeled in the acetyl group, we will have 8 labeled carbon atoms. The only acetyl CoA used

ANSWERS TO PROBLEMS

directly will retain 3 tritium atoms. The 7 acetyl CoA molecules used to make malonyl CoA will lose 1 tritium atom on addition of the CO_2 and another one at the dehydration step. Each of the 7 malonyl CoA molecules will retain 1 tritium atom. Therefore, the total retained tritium is 10 atoms. The ratio of tritium to carbon is 1.25.

27. With a diet rich in raw eggs, avidin will inhibit fatty acid synthesis by reducing the amount of biotin required by acetyl CoA carboxylase. Cooking the eggs will denature avidin, and so it will no longer bind biotin.

28. The only acetyl CoA used directly, not in the form of malonyl CoA, provides the two carbon atoms at the ω end of the fatty acid chain. Because palmitic acid is a C_{16} fatty acid, acetyl CoA will have provided carbons 15 and 16.

29. HCO_3^- is attached to acetyl CoA to form malonyl CoA. When malonyl CoA condenses with acetyl CoA to form the four-carbon keto acyl CoA, the HCO_3^- is lost as CO_2 .

30. Phosphofructokinase controls the flux down the glycolytic pathway. Glycolysis functions to generate ATP or building blocks for biosynthesis, depending on the tissue. The presence of citrate in the cytoplasm indicates that those needs are met, and there is no need to metabolize glucose.

31. C-1 is more radioactive.

32. The mutant enzyme will be persistently active because it cannot be inhibited by phosphorylation. Fatty acid synthesis will be abnormally active. Such a mutation might lead to obesity.

33. (a) Palmitoleate; (b) linoleate; (c) linoleate; (d) oleate; (e) oleate; (f) linolenate.

34. Decarboxylation drives the condensation of malonyl ACP and acetyl ACP. In contrast, the condensation of two molecules of acetyl ACP is energetically unfavorable. In gluconeogenesis, decarboxylation drives the formation of phosphoenolpyruvate from oxaloacetate.

35. Fat mobilization in adipocytes is activated by phosphorylation. Hence, overproduction of the cAMP-activated kinase will lead to an accelerated breakdown of triacylglycerols and a depletion of fat stores.

36. Carnitine translocase deficiency and glucose 6-phosphate transporter deficiency.

37. In the fifth round of β oxidation, *cis*- Δ^2 -enoyl CoA is formed. Dehydration by the classic hydratase yields D-3-hydroxyacyl CoA, the wrong isomer for the next enzyme in β oxidation. This dead end is circumvented by a second hydratase that removes water to give *trans*- Δ^2 -enoyl CoA. The addition of water by the classic hydratase then yields L-3-hydroxyacyl CoA, the appropriate isomer. Thus, hydratases of opposite stereospecificities serve to *epimerize* (invert the configuration of) the 3-hydroxyl group of the acyl CoA intermediate.

38. The probability of synthesizing an error-free polypeptide chain decreases as the length of the chain increases. A single mistake can make the entire polypeptide ineffective. In contrast, a defective subunit can be spurned in the formation of a noncovalent multienzyme complex; the good subunits are not wasted.

39. The absence of ketone bodies is due to the fact that the liver, the source of ketone bodies in the blood, cannot oxidize fatty acids to produce acetyl CoA. Moreover, because of the impaired fatty acid oxidation, the liver becomes more dependent on glucose as an energy source. This dependency results in a decrease in gluconeogenesis and a drop in blood-glucose levels, which is exacerbated by the lack of fatty acid oxidation in muscle and a subsequent increase in glucose uptake from the blood.

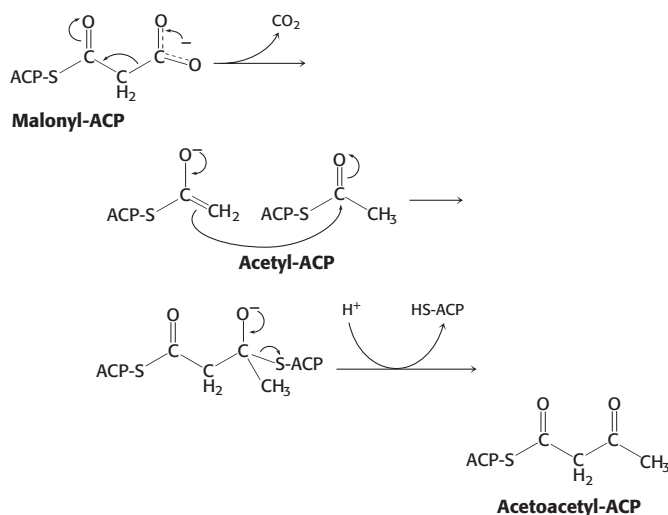
40. Peroxisomes enhance the degradation of fatty acids. Consequently, increasing the activity of peroxisomes could help

to lower levels of blood triglycerides. In fact, clofibrate is rarely used because of serious side effects.

41. Citrate works by facilitating the formation of active filaments from inactive monomers. In essence, it increases the number of active sites available, or the concentration of enzyme. Consequently, its effect is visible as an increase in the value of V_{\max} . Allosteric enzymes that alter their V_{\max} values in response to regulators are sometimes called V-class enzymes. The more common type of allosteric enzyme, in which K_m is altered, comprises K-class enzymes. Palmitoyl CoA causes depolymerization and thus inactivation.

42. The thiolate anion of CoA attacks the 3-keto group to form a tetrahedral intermediate. This intermediate collapses to form acyl CoA and the enolate anion of acetyl CoA. Protonation of the enolate yields acetyl CoA.

43.



44. (a) Fats burn in the flame of carbohydrates. Without carbohydrates, there would be no anapleurotic reactions to replenish the components of the citric acid cycle. With a diet of fats only, the acetyl CoA from fatty acid degradation would build up.

(b) Acetone from ketone bodies

(c) Yes. Odd-chain fatty acids would lead to the production of propionyl CoA, which can be converted into succinyl CoA, a citric acid cycle component. It would serve to replenish the citric acid cycle and mitigate the halitosis.

45. A labeled fat can enter the citric acid cycle as acetyl CoA and yield labeled oxaloacetate, but only after two carbon atoms have been lost as CO_2 . Consequently, even though oxaloacetate may be labeled, there can be no net synthesis of oxaloacetate and hence no net synthesis of glucose or glycogen.

46. (a) The V_{\max} is decreased and the K_m is increased. V_{\max} (wild type) = $13 \text{ nmol minute}^{-1} \text{ mg}^{-1}$; K_m (wild type) = $45 \text{ }\mu\text{M}$; V_{\max} (mutant) = $8.3 \text{ nmol minute}^{-1} \text{ mg}^{-1}$; K_m (mutant) = $74 \text{ }\mu\text{M}$.

(b) Both the V_{\max} and the K_m are decreased. V_{\max} (wild type) = $41 \text{ nmol minute}^{-1} \text{ mg}^{-1}$; K_m (wild type) = $104 \text{ }\mu\text{M}$; V_{\max} (mutant) = $23 \text{ nmol minute}^{-1} \text{ mg}^{-1}$; K_m (mutant) = $69 \text{ }\mu\text{M}$.

(c) The wild type is significantly more sensitive to malonyl CoA.

(d) With respect to carnitine, the mutant displays approximately 65% of the activity of the wild type; with respect to palmitoyl CoA, approximately 50% activity. On the other hand, $10 \text{ }\mu\text{M}$ of malonyl CoA inhibits approximately 80% of the wild type but has essentially no effect on the mutant enzyme.

(e) The glutamate appears to play a more prominent role in regulation by malonyl CoA than in catalysis.

Chapter 23

1. When the proteins are denatured, all of the peptide bonds are accessible to proteolytic enzymes. If the three-dimensional structure of a protein is maintained, access to many peptide bonds is denied to the proteolytic enzymes.

2. First, the ubiquitin-activating enzyme (E1) links ubiquitin to a sulfhydryl group on E1 itself. Next, the ubiquitin is transferred to a cysteine residue on the ubiquitin-conjugating enzyme (E2) by E2. The ubiquitin-protein ligase (E3), using the ubiquitinated E2 as a substrate, transfers the ubiquitin to the target protein.

3. (a) 7; (b) 4; (c) 2; (d) 10; (e) 5; (f) 3; (g) 9; (h) 1; (i) 6; (j) 8.

4. (a) The ATPase activity of the 26S proteasome resides in the 19S subunit. The energy of ATP hydrolysis could be used to unfold the substrate, which is too large to enter the catalytic barrel. ATP may also be required for translocation of the substrate into the barrel.

(b) Substantiates the answer in part a. Because they are small, the peptides do not need to be unfolded. Moreover, small peptides could probably enter all at once and not require translocation.

5. (a) Pyruvate; (b) oxaloacetate; (c) α -ketoglutarate; (d) α -ketoisocaproate; (e) phenylpyruvate; (f) hydroxyphenylpyruvate.

6. (a) $\text{Aspartate} + \alpha\text{-ketoglutarate} + \text{GTP} + \text{ATP} + 2\text{H}_2\text{O} + \text{NADH} + \text{H}^+ \rightarrow \frac{1}{2}\text{glucose} + \text{glutamate} + \text{CO}_2 + \text{ADP} + \text{GDP} + \text{NAD}^+ + 2\text{P}_i$.

The required coenzymes are pyridoxal phosphate in the transamination reaction and NAD^+/NADH in the redox reactions.

(b) $\text{Aspartate} + \text{CO}_2 + \text{NH}_4^+ + 3\text{ATP} + \text{NAD}^+ + 4\text{H}_2\text{O} \rightarrow \text{oxaloacetate} + \text{urea} + 2\text{ADP} + 4\text{P}_i + \text{AMP} + \text{NADH} + \text{H}^+$.

7. In the eukaryotic proteasome, the distinct β subunits have different substrate specificities, allowing proteins to be more thoroughly degraded.

8. The six subunits probably exist as a heterohexamer. Cross-linking experiments could test the model and help determine which subunits are adjacent to one another.

9. Thiamine pyrophosphate

10. Aminotransferases transfer the α -amino group to α -ketoglutarate to form glutamate. Glutamate is oxidatively deaminated to form an ammonium ion.

11. Aspartate (oxaloacetate), glutamate (α -ketoglutarate), alanine (pyruvate).

12. Serine and threonine

13. They are either fuels for the citric acid cycle, components of the citric acid cycle, or molecules that can be converted into a fuel for the citric acid cycle in one step.

14. It acts as an electron sink.

15. Carbamoyl phosphate and aspartate

16. (a) 4; (b) 5; (c) 1; (d) 6; (e) 7; (f) 3; (g) 2.

17. A, arginine; B, citrulline; C, ornithine; D, arginosuccinate.

The order of appearance: C, B, D, E.

18. $\text{CO}_2 + \text{NH}_4^+ + 3\text{ATP} + \text{NAD}^+ + \text{aspartate} + 3\text{H}_2\text{O} \rightarrow \text{urea} + 2\text{ADP} + 2\text{P}_i + \text{AMP} + \text{PP}_i + \text{NADH} + \text{H}^+ + \text{oxaloacetate}$.

Four high-transfer-potential phosphoryl groups are spent. Note, however, that an NADH is generated if fumarate is converted into oxaloacetate. NADH can generate 2.5 ATP in the electron-transport chain. Taking these ATP into account, only 1.5 high-transfer-potential phosphoryl groups are spent.

19. The synthesis of fumarate by the urea cycle is important because it links the urea cycle and the citric acid cycle. Fumarate is hydrated

to malate, which, in turn, is oxidized to oxaloacetate. Oxaloacetate has several possible fates: (1) transamination to aspartate, (2) conversion into glucose by the gluconeogenic pathway, (3) condensation with acetyl CoA to form citrate, or (4) conversion into pyruvate. You can collect.

20. Ornithine transcarbamoylase (analogous to PALA; see Chapter 10).

21. Ammonia could lead to the amination of α -ketoglutarate, producing a high concentration of glutamate in an unregulated fashion. α -Ketoglutarate for glutamate synthesis could be removed from the citric acid cycle, thereby diminishing the cell's respiration capacity.

22. The mass spectrometric analysis strongly suggests that three enzymes—pyruvate dehydrogenase, α -ketoglutarate dehydrogenase, and the branched-chain α -ketoacid dehydrogenase—are deficient. Most likely, the common E_3 component of these enzymes is missing or defective. This proposal could be tested by purifying these three enzymes and assaying their ability to catalyze the regeneration of lipoamide.

23. Benzoate, phenylacetate, and arginine would be given to supply a protein-restricted diet. Nitrogen would emerge in hippurate, phenylacetylglutamine, and citrulline.

24. The liver is the primary tissue for capturing nitrogen as urea. If the liver is damaged (for instance, by hepatitis or the excessive consumption of alcohol), free ammonia is released into the blood.

25. This defect can be partly bypassed by providing a surplus of arginine in the diet and restricting the total protein intake. In the liver, arginine is split into urea and ornithine, which then reacts with carbamoyl phosphate to form citrulline. This urea-cycle intermediate condenses with aspartate to yield argininosuccinate, which is then excreted. Note that two nitrogen atoms—one from carbamoyl phosphate and the other from aspartate—are eliminated from the body per molecule of arginine provided in the diet. In essence, argininosuccinate substitutes for urea in carrying nitrogen out of the body. The formation of argininosuccinate removes the nitrogen, and the restriction on protein intake relieves the aciduria.

26. Aspartame, a dipeptide ester (L-aspartyl-L-phenylalanine methyl ester), is hydrolyzed to L-aspartate and L-phenylalanine. High levels of phenylalanine are harmful in phenylketonurics.

27. N-Acetylglutamate is synthesized from acetyl CoA and glutamate. Once again, acetyl CoA serves as an activated acetyl donor. This reaction is catalyzed by N-acetylglutamate synthase.

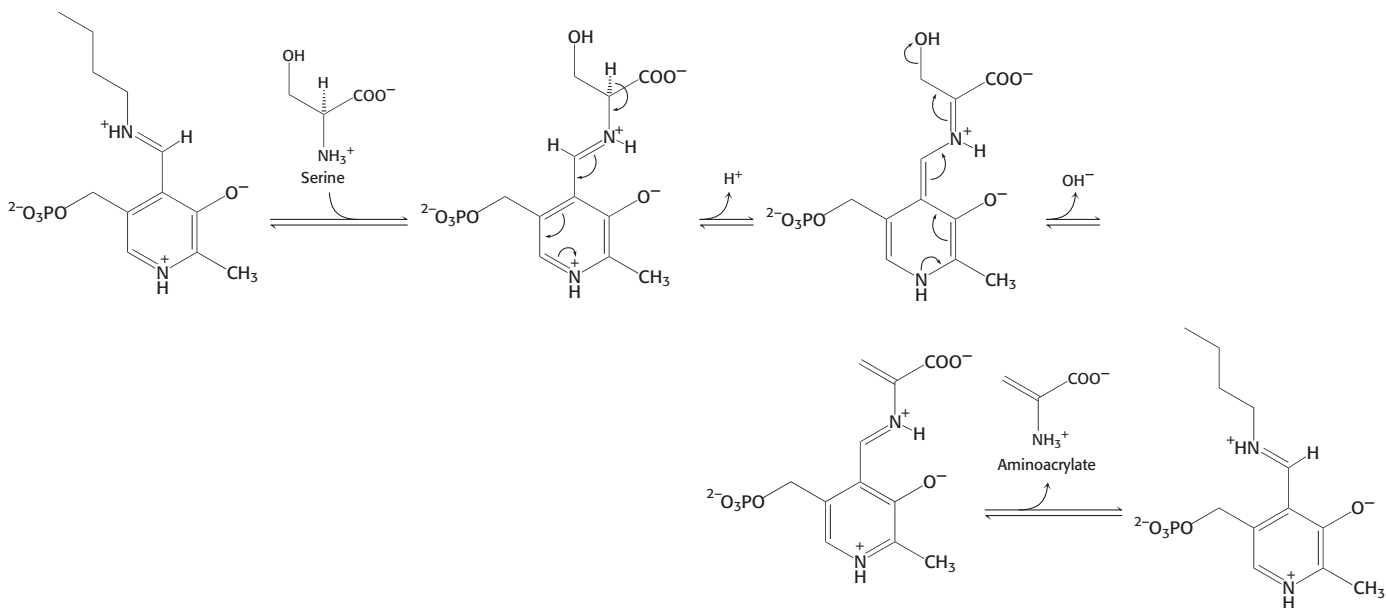
28. Not all proteins are created equal: some are more important than others. Some proteins would be degraded to provide the missing amino acid. The nitrogen from the other amino acids would be excreted as urea. Consequently, more nitrogen would be excreted than ingested.

29. The carbon skeletons of ketogenic amino acids can be converted into ketone bodies or fatty acids. Only leucine and lysine are purely ketogenic. Glucogenic amino acids are those whose carbon skeletons can be converted into glucose.

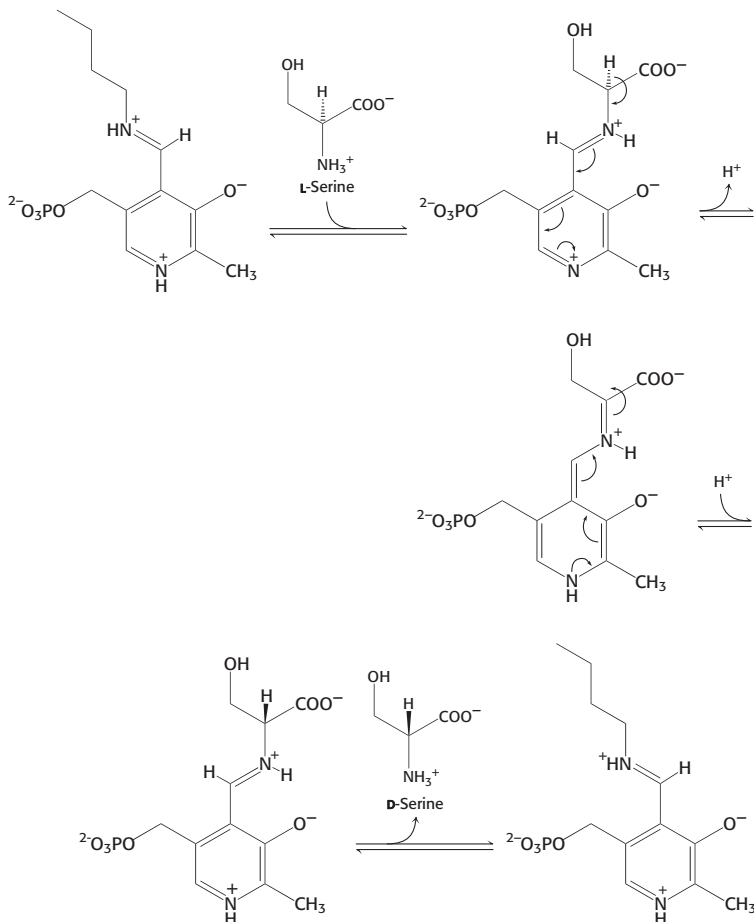
30. The branched-chain amino acids leucine, isoleucine, and valine. The required enzyme is the branched-chain α -ketoacid dehydrogenase complex.

31. Pyruvate (glycolysis and gluconeogenesis), acetyl CoA (citric acid cycle and fatty acid synthesis), acetoacetyl CoA (ketone-body formation), α -ketoglutarate (citric acid cycle), succinyl CoA (citric acid cycle), fumarate (citric acid cycle), and oxaloacetate (citric acid cycle and gluconeogenesis).

32.



33.



The equilibrium constant for the interconversion of L-serine and D-serine is exactly 1.

34. Exposure of such a domain suggests that a component of a multiprotein complex has failed to form properly or that one component has been synthesized in excess. This exposure leads to rapid degradation and the restoration of appropriate stoichiometries.

35. (a) Depletion of glycogen stores. When they are gone, proteins must be degraded to meet the glucose needs of the brain. The resulting amino acids are deaminated, and the nitrogen atoms are excreted as urea.

(b) The brain has adapted to the use of ketone bodies, which are derived from fatty acid catabolism. In other words, the brain is being powered by fatty acid breakdown.

(c) When the glycogen and lipid stores are gone, the only available energy source is protein.

36. Deamination to α -keto- β -methylvalerate; oxidative decarboxylation to α -methylbutyryl CoA; oxidation to tiglyl CoA; hydration, oxidation, and thiolysis yield acetyl CoA and propionyl CoA; propionyl CoA to succinyl CoA.

37. Glycogen phosphorylase. The coenzyme serves as an acid-base catalyst.

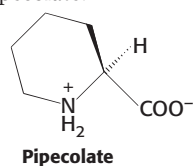
38. In the Cori cycle, the carbon atoms are transferred from muscle to liver as lactate. For lactate to be of any use, it must be reduced to pyruvate. This reduction requires high-energy electrons in the form of NADH. When the carbon atoms are transferred as alanine, transamination yields pyruvate directly.

39. (a) Virtually no digestion in the absence of nucleotides. (b) Protein digestion is greatly stimulated by the presence of ATP. (c) AMP-PNP, a nonhydrolyzable analog of ATP, is no more effective than ADP. (d) The proteasome requires neither ATP nor PAN to digest small substrates. (e) PAN and ATP hydrolysis may be required to unfold the peptide and translocate it into the proteasome. (f) Although *Thermoplasma* PAN is not as effective with the other proteasomes, it nonetheless results in threefold to fourfold stimulation of digestion. (g) In light of the fact that the archaea and eukarya diverged several billion years ago, the fact that

Thermoplasma PAN can stimulate rabbit muscle suggests homology not only between the proteasomes, but also between PAN and the 19S subunit (most likely the ATPases) of the mammalian 26S proteasome.

Chapter 24

- Nitrogen fixation is the conversion of atmospheric N_2 into NH_3^+ . Diazotrophic (nitrogen-fixing) microorganisms are able to fix nitrogen.
- Oxaloacetate, pyruvate, ribose-5-phosphate, phosphoenolpyruvate, erythrose-4-phosphate, α -ketoglutarate, and 3-phosphoglycerate.
- Human beings do not have the biochemical pathways to synthesize certain amino acids from simpler precursors. Consequently, these amino acids are "essential" and must be obtained from the diet.
- $Glucose + 2 ADP + 2 P_i + 2 NAD^+ + 2 glutamate \rightarrow 2 alanine + 2 \alpha\text{-ketoglutarate} + 2 ATP + 2 NADH + 2 H_2O + 2 H^+$.
- $N_2 \rightarrow NH_4^+ \rightarrow glutamate \rightarrow serine \rightarrow glycine \rightarrow \delta\text{-aminolevulinatate} \rightarrow porphobilinogen \rightarrow heme$.
- False. Nitrogen fixation is thermodynamically favorable. Nitrogenase is required because the process is kinetically disfavored.
- Pyridoxal phosphate (PLP)
- S-Adenosylmethionine, tetrahydrofolate, and methylcobalamin.
- (a) N^5, N^{10} -Methylenetetrahydrofolate;
(b) N^5 -methyltetrahydrofolate.
- γ -Glutamyl phosphate is a likely reaction intermediate.
- The synthesis of asparagine from aspartate passes through an acyl-adenylate intermediate. One of the products of the reaction will be ^{18}O -labeled AMP.
- The administration of glycine leads to the formation of isovalerylglycine. This water-soluble conjugate, in contrast with isovaleric acid, is excreted very rapidly by the kidneys.
- The nitrogen atom shaded red is derived from glutamine. The carbon atom shaded blue is derived from serine.
- They carry out nitrogen fixation. The absence of photosystem II provides an environment in which O_2 is not produced. Recall that the nitrogenase is very rapidly inactivated by O_2 .
- The cytoplasm is a reducing environment, whereas the extracellular milieu is an oxidizing environment.
- (a) None; (b) D-glutamate and oxaloacetate.
- Succinyl CoA is formed in the mitochondrial matrix.
- Alanine from pyruvate; aspartate from oxaloacetate; glutamate from α -ketoglutarate.
- Lysine cyclodeaminase converts L-lysine into the six-membered ring analog of proline, also referred to as L-homoproline or L-pipecolate:



- Y could inhibit the $C \rightarrow D$ step, Z could inhibit the $C \rightarrow F$ step, and C could inhibit $A \rightarrow B$. This scheme is an example of sequential feedback inhibition. Alternatively, Y could inhibit the $C \rightarrow D$ step, Z could inhibit the $C \rightarrow F$ step, and the $A \rightarrow B$

step would be inhibited only in the presence of both Y and Z. This scheme is called concerted feedback inhibition.

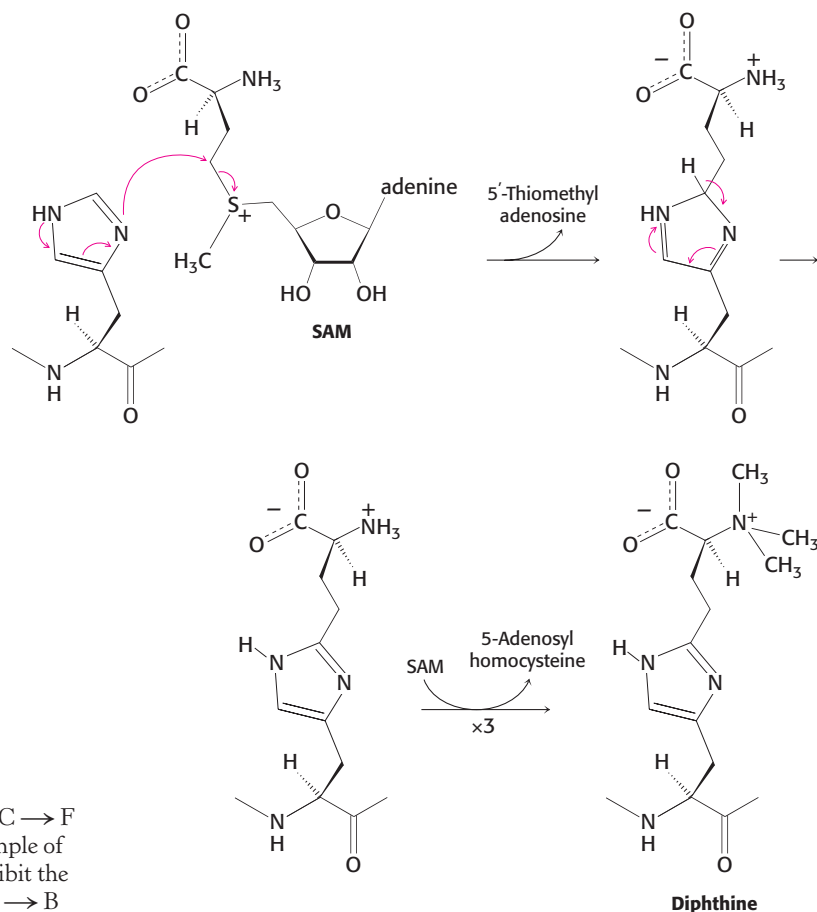
21. The rate of the $A \rightarrow B$ step in the presence of high levels of Y and Z would be $24 s^{-1}$ ($0.6 \times 0.4 \times 100 s^{-1}$).

22. Lysine 258 is absolutely essential for the activity of aspartate aminotransferase, as it is responsible both for the formation of the internal aldimine with the pyridoxal phosphate cofactor and for transferring the proton between the ketimine and quinonoid intermediates. Mutation of this residue to cysteine would be expected to dramatically impair catalysis, as cysteine cannot occupy the same space as lysine and also exhibits differing pK_a properties. Upon treatment with 2-bromoethylamine, however, the resulting thioether now has a shape and pK_a similar to the original lysine side chain. Hence, some catalytic activity is restored.

23. An external aldimine forms with SAM, which is deprotonated to form the quinonoid intermediate. The deprotonated carbon atom attacks the carbon atom adjacent to the sulfur atom to form the cyclopropane ring and release methylthioadenosine, the other product.

24. An external aldimine forms with L-serine, which is deprotonated to form the quinonoid intermediate. This intermediate is reprotonated on its opposite face to form an aldimine with D-serine. This compound is cleaved to release D-serine. The equilibrium constant for a racemization reaction is 1 because the reactant and product are exact mirror images of each other.

25. (a) In the first step, histidine attacks the methylene group from the methionine subgroup of SAM (rather than the usual methyl substituent), resulting in the transfer of an aminocarboxypropyl group. Three subsequent conventional SAM-mediated methylations of the primary amine yield diphthine.



- (b) In this chapter, we have observed two examples of an ATP-dependent conversion of a carboxylate into an amide: glutamine synthetase, which uses an acyl-phosphate intermediate, and asparagine synthetase, which uses an acyl-adenylate intermediate. Either mechanism is possible in formation of diphthamide from diphthine.
26. Synthesis from oxaloacetate and α -ketoglutarate would deplete the citric acid cycle, which would decrease ATP production. Anapleurotic reactions would be required to replenish the citric acid cycle.
27. SAM is the donor for DNA methylation reactions that protect a host from digestion by its own restriction enzymes. A lack of SAM would render the bacterial DNA susceptible to digestion by the cell's own restriction enzymes.
28. Acetate \rightarrow acetyl-CoA \rightarrow citrate \rightarrow isocitrate \rightarrow α -ketoglutarate \rightarrow succinyl-CoA.
29. (a) Asparagine is much more abundant in the dark. More glutamine is present in the light. These amino acids show the most dramatic effects. Glycine also is more abundant in the light.
- (b) Glutamine is a more metabolically reactive amino acid, used in the synthesis of many other compounds. Consequently, when energy is available as light, glutamine will be preferentially synthesized. Asparagine, which carries more nitrogen per carbon atom and is thus a more-efficient means of storing nitrogen when energy is short, is synthesized in the dark. Glycine is more prevalent in the light because of photorespiration.
- (c) White asparagus has an especially high concentration of asparagine, which accounts for its intense taste. All asparagus has a large amount of asparagine. In fact, as suggested by its name, asparagine was first isolated from asparagus.

Chapter 25

- In de novo synthesis, the nucleotides are synthesized from simpler precursor compounds, in essence from scratch. In salvage pathways, preformed bases are recovered and attached to riboses.
- Carbon 2 and nitrogen 3 come from carbamoyl phosphate. Nitrogen 1 and carbons 4, 5, and 6 are derived from aspartate.
- Nitrogen 1: aspartate; carbon 2: N^{10} -formyltetrahydrofolate; nitrogen 3: glutamine; carbons 4 and 5 and nitrogen 7: glycine; carbon 6: CO_2 ; carbon 8: N^{10} -formyltetrahydrofolate; nitrogen 9: glutamine.
- Energy currency: ATP; signal transduction: ATP and GTP; RNA synthesis: ATP, GTP, CTP, and UTP; DNA synthesis: dATP, dCTP, dGTP, and TTP; components of coenzymes: ATP in CoA, FAD, and $NAD(P)^+$; carbohydrate synthesis: UDP-glucose. They are just some of the uses.
- A nucleoside is a base attached to ribose. A nucleotide is a nucleoside with the ribose bearing one or more phosphates.
- (a) 9; (b) 7; (c) 6; (d) 10; (e) 2; (f) 4; (g) 1; (h) 11; (i) 8; (j) 3; (k) 5.
- Substrate channeling is the process whereby the product of one active site moves to become a substrate at another active site without ever leaving the enzyme. A channel connects the active sites. Substrate channeling greatly enhances enzyme efficiency and minimizes the diffusion of a substrate to an active site.
- $Glucose + 2 ATP + 2 NADP^+ + H_2O \rightarrow PRPP + CO_2 + ADP + AMP + 2 NADPH + 3 H^+$.
- $Glutamine + aspartate + CO_2 + 2 ATP + NAD^+ \rightarrow$ orotate $+ 2 ADP + 2 P_i + glutamate + NADH + H^+$.
- (a, c, and d) PRPP; (b) carbamoyl phosphate.
- PRPP and formylglycinamide ribonucleotide
- $dUMP + serine + NADPH + H^+ \rightarrow dTMP + NADP^+ + glycine$.

- There is a deficiency of N^{10} -formyltetrahydrofolate. Sulfanilamide inhibits the synthesis of folate by acting as an analog of *p*-aminobenzoate, one of the precursors of folate.
- (a) Cell A cannot grow in a HAT medium, because it cannot synthesize TMP either from thymidine or from dUMP. Cell B cannot grow in this medium, because it cannot synthesize purines by either the de novo pathway or the salvage pathway. Cell C can grow in a HAT medium because it contains active thymidine kinase from cell B (enabling it to phosphorylate thymidine to TMP) and hypoxanthine guanine phosphoribosyltransferase from cell A (enabling it to synthesize purines from hypoxanthine by the salvage pathway).
- (b) Transform cell A with a plasmid containing foreign genes of interest and a functional thymidine kinase gene. The only cells that will grow in a HAT medium are those that have acquired a thymidylate kinase gene; nearly all of these transformed cells will also contain the other genes on the plasmid.
- The reciprocal substrate relation refers to the fact that AMP synthesis requires GTP, whereas GMP synthesis requires ATP. These requirements tend to balance the synthesis of ATP and GTP.
- Ring carbon 6 in cytosine will be labeled. In guanine, only carbon 5 will be labeled with ^{13}C .
- The enzyme that uses ammonia synthesizes carbamoyl phosphate for a reaction with ornithine, the first step of the urea cycle. The enzyme that uses glutamine synthesizes carbamoyl phosphate for use in the first step of pyrimidine biosynthesis.
- These patients have a high level of urate because of the breakdown of nucleic acids. Allopurinol prevents the formation of kidney stones and blocks other deleterious consequences of hyperuricemia by preventing the formation of urate.
- The free energies of binding are -57.7 (wild type), -49.8 (Asn 27), and -38.1 (Ser 27) kJ mol^{-1} (-13.8 , -11.9 , and -9.1 kcal mol^{-1} , respectively). The loss in binding energy is 7.9 kJ mol^{-1} (1.9 kcal mol^{-1}) and 19.7 kJ mol^{-1} (4.7 kcal mol^{-1}).
- Inosine or hypoxanthine could be administered.
- N*-1 in both cases, and the amine group linked to C-6 in ATP.
- Nitrogen atoms 3 and 9 in the purine ring
- Allopurinol, an analog of hypoxanthine, is a suicide inhibitor of xanthine oxidase.
- An oxygen atom is added to allopurinol to form alloxanthine.
-

The synthesis of carbamoyl phosphate requires 2 ATP	2 ATP
The formation of PRPP from ribose 5-phosphate yields an AMP*	2 ATP
The conversion of UMP to UTP requires 2 ATP	2 ATP
The conversion of UTP to CTP requires 1 ATP	1 ATP
Total	7 ATP

*Remember that AMP is the equivalent of 2 ATP because an ATP must be expended to generate ADP, the substrate for ATP synthesis.

- (a) Carboxyaminoimidazole ribonucleotide; (b) glycinamide ribonucleotide; (c) phosphoribosyl amine; (d) formylglycinamide ribonucleotide.
- The first reaction proceeds by phosphorylation of glycine to form an acyl phosphate followed by nucleophilic attack by the amine of phosphoribosylamine to displace orthophosphate. The second reaction consists of adenylation of the carbonyl group of xanthylate followed by nucleophilic attack by ammonia to displace AMP.

28. The $-\text{NH}_2$ group attacks the carbonyl carbon atom to form a tetrahedral intermediate. Removal of a proton leads to the elimination of water to form inosinate.

29. PRPP is the activated intermediate in the synthesis of phosphoribosylamine in the de novo pathway of purine formation; of purine nucleotides from free bases by the salvage pathway; of orotidylate in the formation of pyrimidines; of nicotinate ribonucleotide; of phosphoribosyl ATP in the pathway leading to histidine; and of phosphoribosylanthranilate in the pathway leading to tryptophan.

30. (a) cAMP; (b) ATP; (c) UDP-glucose; (d) acetyl CoA; (e) NAD^+ , FAD; (f) dideoxynucleotides; (g) fluorouracil; (h) CTP inhibits ATCase.

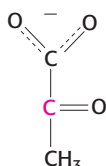
31. In vitamin B_{12} deficiency, methyltetrahydrofolate cannot donate its methyl group to homocysteine to regenerate methionine. Because the synthesis of methyltetrahydrofolate is irreversible, the cell's tetrahydrofolate will ultimately be converted into this form. No formyl or methylene tetrahydrofolate will be left for nucleotide synthesis. Vitamin B_{12} is also required to metabolize propionyl CoA generated in the oxidation of odd-chain fatty acids and in the degradation of methionine.

32. Because folate is required for nucleotide synthesis, cells that are dividing rapidly would be most readily affected. They would include cells of the intestine, which are constantly replaced, and precursors to blood cells. A lack of intestinal cells and blood cells would account for the symptoms often observed.

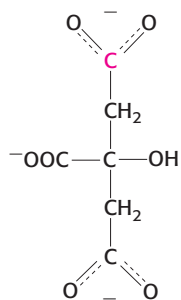
33. The cytoplasmic level of ATP in the liver falls and that of AMP rises above normal in all three conditions. The excess AMP is degraded to urate.

34. Succinate \rightarrow malate \rightarrow oxaloacetate by the citric acid cycle. Oxaloacetate \rightarrow aspartate by transamination, followed by pyrimidine synthesis. Carbons 4, 5, and 6 are labeled.

35. Glucose will most likely be converted into two molecules of pyruvate, one of which will be labeled in the 2 position:

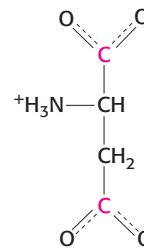


Now consider two common fates of pyruvate—conversion into acetyl CoA and subsequent processing by the citric acid cycle or carboxylation by pyruvate carboxylase to form oxaloacetate. Formation of citrate by condensing the labeled pyruvate with oxaloacetate will yield labeled citrate:



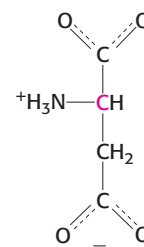
The labeled carbon will be retained through one round of the citric acid cycle but, on the formation of the symmetric succinate, the label will appear in two different positions. Thus, when succinate

is metabolized to oxaloacetate, which may be aminated to form aspartate, two carbons will be labeled:



When this aspartate is used to form uracil, the labeled COO^- attached to the α -carbon is lost and the other COO^- becomes incorporated into uracil as carbon 4.

Suppose, instead, that labeled 2- $[^{14}\text{C}]$ pyruvate is carboxylated to form oxaloacetate and processed to form aspartate. In this case, the α -carbon of aspartate bears the label.



When this aspartate is used to synthesize uracil, carbon 6 bears the label.

36. (a) Some ATP can be salvaged from the ADP that is being generated. (b) There are equal numbers of high-phosphoryl-transfer-potential groups on each side of the equation. (c) Because the adenylate kinase reaction is at equilibrium, the removal of AMP would lead to the formation of more ATP. (d) Essentially, the cycle serves as an anaplerotic reaction for the generation of the citric acid cycle intermediate fumarate.

37. (i) The formation of 5-aminoimidazole-4-carboxamide ribonucleotide from 5-aminoimidazole-4-(*N*-succinylcarboxamide) ribonucleotide in the synthesis of IMP. (ii) The formation of AMP from adenylosuccinate. (iii) The formation of arginine from argininosuccinate in the urea cycle.

38. Allopurinol is an inhibitor of xanthine oxidase, which is on the pathway for urate synthesis. In your pet duck, this pathway is the means by which excess nitrogen is excreted. If xanthine oxidase were inhibited in your duck, nitrogen could not be excreted, with severe consequences such as the formation of a dead duck.

Chapter 26

1. Glycerol 3-phosphate is the foundation for both triacylglycerol and phospholipid synthesis. Glycerol 3-phosphate is acylated twice to form phosphatidate. In triacylglycerol synthesis, the phosphoryl group is removed from glycerol 3-phosphate to form diacylglycerol, which is then acylated to form triacylglycerol. In phospholipid synthesis, phosphatidate commonly reacts with CTP to form CDP-diacylglycerol, which then reacts with an alcohol to form a phospholipid. Alternatively, diacylglycerol may react with a CDP-alcohol to form a phospholipid.

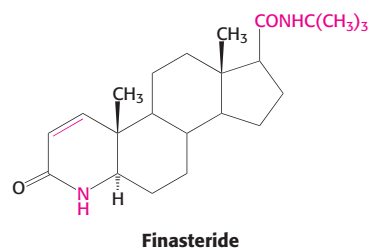
2. Glycerol 3-phosphate is formed primarily by the reduction of dihydroxyacetone phosphate, a gluconeogenic intermediate, and to a lesser extent by the phosphorylation of glycerol.

ANSWERS TO PROBLEMS

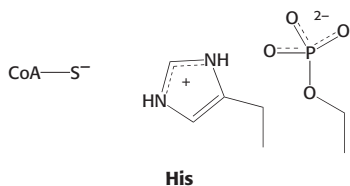
3. Glycerol + 4 ATP + 3 fatty acids + 4 H₂O → triacylglycerol + ADP + 3 AMP + 7 P_i + 4 H⁺.
4. Glycerol + 3 ATP + 2 fatty acids + 2 H₂O + CTP + ethanolamine → phosphatidylethanolamine + CMP + ADP + 2 AMP + 6 P_i + 3 H⁺.
5. Three. One molecule of ATP to form phosphorylethanolamine and two molecules of ATP to regenerate CTP from CMP.
6. All are synthesized from ceramide. In sphingomyelin, the terminal hydroxyl group of ceramide is modified with phosphorylcholine. In a cerebroside, the hydroxyl group has a glucose or galactose attached. In a ganglioside, oligosaccharide chains are attached to the hydroxyl group.
7. (i) Activate the diacylglycerol as CDP-DAG. (ii) Activate the alcohol as CDP-alcohol. (iii) Use the base-exchange reaction.
8. (a) CDP-diacylglycerol; (b) CDP-ethanolamine; (c) acyl CoA; (d) phosphatidylcholine; (e) UDP-glucose or UDP-galactose; (f) UDP-galactose; (g) geranyl pyrophosphate.
9. Such mutations are seen in mice. The amount of adipose tissue would decrease severely because diacylglycerol could not be formed. Normally, diacylglycerol is acylated to form triacylglycerols. If there were deficient phosphatidic acid phosphatase activity, no triacylglycerols would form.
10. (i) The synthesis of activated isoprene units (isopentyl pyrophosphate), (ii) the condensation of six of the activated isoprene units to form squalene, and (iii) cyclization of the squalene to form cholesterol.
11. The amount of reductase and its activity control the regulation of cholesterol biosynthesis. Transcriptional control is mediated by SREBP. Translation of the reductase mRNA also is controlled. The reductase itself may undergo regulated proteolysis. Finally, the activity of the reductase is inhibited by phosphorylation by AMP kinase when ATP levels are low.
12. (a and b) None, because the label is lost as CO₂.
13. The hallmark of this genetic disease is elevated cholesterol levels in the blood of even young children. The excess cholesterol is taken up by macrophages, which eventually results in the formation of plaques and heart disease. There are many mutations that cause the disease, but all result in malfunctioning of the LDL receptor.
14. The categories of mutations are: (i) no receptor is synthesized; (ii) receptors are synthesized but do not reach the plasma membrane, because they lack signals for intracellular transport or do not fold properly; (iii) receptors reach the cell surface, but they fail to bind LDL normally because of a defect in the LDL-binding domain; (iv) receptors reach the cell surface and bind LDL, but they fail to cluster in coated pits because of a defect in their carboxyl-terminal regions.
15. "None of your business" and "I don't talk biochemistry until after breakfast" are appropriate but rude and uninformative answers. A better answer might be: "Although it is true that cholesterol is a precursor to steroid hormones, the rest of the statement is oversimplified. Cholesterol is a component of membranes, and membranes literally define cells, and cells make up tissues. But to say that cholesterol 'makes' cells and tissues is wrong."
16. Statins are competitive inhibitors of HMG-CoA reductase. They are used as drugs to inhibit cholesterol synthesis in patients with high levels of cholesterol.
17. No. Cholesterol is essential for membrane function and as a precursor for bile salts and steroid hormones. The complete lack of cholesterol would be lethal.
18. Deamination of cytidine to uridine changes CAA (Gln) into UAA (stop).
19. The LDL contains apolipoprotein B-100, which binds to an LDL receptor on the cell surface in a region known as a coated pit. On binding, the complex is internalized by endocytosis to

form an internal vesicle. The vesicle is separated into two components. One, with the receptor, is transported back to the cell surface and fuses with the membrane, allowing continued use of the receptor. The other vesicle fuses with lysosomes inside the cell. The cholesteryl esters are hydrolyzed, and free cholesterol is made available for cellular use. The LDL protein is hydrolyzed to free amino acids.

20. Benign prostatic hypertrophy can be treated by inhibiting 5 α -reductase. Finasteride, the 4-azasteroid analog of dihydrotestosterone, competitively inhibits the reductase but does not act on androgen receptors. Patients taking finasteride have a markedly lower plasma level of dihydrotestosterone and a nearly normal level of testosterone. The prostate gland becomes smaller, whereas testosterone-dependent processes such as fertility, libido, and muscle strength appear to be unaffected.



21. Patients who are most sensitive to debrisoquine have a deficiency of a liver P450 enzyme encoded by a member of the CYP2 subfamily. This characteristic is inherited as an autosomal recessive trait. The capacity to degrade other drugs may be impaired in people who hydroxylate debrisoquine at a slow rate, because a single P450 enzyme usually handles a broad range of substrates.
22. Many hydrophobic odorants are deactivated by hydroxylation. Molecular oxygen is activated by a cytochrome P450 monooxygenase. NADPH serves as the reductant. One oxygen atom of O₂ goes into the odorant substrate, whereas the other is reduced to water.
23. Recall that dihydrotestosterone is crucial for the development of male characteristics in the embryo. If a pregnant woman were to be exposed to Propecia, the 5 α -reductase of the male embryo would be inhibited, which could result in severe developmental abnormalities.
24. The oxygenation reactions catalyzed by the cytochrome P450 family permit greater flexibility in biosynthesis. Because plants are not mobile, they must rely on physical defenses, such as thorns, and chemical defenses, such as toxic alkaloids. The larger P450 array might permit greater biosynthetic versatility.
25. This knowledge would enable clinicians to characterize the likelihood of a patient's having an adverse drug reaction or being susceptible to chemical-induced illnesses. It would also permit a personalized and especially effective drug-treatment regime for diseases such as cancer.
26. The honey bees may be especially sensitive to environmental toxins, including pesticides, because these chemicals are not readily detoxified, owing to the minimal P450 system.
27. The core structure of a steroid is four fused rings: three cyclohexane rings and one cyclopentane ring. In vitamin D, the B ring is split by ultraviolet light.
28. The negatively charged phosphoserine residue interacts with the positively charged protonated histidine residue and decreases its ability to transfer a proton to the thiolate.



29. The methyl group is first hydroxylated. The hydroxymethylamine eliminated formaldehyde to form methylamine.

30. Note that a cytidine nucleotide plays the same role in the synthesis of these phosphoglycerides as a uridine nucleotide does in the formation of glycogen (Section 21.4). In all of these biosyntheses, an activated intermediate (UDP-glucose, CDP-diacylglycerol, or CDP-alcohol) is formed from a phosphorylated substrate (glucose 1-phosphate, phosphatidate, or a phosphoryl alcohol) and a nucleoside triphosphate (UTP or CTP). The activated intermediate then reacts with a hydroxyl group (the terminus of glycogen, the side chain of serine, or a diacylglycerol).

31. The attachment of isoprenoid side chains confers hydrophobic character. Proteins having such a modification are targeted to membranes.

32. 3-Hydroxy-3-methylglutaryl CoA is also a precursor for ketone-body synthesis. If fuel is needed elsewhere in the body, as might be the case during a fast, 3-hydroxy-3-methylglutaryl CoA is converted into the ketone acetoacetate. If energy needs are met, the liver will synthesize cholesterol.

33. One way in which phosphatidylcholine can be synthesized is by the addition of three methyl groups to phosphatidylethanolamine. The methyl donor is a modified form of methionine, S-adenosylmethionine or SAM (Section 24.2).

34. Citrate is transported out of the mitochondria in times of plenty. ATP-citrate lyase yields acetyl CoA and oxaloacetate. The acetyl CoA can then be used to synthesize cholesterol.

35. (a) There is no effect. (b) Because actin is not controlled by cholesterol, the amount isolated should be the same in both experimental groups; a difference would suggest a problem in the RNA isolation. (c) The presence of cholesterol in the diet dramatically reduces the amount of HMG-CoA reductase protein. (d) A common means of regulating the amount of a protein present is to regulate transcription, which is clearly not the case here. (e) The translation of mRNA could be inhibited, and the protein could be rapidly degraded.

Chapter 27

- Adipose tissue is now known to be an active endocrine organ, secreting signal molecules called adipokines.
- Caloric homeostasis is the condition in which the energy expenditure of an organism is equal to the energy intake.
- Leptin and insulin
- CCK produces a feeling of satiety and stimulates the secretion of digestive enzymes by the pancreas and the secretion of bile salts by the gall bladder. GLP-1 also produces a feeling of satiety; in addition, it potentiates the glucose-induced secretion of insulin by the β cells of the pancreas.
- Obviously, something is amiss. Although the answer is not known, the leptin-signaling pathway appears to be inhibited by suppressors of cytokine signaling, the regulatory proteins.
- 1: a, b; 2: f; 3: c, d, f; 4: c, d; 5: c; 6: f; 7: e; 8: e; 9: e.
- Phosphorylation of dietary glucose after it enters the liver; gluconeogenesis; glycogen breakdown.

8. Type 1 diabetes is due to autoimmune destruction of the insulin-producing cells of the pancreas. Type 1 diabetes is also called insulin-dependent diabetes because affected people require insulin to survive. Type 2 diabetes is characterized by insulin resistance. Insulin is produced, but the tissues that should respond to insulin, such as muscle, do not.

9. Leptin stimulates processes impaired in diabetes. For instance, leptin stimulates fatty acid oxidation, inhibits triacylglycerol synthesis, and increases the sensitivity of muscle and the liver to insulin.

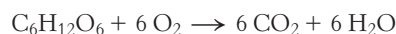
10. (a) A watt is equal to 1 joule (J) per second (0.239 calorie per second). Hence, 70 W is equivalent to 0.07 kJ s^{-1} ($0.017 \text{ kcal s}^{-1}$).

(b) A watt is a current of 1 ampere (A) across a potential of 1 volt (V). For simplicity, let us assume that all the electron flow is from NADH to O_2 (a potential drop of 1.14 V). Hence, the current is 61.4 A, which corresponds to 3.86×10^{20} electrons per second ($1 \text{ A} = 1 \text{ coulomb s}^{-1} = 6.28 \times 10^{18} \text{ charge s}^{-1}$).

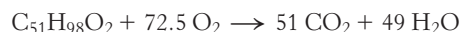
(c) About 2.5 molecules of ATP are formed per molecule of NADH oxidized (two electrons). Hence, 1 molecule of ATP is formed per 0.8 electron transferred. A flow of 3.86×10^{20} electrons per second therefore leads to the generation of 4.83×10^{20} molecules of ATP per second, or 0.80 mmol s^{-1} .

(d) The molecular weight of ATP is 507. The total body content of ATP of 50 g is equal to 0.099 mol. Hence, ATP turns over about once in 125 seconds when the body is at rest.

11. (a) The stoichiometry of the complete oxidation of glucose is



and that of tripalmitoylglycerol is



Hence, the RQ values are 1.0 and 0.703, respectively.

(b) An RQ value reveals the relative use of carbohydrates and fats as fuels. The RQ of a marathon runner typically decreases from 0.97 to 0.77 in the course of a race. The lowering of the RQ indicates the shift in fuel from carbohydrates to fat.

12. One gram of glucose (molecular weight 180.2) is equal to 5.55 mmol, and one gram of tripalmitoylglycerol (molecular weight 807.3) is equal to 1.24 mmol. The reaction stoichiometries (see Problem 11) indicate that 6 mol of H_2O is produced per mole of glucose oxidized, and 49 mol of H_2O is produced per mole of tripalmitoylglycerol oxidized. Hence, the H_2O yields per gram of fuel are 33.3 mmol (0.6 g) for glucose and 60.8 mmol (1.09 g) for tripalmitoylglycerol. Thus, complete oxidation of this fat gives 1.82 times as much water as does glucose. Another advantage of triacylglycerols is that they can be stored in essentially anhydrous form, whereas glucose is stored as glycogen, a highly hydrated polymer. A hump consisting mainly of glycogen would be an intolerable burden—far more than the straw that broke the camel's back.

13. The starved–fed cycle is the nightly hormonal cycle that humans experience during sleep and on eating. The cycle maintains adequate amounts of blood glucose. The starved part—sleep—is characterized by increased glucagon secretion and decreased insulin secretion. After a meal, glucagon concentration falls and insulin concentration rises.

14. Ethanol is oxidized to yield acetaldehyde by alcohol dehydrogenase, which is subsequently oxidized to acetate acetaldehyde. Ethanol is also metabolized to acetaldehyde by the MEOS, with the subsequent depletion of NADPH.

15. First, fatty liver develops owing to the increased amounts of NADH that inhibit fatty acid oxidation and stimulate fatty acid

synthesis. Second, alcoholic hepatitis begins owing to oxidative damage and damage due to excess acetaldehyde that results in cell death. Finally, fibrous tissues form, creating scars that impair blood flow and biochemical function. Ammonia cannot be converted into urea, and its toxicity leads to coma and death.

16. A typical macadamia nut has a mass of about 2 g. Because it consists mainly of fats ($\sim 37 \text{ kJ g}^{-1}$, $\sim 9 \text{ kcal g}^{-1}$), a nut has a value of about 75 kJ (18 kcal). The ingestion of 10 nuts results in an intake of about 753 kJ (180 kcal). As stated in the answer to Problem 10, a power consumption of 1 W corresponds to 1 J s^{-1} (0.239 cal s^{-1}), and so 400-W running requires 0.4 kJ s^{-1} ($0.0956 \text{ kcal s}^{-1}$). Hence, a person would have to run 1882 s, or about 31 minutes, to spend the calories provided by 10 nuts.

17. A high blood-glucose level triggers the secretion of insulin, which stimulates the synthesis of glycogen and triacylglycerols. A high insulin level would impede the mobilization of fuel reserves during the marathon.

18. A lack of adipose tissue leads to an accumulation of fats in the muscle, with the generation of insulin resistance. The experiment shows that adipokines secreted by the adipose tissue, here leptin, facilitate in some fashion the action of insulin in muscle.

19. Such a mutation would increase the phosphorylation of the insulin receptor and IRS in muscle and would improve insulin sensitivity. Indeed, PTP1B is an attractive therapeutic target for type 2 diabetes.

20. Lipid mobilization can be so rapid that it exceeds the ability of the liver to oxidize the lipids or convert them into ketone bodies. The excess is reesterified and released into the blood as VLDLs.

21. A role of the liver is to provide glucose for other tissues. In the liver, glycolysis is used not for energy production but for biosynthetic purposes. Consequently, in the presence of glucagon, liver glycolysis stops so that the glucose can be released into the blood.

22. The urea cycle and gluconeogenesis

23. (a) Insulin inhibits lipid utilization.

(b) Insulin stimulates protein synthesis, but there are no amino acids in the children's diet. Moreover, insulin inhibits protein breakdown. Consequently, muscle proteins cannot be broken down and used for the synthesis of essential proteins.

(c) Because proteins cannot be synthesized, blood osmolarity is too low. Consequently, fluid leaves the blood. An especially important protein for maintaining blood osmolarity is albumin.

24. During strenuous exercise, muscle converts glucose into pyruvate through glycolysis. Some of the pyruvate is processed by cellular respiration. However, some of it is converted into lactate and released into the blood. The liver takes up the lactate and converts it into glucose through gluconeogenesis. Muscle may process the carbon skeletons of branched-chain amino acids aerobically. The nitrogens of these amino acids are transferred to pyruvate to form alanine, which is released into the blood and taken up by the liver. After the transamination of the amino group to α -ketoglutarate, the resulting pyruvate is converted into glucose. Finally, muscle glycogen may be mobilized, and the released glucose can be used by muscle.

25. This conversion allows muscle to function anaerobically. NAD^+ is regenerated when pyruvate is reduced to lactate, and so energy can continue to be extracted from glucose during strenuous exercise. The liver converts the lactate into glucose.

26. Fatty acids and glucose, respectively.

27. This practice is called carbo-loading. Depleting the glycogen stores will initially cause the muscles to synthesize a large amount of glycogen when dietary carbohydrates are provided and will lead to the supercompensation of glycogen stores.

28. The oxygen consumption at the end of exercise is used to replenish ATP and creatine phosphate and to oxidize any lactate produced.

29. Oxygen is used in oxidative phosphorylation to resynthesize ATP and creatine phosphate. The liver converts lactate released by the muscle into glucose. Blood must be circulated to return the body temperature to normal, and so the heart cannot return to its resting rate immediately. Hemoglobin must be reoxygenated to replace the oxygen used in exercise. The muscles that power breathing must continue working at the same time as the exercised muscles are returning to resting states. In essence, all the biochemical systems activated in intense exercise need increased oxygen to return to the resting state.

30. Ethanol may replace water that is hydrogen bonded to proteins and membrane surfaces. This alteration of the hydration state of the protein would alter its conformation and hence function. Ethanol may also alter phospholipid packing in membranes. The two effects suggest that integral membrane proteins would be most sensitive to ethanol, as indeed seems to be the case.

31. Cells from the type I fiber would be rich in mitochondria, whereas those of the type II fiber would have few mitochondria.

32. (a) The ATP expended during this race amounts to about 8380 kg, or 18,400 pounds. (b) The cyclist would need about \$1,260,000,000 to complete the race.

33. 55 pounds = 25 kg = 25,000 g = total weight gain

$$40 \text{ years} \times 365 \text{ days year}^{-1} = 14,600 \text{ days}$$

$$25,000 \text{ g}/14,600 \text{ days} = 1.7 \text{ g day}^{-1}$$

which is equivalent to an extra pat of butter per day. Her BMI is 26.5, and she would be considered overweight but not obese.

34. Exercise greatly enhances the ATP needs of muscle cells. To more efficiently meet these needs, more mitochondria are synthesized.

35. The inability of muscle mitochondria to process all of the fatty acids produced by overnutrition leads to excessive levels of diacylglycerol and ceramide in the muscle cytoplasm. These second-messenger molecules activate enzymes that impair insulin signaling.

36. Both are due to a lack of thiamine (vitamin B_1). Thiamine, which is sometimes called aneurin, is required most notably for the proper functioning of pyruvate dehydrogenase.

37. (a) Red blood cells always produce lactate, and fast-twitch muscle fibers (see Problem 31) also produce a large amount of lactate.

(b) At that point, the athlete is beginning to move into anaerobic exercise, in which most energy is produced by anaerobic glycolysis.

(c) The lactate threshold is essentially the point at which the athlete switches from aerobic exercise, which can be done for extended periods, to anaerobic exercise, essentially sprinting, which can be done for only short periods. The idea is to race at the extreme of his or her aerobic capacity until the finish line is in sight and then to switch to anaerobic.

(d) Training increases the amount of blood vessels and the number of muscle mitochondria. Together, they increase the ability to process glucose aerobically. Consequently, a greater effort can be expended before the switch to anaerobic energy production.

Chapter 28

1. DNA polymerase I uses deoxyribonucleoside triphosphates; pyrophosphate is the leaving group. DNA ligase uses DNA-adenylate (AMP joined to the 5'-phosphoryl group) as a reaction partner; AMP is the leaving group. Topoisomerase I uses a DNA-tyrosyl intermediate (5'-phosphoryl group linked to the phenolic OH group); the tyrosine residue of the enzyme is the leaving group.

2. Positive supercoiling resists the unwinding of DNA. The melting temperature of DNA increases in proceeding from negatively supercoiled to relaxed to positively supercoiled DNA. Positive supercoiling is probably an adaptation to high temperature.

- (c) RNA polymerase is processive. When the template is bound, heparin cannot enter the DNA-binding site.
- (d) When GTP is absent, synthesis stops when the first cytosine residue downstream of the bubble is encountered in the template strand. In contrast, with all four nucleoside triphosphates present, synthesis will continue to the end of the template.
13. RNA polymerase must backtrack before cleavage, leading to dinucleotide products.
14. The base-pairing energy of the di- and trinucleotide DNA–RNA hybrids formed at the very beginning of transcription is not sufficient to prevent strand separation and loss of product.
15. (a) Because cordycepin lacks a 3′-OH group, it cannot participate in 3′ → 5′ bond formation. (b) Because the poly(A) tail is a long stretch of adenosine nucleotides, the likelihood that a molecule of cordycepin would become incorporated is higher than with most RNA. (c) Yes, it must be converted into cordycepin 5′-triphosphate.
16. There are $2^8 = 256$ possible products.
17. The relation between the –10 and –35 sequences could be affected by torsional strain. The fact that topoisomerase II introduces negative supercoils in DNA prevents this enzyme from overstimulating the expression of its own gene.
18. Ser-Ile-Phe-His-Pro-Stop
19. A mutation that disrupted the normal AAUAAA recognition sequence for the endonuclease could account for this finding. In fact, a change from U to C in this sequence caused this defect in a thalassemic patient. Cleavage was at the AAUAAA 900 nucleotides downstream of this mutant AACAAA site.
20. One possibility is that the 3′ end of the poly(U) donor strand cleaves the phosphodiester bond on the 5′ side of the insertion site. The newly formed 3′ terminus of the acceptor strand then cleaves the poly(U) strand on the 5′ side of the nucleotide that initiated the attack. In other words, a uridine residue could be added by two transesterification reactions. This postulated mechanism is similar to the one in RNA splicing.
21. Alternative splicing and RNA editing. Covalent modification of the proteins subsequent to synthesis further enhances the complexity.
22. Attach an oligo(dT) or oligo(U) sequence to an inert support to create an affinity column. When RNA is passed through the column, only poly(A)-containing RNA will be retained.
23. (a) Different amounts of RNA are present for the various genes. (b) Although all of the tissues have the same genes, the genes are expressed to different extents in different tissues. (c) These genes are called housekeeping genes—genes that most tissues express. They might include genes for glycolysis or citric acid cycle enzymes. (d) The point of the experiment is to determine which genes are initiated in vivo. The initiation inhibitor is added to prevent initiation at start sites that may have been activated during the isolation of the nuclei.
24. DNA is the single strand that forms the trunk of the tree. Strands of increasing length are RNA molecules; the beginning of transcription is where growing chains are the smallest; the end of transcription is where chain growth stops. Direction is left to right. Many enzymes are actively transcribing each gene.

Chapter 30

1. The Oxford English Dictionary defines translation as the action or process of turning from one language into another. Protein synthesis converts nucleic acid sequence information into amino acid sequence information.
2. An error frequency of 1 incorrect amino acid every 10^4 incorporations allows for the rapid and accurate synthesis of proteins as

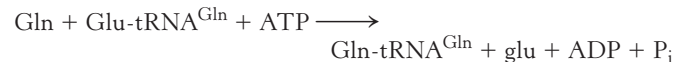
- large as 1000 amino acids. Higher error rates would result in too many defective proteins. Lower error rates would likely slow the rate of protein synthesis without a significant gain in accuracy.
3. (i) Each is a single chain. (ii) They contain unusual bases. (iii) Approximately half of the bases are base-paired to form double helices. (iv) The 5′ end is phosphorylated and is usually pG. (v) The amino acid is attached to the hydroxyl group of the A residue of the CCA sequence at the 3′ end of the tRNA. (vi) The anticodon is located in a loop near the center of the tRNA sequence. (vii) The molecules are L-shaped.
4. First is the formation of the aminoacyl adenylate, which then reacts with the tRNA to form the aminoacyl-tRNA. Both steps are catalyzed by aminoacyl-tRNA synthetase.
5. Unique features are required so that the aminoacyl-tRNA synthetases can distinguish among the tRNAs and attach the correct amino acid to the proper tRNA. Common features are required because all tRNAs must interact with the same protein-synthesizing machinery.
6. An activated amino acid is one linked to the appropriate tRNA.
7. (a) No; (b) no; (c) yes.
8. The ATP is cleaved to AMP and PP_i . Consequently, a second ATP is required to convert AMP into ADP, the substrate for oxidative phosphorylation.
9. Amino acids larger than the correct amino acid cannot fit into the active site of the tRNA. Smaller but incorrect amino acids that become attached to the tRNA fit into the editing site and are cleaved from the tRNA.
10. Recognition sites on both faces of the tRNAs may be required to uniquely identify the 20 different tRNAs.
11. The first two bases in a codon form Watson–Crick base pairs that are checked for fidelity by bases of the 16S rRNA. The third base is not inspected for accuracy, and so some variation is tolerated.
12. Four bands: light, heavy, a hybrid of light 30S and heavy 50S, and a hybrid of heavy 30S and light 50S
13. Two hundred molecules of ATP are converted into 200 AMP + 400 P_i to activate the 200 amino acids, which is equivalent to 400 molecules of ATP. One molecule of GTP is required for initiation, and 398 molecules of GTP are needed to form 199 peptide bonds.
14. (a, d, and e) Type 2; (b, c, and f) type 1.
15. The reading frame is a set of contiguous, nonoverlapping three-nucleotide codons that begins with a start codon and ends with a stop codon.
16. A mutation caused by the insertion of an extra base can be suppressed by a tRNA that contains a fourth base in its anticodon. For example, UUUC rather than UUU is read as the codon for phenylalanine by a tRNA that contains 3′-AAAG-5′ as its anticodon.
17. One approach is to synthesize a tRNA that is acylated with a reactive amino acid analog. For example, bromoacetyl-phenylalanyl-tRNA is an affinity-labeling reagent for the P site of *E. coli* ribosomes.
18. The sequence GAGGU is complementary to a sequence of five bases at the 3′ end of 16S rRNA and is located several bases upstream of an AUG start codon. Hence, this region is a start signal for protein synthesis. The replacement of G by A would be expected to weaken the interaction of this mRNA with the 16S rRNA and thereby diminish its effectiveness as an initiation signal. In fact, this mutation results in a 10-fold decrease in the rate of synthesis of the protein specified by this mRNA.
19. The peptide would be Phe-Cys-His-Val-Ala-Ala. The codons UGC and UGU encode cysteine but, because the

cysteine was modified to alanine, alanine is incorporated in place of cysteine.

20. Proteins are synthesized from the amino to the carboxyl end on ribosomes, whereas they are synthesized in the reverse direction in the solid-phase method. The activated intermediate in ribosomal synthesis is an aminoacyl-tRNA; in the solid-phase method, it is the adduct of the amino acid and dicyclohexylcarbodiimide.
21. The error rates of DNA, RNA, and protein synthesis are of the order of 10^{-10} , 10^{-5} , and 10^{-4} , respectively, per nucleotide (or amino acid) incorporated. The fidelity of all three processes depends on the precision of base-pairing to the DNA or mRNA template. Few errors are corrected in RNA synthesis. In contrast, the fidelity of DNA synthesis is markedly increased by the 3' → 5' proofreading nuclease activity and by postreplicative repair. In protein synthesis, the mischarging of some tRNAs is corrected by the hydrolytic action of aminoacyl-tRNA synthetase. Proofreading also takes place when aminoacyl-tRNA occupies the A site on the ribosome; the GTPase activity of EF-Tu sets the pace of this final stage of editing.
22. GTP is not hydrolyzed until aminoacyl-tRNA is delivered to the A site of the ribosome. An earlier hydrolysis of GTP would be wasteful because EF-Tu-GDP has little affinity for aminoacyl-tRNA.
23. The translation of an mRNA molecule can be blocked by antisense RNA, an RNA molecule with the complementary sequence. The antisense-sense RNA duplex cannot serve as a template for translation; single-stranded mRNA is required. Furthermore, the antisense-sense duplex is degraded by nucleases. Antisense RNA added to the external medium is spontaneously taken up by many cells. A precise quantity can be delivered by microinjection. Alternatively, a plasmid encoding the antisense RNA can be introduced into target cells.
24. (a) A_5 . (b) $A_5 > A_4 > A_3 > A_2$. (c) Synthesis is from the amino terminus to the carboxyl terminus.
25. These enzymes convert nucleic acid information into protein information by interpreting the tRNA and linking it to the proper amino acid.
26. The rate would fall because the elongation step requires that the GTP be hydrolyzed before any further elongation can take place.
27. Protein factors modulate the initiation of protein synthesis. The role of IF1 and IF3 is to prevent premature binding of the 30S and 50S ribosomal subunits, whereas IF2 delivers Met-tRNA_f to the ribosome. Protein factors are also required for elongation (EF-G and EF-Tu), for termination (release factors, RFs), and for ribosome dissociation (ribosome release factors, RRFs).
28. The signal sequence, signal-recognition particle (SRP), the SRP receptor, and the translocon.
29. The formation of peptide bonds, which in turn are powered by the hydrolysis of the aminoacyl-tRNAs.
30. The Shine-Dalgarno sequence of the mRNA base-pairs with a part of the 16S rRNA of the 30S subunit, which positions the subunit so that the initiator AUG is recognized.
- 31.

	Prokaryote	Eukaryote
Ribosome size	60S	80S
mRNA	polycistronic	Not polycistronic
Initiation	Shine-Dalgarno is required	First AUG is used
Protein factors	Required	Many more required
Relation to transcription	Translation can start before transcription is completed	Transcription and translation are spatially separated
First amino acid	fMet	Met

32. The SRP binds to the signal sequence and inhibits further translation. The SRP ushers the inhibited ribosome to the ER, where it interacts with the SRP receptor (SR). The SRP-SR complex binds the translocon and simultaneously hydrolyzes GTP. On GTP hydrolysis, SRP and SR dissociate from each other and from the ribosome. Protein synthesis resumes and the nascent protein is channeled through the translocon.
33. The alternative would be to have a single ribosome translating a single mRNA molecule. The use of polysomes allows more protein synthesis per mRNA molecule in a given period of time and thus the production of more protein.
34. (a) 1, 2, 3, 5, 6, 10; (b) 1, 2, 7, 8; (c) 1, 4, 8, 9.
35. Transfer RNAs have roles in several recognition processes. A tRNA must be recognized by the appropriate aminoacyl-tRNA synthetase, and the tRNA must interact with the ribosome and, in particular, with the peptidyl transferase.
36. The nucleophile is the amino group of the aminoacyl-tRNA. This amino group attacks the carbonyl group of the ester of peptidyl-tRNA to form a tetrahedral intermediate, which eliminates the tRNA alcohol to form a new peptide bond.
37. The aminoacyl-tRNA can be initially synthesized. However, the side-chain amino group attacks the ester linkage to form a six-membered amide, releasing the tRNA.
38. EF-Ts catalyzes the exchange of GTP for GDP bound to EF-Tu. In G-protein cascades, an activated 7TM receptor catalyzes GTP-GDP exchange in a G protein.
39. The α subunits of G proteins are inhibited by a similar mechanism in cholera and whooping cough (Section 14.5).
40. Glu-tRNA^{Gln} is formed by misacylation. The activated glutamate is subsequently amidated to form Gln-tRNA^{Gln}. Ways in which glutamine is formed from glutamate were discussed in Section 24.2. In regard to *H. pylori*, a specific enzyme, Glu-tRNA^{Gln} amidotransferase, catalyzes the following reaction:



- Glu-tRNA^{Glu} is not a substrate for the enzyme; so the transferase must also recognize aspects of the structure of tRNA^{Gln}.
41. The primary structure determines the three-dimensional structure of the protein. Thus, the final phase of information transfer from DNA to RNA to protein synthesis is the folding of the protein into its functional state.
42. (a) eIF-4H has two effects: (1) the extent of unwinding is increased and (2) the rate of unwinding is increased, as indicated by the increased rise in activity at early reaction times.
- (b) To firmly establish that the effect of eIF-H4 was not due to any inherent helicase activity.
- (c) Half-maximal activity was achieved at 0.11 μM of eIF-4H. Therefore, maximal stimulation would be achieved at a ratio of 1:1.
- (d) eIF-4H enhances the rate of unwinding of all helices, but the effect is greater as the helices increase in stability.
- (e) The results in graph C suggest that eIF-4H increases the processivity.
43. (a) The three peaks represent, from left to right, the 40S ribosomal subunit, the 60S ribosomal subunit, and the 80S ribosome.
- (b) Not only are ribosomal subunits and the 80S ribosome present, but polysomes of various lengths also are apparent. The individual peaks in the polysome region represent polysomes of discrete length.
- (c) The treatment significantly inhibited the number of polysomes while increasing the number of free ribosomal subunits. This outcome could be due to inhibited protein-synthesis initiation or inhibited transcription.

Chapter 31

- (a) Cells will express β -galactosidase, *lac* permease, and thiogalactoside transacetylase even in the absence of lactose. (b) Cells will express β -galactosidase, *lac* permease, and thiogalactoside transacetylase even in the absence of lactose. (c) The levels of catabolic enzymes such as β -galactosidase and arabinose isomerase will remain low even at low levels of glucose.
- The concentration is $1/(6 \times 10^{23})$ moles per 10^{-15} liter = 1.7×10^{-9} M. Because $K_d = 10^{-13}$ M, the single molecule should be bound to its specific binding site.
- The number of possible 8-bp sites is $4^8 = 65,536$. In a genome of 4.6×10^6 base pairs, the average site should appear $(4.6 \times 10^6)/65,536 = 70$ times. Each 10-bp site should appear 4 times. Each 12-bp site should appear 0.27 times (many 12-bp sites will not appear at all).
- The *lac* repressor does not bind DNA when the repressor is bound to a small molecule (the inducer), whereas the *pur* repressor binds DNA only when the repressor is bound to a small molecule (the corepressor). The *E. coli* genome contains only a single *lac* repressor-binding region, whereas it has many sites for the *pur* repressor.
- Anti-inducers bind to the conformation of repressors, such as the *lac* repressor, that are capable of binding DNA. They occupy a site that overlaps that for the inducer and, therefore, compete for binding to the repressor.
- The inverted repeat may be a binding site for a dimeric DNA-binding protein or it may correspond to a stem-loop structure in the encoded RNA.
- Bacteriophage λ would be more likely to enter the lytic phase because the cooperative binding of the λ repressor to O_R2 and O_R1 , which supports the lysogenic pathway, would be disrupted.
- λ repressor gene -10 region GATTTA -35 region TAGATA
Cro gene -10 region TAATGG -35 region TTGACT
There are four differences in the -10 region and three differences in the -35 region.
- Increased Cro concentration reduces the expression of the λ repressor gene. Increased λ repressor concentration reduces the expression of the Cro gene. At low λ repressor concentration, increased λ repressor concentration increases the expression of the λ repressor gene. At higher λ repressor concentrations, increased λ repressor concentration decreases the expression of the λ repressor gene.
- Normally, bacterial mRNAs have a leader sequence in which a Shine–Delgarno sequence precedes the AUG start codon. The absence of a leader would be expected to lead to inefficient translation.
- Add each compound to a culture of *V. fischeri* at low density and look for the development of luminescence.
- ACC, 7; ACA, 1; ACU, 0; ACG, 0.
- The reaction takes place with overall retention of configuration. Each step likely takes place with inversion of configuration, which suggests that the reaction consists of two (or some other even number of) steps. A possible mechanism is nucleophilic attack by the carboxylate group of Glu 537 on the C-1 carbon atom of the galactose moiety within glucose, releasing glucose and forming an intermediate with the galactose linked to the enzyme through an ester linkage. Water then attacks this carbon atom, displacing the glutamate carboxylate and releasing galactose.
- The binding appears to be half complete at a concentration of λ repressor near 3.7 nM. Thus, K_d is approximately 3.7 nM and $\Delta G^\circ = -48$ kJ/mol (-11 kcal/mol) at 298 K.

Chapter 32

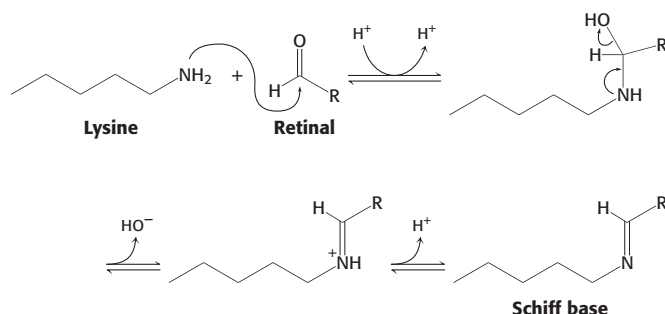
- The distribution of charged amino acids is H2A (13 K, 13 R, 2 D, 7 E, charge = +17), H2B (20 K, 8 R, 3 D, 7 E, charge = +18), H3 (13 K, 18 R, 4 D, 7 E, charge = +20), H4 (11 K, 14 R,

- 3 D, 4 E, charge = +18). The total charge of the histone octamer is estimated to be $2 \times (17 + 18 + 20 + 18) = +146$. The total charge on 150 base pairs of DNA is -300 . Thus, the histone octamer neutralizes approximately one-half of the charge.
- The presence of a particular DNA fragment could be detected by hybridization, by PCR, or by direct sequencing.
- The total length of the DNA is estimated to be $145 \text{ bp} \times 3.4 \text{ \AA/bp} = 493 \text{ \AA}$, which represents 1.75 turns or $1.75 \times 2\pi r = 11.0r$. Thus, the radius is estimated to be $r = 493 \text{ \AA}/11.0 = 44.8 \text{ \AA}$.
- 5-Azacytidine cannot be methylated. Some genes, normally repressed by methylation, will be active.
- Proteins containing these domains will be targeted to methylated DNA in repressed promoter regions. They would likely bind in the major groove because that is where the methyl group is located.
- Gene expression is not expected to respond to the presence of estrogen. However, genes for which expression normally responds to estrogen will respond to the presence of progesterone.
- The acetylation of lysine will reduce the charge from +1 to 0. The methylation of lysine will not reduce the charge.
- On the basis of the pattern of cysteine and histidine residues, this region appears to contain three zinc-finger domains.
- $10/4000 = 0.25\%$. 0.25% of 12 Mb = 30 kilobase pairs.
- The addition of an IRE to the 5' end of the mRNA is expected to block translation in the absence of iron. The addition of an IRE to the 3' end of the mRNA is not expected to block translation, but it might affect mRNA stability.
- The sequences of all of the mRNAs would be searched for sequences that are fully or nearly complementary to the sequence of the miRNA. These sequences would be candidates for regulation by this miRNA.
- The amino group of the lysine residue, formed from the protonated form by a base, attacks the carbonyl group of acetyl CoA to generate a tetrahedral intermediate. This intermediate collapses to form the amide bond and release CoA.
- In mouse DNA, most of the *HpaII* sites are methylated and therefore not cut by the enzyme, resulting in large fragments. Some small fragments are produced from CpG islands that are unmethylated. For *Drosophila* and *E. coli* DNA, there is no methylation and all sites are cut.

Chapter 33

- The transgenic nematode would avoid the compound. The identity of the ligand is determined by the receptor, whereas the behavioral response is dictated by the neuron in which the receptor is expressed.
- Only a mixture of compounds $C_5\text{-COOH}$ and $\text{HOOC-}C_7\text{-COOH}$ is predicted to yield this pattern.
- Bitter and sweet sensations are mediated by G proteins coupled to 7TM receptors, leading to millisecond time resolution. Salty and sour sensations are mediated directly by ion channels, which may lead to faster time resolution.
- Sound travels 0.15 m in 428 μs . The human hearing system is capable of sensing time differences of close to a microsecond, and so the difference in arrival times at the two ears is substantial. A system based on G proteins is unlikely to be able to reliably distinguish between signals arriving at the two ears, because G proteins typically respond in milliseconds.
- If a plant tastes bitter, animals will avoid eating it even if it is nontoxic, which may provide a selective advantage to the plant.
- Using mice in which either the gene for T1R1 or the gene for T1R3 has been disrupted, test the taste responses of these mice to glutamate, aspartate, and a wide variety of other amino acids.

7. These women have four functional color receptors: blue, red, green, and a red–green hybrid. The additional color receptor allows some colors that appear identical to most people to be distinguished.
8. 380 (one for each receptor); there are $(380 \times 379)/2! = 72,010$ combinations of two receptors; $(380 \times 379 \times 378)/3! = 9,073,260$ combinations of three receptors.
9. The absorption of light converts 11-*cis*-retinal into all-*trans*-retinal.
10. These compounds are enantiomers and must bind to protein receptors to elicit a smell. Even these subtle structural differences can affect relative receptor binding affinities and, hence, the elicited odor.
11. Vision: cGMP-gated channel; taste: amiloride-sensitive sodium channel; hearing; tip-link channel.
12. For all senses, ATP hydrolysis is required to generate and maintain ion gradients and membrane potential. Olfaction: ATP is required for the synthesis of cAMP. Gustation: ATP is required for the synthesis of cyclic nucleotides, and GTP is required for the action of gustducin in the detection of bitter and sweet tastes. Vision: GTP is required for the synthesis of cGMP and for the action of transducin. Hearing and touch: ATP hydrolysis is required to generate and maintain ion gradients and membrane potential and may be required for other roles as well.
- 13.



Chapter 34

1. The innate immune system responds rapidly to common features present in many pathogens. The genes for the innate immune system's key molecules are expressed without substantial modification. In contrast, the adaptive immune system responds to specific features present only in a given pathogen. Its genes undergo significant rearrangement and mutation to enable specific recognition of a vast number of potential binding surfaces.
2. VJ and V(D)J recombination; variability in segment joining by the action of terminal deoxyribonucleotidyl transferase; somatic mutation.
3. *Affinity* refers to the strength of a single interaction; *avidity* refers to the cumulative strength of multiple independent binding interactions. *Avidity* may play a significant role in the interaction between IgM and antigen because this immunoglobulin class features 10 binding sites.
4. The intracellular signaling domain common to each of the TLRs is responsible for docking other proteins and reporting that a targeted pathogen-associated molecular pattern (PAMP), such as LPS, has been detected. If a mutation within this domain interfered with the intracellular docking and signal transduction, then TLR-4 would not respond to LPS.
5. Viruses that contain dsRNA genomes would be expected to stimulate a TLR-3-mediated immune response.
6. (a) $\Delta G^{\circ} = -37 \text{ kJ mol}^{-1}$ ($-8.9 \text{ kcal mol}^{-1}$)
 (b) $K_a = 3.3 \times 10^6 \text{ M}^{-1}$
 (c) $k_{\text{on}} = 4 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$. This value is close to the diffusion-controlled limit for the combination of a small molecule with a protein (see p. 245). Hence, the extent of structural change is likely to be small; extensive conformational transitions take time.
7. The fluorescence enhancement and the shift to blue indicate that water is largely excluded from the combining site when the hapten is bound. Hydrophobic interactions contribute significantly to the formation of most antigen–antibody complexes.
8. (a) An antibody combining site is formed by CDRs from both the H and the L chains. The V_H and V_L domains are essential. A small proportion of F_{ab} fragments can be further digested to produce F_v, a fragment that contains just these two domains. C_{H1} and C_L contribute to the stability of F_{ab} but not to antigen binding.
 (b) A synthetic F_v analog 248 residues long was prepared by expressing a synthetic gene consisting of a V_H gene joined to a V_L gene through a linker. See J. S. Huston et al., *Proc. Natl. Acad. Sci. U. S. A.* 85:5879–5883, 1988.
9. (a) Multivalent antigens lead to the dimerization or oligomerization of transmembrane immunoglobulins, an essential step in their activation. This mode of activation is reminiscent of that of receptor tyrosine kinases (Section 14.2).
 (b) An antibody specific for a transmembrane immunoglobulin will activate a B cell by cross-linking these receptors. This experiment can be carried out by using, for example, a goat antibody to cross-link receptors on a mouse B cell.
10. B cells do not express T-cell receptors. The hybridization of T-cell cDNAs with B-cell mRNAs removes cDNAs that are expressed in both cells. Hence, the mixture of cDNAs subsequent to this hybridization are enriched in those encoding T-cell receptors. This procedure, called subtractive hybridization, is generally useful in isolating low-abundance cDNAs. Hybridization should be carried out by using mRNAs from a closely related cell that does not express the gene of interest. See S. M. Hedrick, M. M. Davis, D. I. Cohen, E. A. Nielsen, and M. M. Davis, *Nature* 308:149–153, 1984, for an interesting account of how this method was used to obtain genes for T-cell receptors.
11. TLR-4 is the receptor for LPS, a toxin found specifically in the walls of Gram-negative bacteria. Mutations that inhibit the function of TLR4 impair an affected person's defenses against this class of bacteria.
12. If the HLA alleles are not matched, then the recipient's T cell receptors will identify the MHC proteins of the transplanted tissue as nonself and transplant rejection is likely.
13. Purify an antibody with a specificity to one antigen. Unfold the antibody and allow it to re-fold either in the presence of the antigen or in the absence of the antigen. Test the re-folded antibodies for antigen-binding ability.
14. In some cases, V–D–J rearrangement will result in combining V, D, and J segments out of frame. mRNA molecules produced from such rearranged genes will produce truncated molecules if translated. This possibility is excluded by degrading the mRNA.
15. The mutant bacteria may still stimulate an immune response without causing disease. Hence, they may be valuable starting points for the design of a live attenuated vaccine for the original pathogenic strain.
16. The peptide is LLQATYSAV (L in second position, V in last).
17. Catalysis is likely to require a base for removing a proton from a water molecule. A histidine, glutamate, or aspartate residue is most likely. In addition, a potential hydrogen-bond donor may be present and will interact with the negatively charged oxygen atom that forms in the transition state.
18. A phosphotyrosine residue in the carboxyl terminus of Src and related protein tyrosine kinases binds to its own SH2 domain to generate the inhibited form of Src (Section 14.5). Removal of the phosphoryl group from this residue will activate the kinase.

ANSWERS TO PROBLEMS

19. (a) $K_d = 10^{-7}$ M; (b) $K_d = 10^{-9}$ M. The gene was probably generated by a point mutation in the gene for antibody A rather than by de novo rearrangement.

Chapter 35

- (a) Skeletal muscle and eukaryotic cilia derive their free energy from ATP hydrolysis; the bacterial flagellar motor uses a proton-motive force.
(b) Skeletal muscle requires myosin and actin. Eukaryotic cilia require microtubules and dynein. The bacterial flagellar motor requires MotA, MotB, and FliG, as well as many ancillary components.
- $6400 \text{ \AA}/80 \text{ \AA} = 80$ body lengths per second. For a 10-foot automobile, this body-length speed corresponds to a speed of $80 \times 10 \text{ feet} = 800 \text{ feet per second}$, or 545 miles per hour.
- $4 \text{ pN} = 8.8 \times 10^{-13}$ pounds. The weight of a single motor domain is $100,000 \text{ g mol}^{-1}/(6.023 \times 10^{23} \text{ molecules mol}^{-1}) = 1.7 \times 10^{-19} \text{ g} = 3.7 \times 10^{-22}$ pounds. Thus, a motor domain can lift $(8.8 \times 10^{-13}/3.7 \times 10^{-22}) = 2.4 \times 10^9$ times its weight.
- Both actin filaments and microtubules are built from subunits and these subunits bind and hydrolyze nucleoside triphosphates. Actin filaments are built of a single type of subunit and these subunits bind ATP. Microtubules are built of two different types of subunits and these subunits bind GTP.
- The light chains in myosin stiffen the lever arm. The light chains in kinesin bind cargo to be transported.
- After death, the ratio of ADP to ATP increases rapidly. In the ADP form, myosin motor domains bind tightly to actin. Myosin-actin interactions are possible because the drop in ATP concentration also allows the calcium concentration to rise, clearing the blockage of actin by tropomyosin through the action of the troponin complex.
- Above its critical concentration, ATP-actin will polymerize. The ATP will hydrolyze through time to form ADP-actin, which has a higher critical concentration. Thus, if the initial subunit concentration is between the critical concentrations of ATP-actin and ADP-actin, filaments will form initially and then disappear on ATP hydrolysis.
- A one-base step is approximately $3.4 \text{ \AA} = 3.4 \times 10^{-4} \text{ \mu m}$. If a stoichiometry of one molecule of ATP per step is assumed, this distance corresponds to a velocity of $0.017 \text{ \mu m s}^{-1}$. Kinesin moves at a velocity of $6400 \text{ \AA per second}$, or $0.64 \text{ \mu m s}^{-1}$.
- A proton-motive force across the plasma membrane is necessary to drive the flagellar motor. Under conditions of starvation, this proton-motive force is depleted. In acidic solution, the pH difference across the membrane is sufficient to power the motor.
- The mean distance between tumbles would be longer when the bacterium is moving up a gradient of a chemoattractant.
- (a) 1.13×10^{-9} dyne
(b) 6.8×10^{14} erg
(c) 6.6×10^{-11} erg per 80 molecules of ATP. A single kinesin motor provides more than enough free energy to power the transport of micrometer-size cargoes at micrometer-per-second velocities.
- The spacing between identical subunits on microtubules is 8 nm. Thus, a kinesin molecule with a step size that is not a multiple of 8 nm would have to be able to bind at more than one type of site on the microtubule surface.
- KIF1A must be tethered to an additional microtubule-binding element that retains an attachment to the microtubule when the motor domain releases.
- Filaments built from subunits can be arbitrarily long, can be dynamically assembled and disassembled, and require only a small amount of genetic information to encode.

15. Protons still flow from outside to inside the cell. Each proton might pass into the outer half-channel of one MotA–MotB complex, bind to the MS ring, rotate clockwise, and pass into the inner half-channel of the neighboring MotA–MotB complex.

16. At a high concentration of calcium ion, Ca^{2+} binds to calmodulin. In turn, calmodulin binds to a protein kinase that phosphorylates myosin light chains and activates it. At low calcium ion concentration, the light chains are dephosphorylated by a Ca^{2+} -independent phosphatase.

17. (a) The value of k_{cat} is approximately 13 molecules per second, whereas the K_M value for ATP is approximately 12 \mu M .

(b) The step size is approximately $(380 - 120)/7 = 37 \text{ nm}$.

(c) The step size is very large, which is consistent with the presence of six light-chain-binding sites and, hence, very long lever arms. The rate of ADP release is essentially identical with the overall k_{cat} ; so ADP release is rate limiting, which suggests that both motor domains can bind to sites 37 nm apart simultaneously. ADP release from the hindmost domain allows ATP to bind, leading to actin release and lever-arm motion.

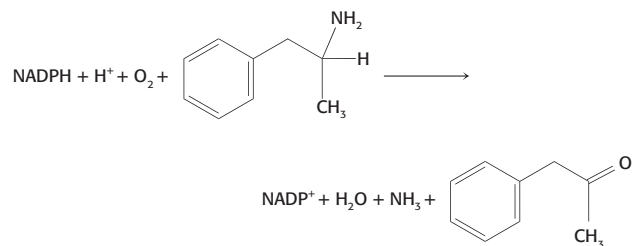
Chapter 36

- (a) Before; (b) after; (c) after; (d) after; (e) before; (f) after.
- (a) Yes; (b) yes; (c) no ($\text{MW} > 600$).
- If computer programs could estimate $\log(P)$ values on the basis of chemical structure, then the required laboratory time for drug development could be shortened. The determination of the relative solubilities of pharmaceutical candidates by allowing each compound to equilibrate between water and an organic phase would no longer be necessary.
- Perhaps *N*-acetylcysteine would conjugate to some of the *N*-acetyl-*p*-benzoquinone imine that is produced by the metabolism of acetaminophen, thereby preventing the depletion of the liver's supply of glutathione.
- In phase 1 clinical trials, approximately 10 to 100 healthy volunteers are typically enrolled in a study designed to assess safety. In contrast, a larger number of subjects are enrolled in a typical phase 2 trial. Moreover, these persons may benefit from the drug administered. In a phase 2 trial, efficacy, dosage, and safety can be assessed.
- The binding of other drugs to albumin could cause extra coumadin to be released. (Albumin is a general carrier for hydrophobic molecules.)
- A drug that inhibits a P450 enzyme may dramatically affect the disposition of another drug that is metabolized by that same enzyme. If this inhibited metabolism is not accounted for when dosing, the second drug may reach very high, and sometimes toxic, levels in the blood.
- Unlike competitive inhibition, noncompetitive inhibition cannot be overcome with additional substrate. Hence, a drug that acts by a noncompetitive mechanism will be unaffected by changing levels of the physiological substrate.
- An inhibitor of MDR could prevent the efflux of a chemotherapeutic drug from tumor cells. Hence, this type of an inhibitor could be useful in averting resistance to cancer chemotherapy.
- Agents that inhibit one or more enzymes of the glycolytic pathway could act to deprive trypanosomes of energy and thus be useful for treating sleeping sickness. A difficulty is that glycolysis in the host cells also would be inhibited.
- Imatinib is an inhibitor of the Bcr–Abl kinase, a mutant kinase present only in tumor cells that have undergone a translocation between chromosomes 9 and 22 (see Figure 14.33). Before initiating treatment with imatinib, we could sequence the DNA of the tumor cells and determine (a) whether this translocation has taken place and (b) whether the sequence of *bcr-abl* carries any mutations

that would render the kinase resistant to imatinib. If the translocation has not taken place or if the gene carries resistance mutations, then imatinib would likely not be an effective treatment for the patient carrying this particular tumor.

12. Sildenafil increases cGMP levels by inhibiting the phosphodiesterase-mediated breakdown of cGMP to GMP. Intracellular cGMP levels can also be increased by activating its synthesis. This activation can be achieved with the use of NO donors (such as sodium nitroprusside and nitroglycerin) or compounds that activate guanylate cyclase activity. Drugs that act by the latter mechanism are currently in clinical trials.

13. A reasonable mechanism would be an oxidative deamination following an overall mechanism similar to that in Figure 36.9, with release of ammonia.



14. $K_I \approx 0.3 \text{ nM}$. $\text{IC}_{50} \approx 2.0 \text{ nM}$. Yes, compound A should be effective when taken orally because 400 nM is much greater than the estimated values of K_I and IC_{50} .

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Chapter 36

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Note: Page numbers followed by f, t, and b refer to figures, tables, and boxed material, respectively. **Boldface** page numbers indicate structural formulas and ribbon diagrams.

- A band, 1016, 1016f
 A site, ribosomal, 900, 900f, 902–904
 AAA ATPases
 in amino acid degradation, 677
 DnaA as, 834
 in dynein, 1010, 1011f
 Ab initio prediction, of protein structure, 54
 ABC transporters, 378–380, 378f, 379f
 ABO blood groups, glycosyltransferases
 in, 335
 Absorption, drug, 1031–1033, 1032f
 Abzymes, production of, 244
 Acceptor control, 556
 Acceptor stem, 891
 Accessory pigments, in photosynthesis,
 581–584, 582f, 583f
 Acetaminophen, **1037**
 hepatic toxicity of, 1036, 1037
 Acetate, molecular models of, 23f
 Acetoacetate, **653**, 653–654. *See also*
 Ketone bodies
 in amino acid degradation, 694
 from phenylalanine, 696, 696f
 from tryptophan, 696, 696f
 Acetoacetyl ACP, 658–659, 658t, **659**
 Acetoacetyl CoA, 653
 Acetyl ACP, 658–659, 658t, **659**
 Acetyl CoA (acetyl coenzyme A), 440,
 440, 497
 in amino acid degradation, 694
 carboxylation of, 657
 in cholesterol synthesis, 767
 in citric acid cycle, 497, 500–501, 501,
 503–505, 514–515, 653, 656
 in ethanol metabolism, 811
 in fatty acid metabolism, 646–647, 656
 formation of, 468
 in fatty acid oxidation, 646–647
 from ketone bodies, 633f,
 653–655
 in glyoxylate cycle, 518
 oxidation of, ATP synthesis from, 437–438
 transfer from mitochondria to cytoplasm,
 662, 662f
 Acetyl CoA carboxylase, 657, 658t,
 666–667, 666f
 Acetyl CoA synthetase, in glyoxylate
 cycle, 518
 Acetylation, 297–298, 298t
 in gene regulation, 949–951
 histone, 298t, 949–950, 950f
 protein, 57
 Acetylcholine, 389
 Acetylcholine receptor
 generation of, 392, 392f
 as ligand-gated ion channel, 389–390, 391f
 structure of, 389–390, 390f
 Acetylcholinesterase, inhibitors of, 241, 241f
 N-Acetylglutamate, 686, 688
 N-Acetyl-L-phenylalanine *p*-nitrophenyl
 ester, 256, 257f
 Acetyllysine-binding domain, 949–950, 950f
 Acid(s). *See also* Hydrogen ion(s)
 fatty. *See* Fatty acid(s)
 protonation/deprotonation of, 15–16,
 15f, 16f
 sour taste of, 962, 965–966
 tactile response to, 974
 Acid–base catalysis, 254
 Acid–base reactions, 13–17
 buffers in, 15–17, 15f, 16f
 double helix disruption in, 14–15
 Aconitase, 952, **953**
 in citric acid cycle, 506
 iron-response element-binding protein as,
 952, **953**
 Acquired immunodeficiency syndrome. *See*
 Human immunodeficiency virus
 infection
 Actin, decorated, 1014
 Actin/actin filaments, 90, 90f, 1012–1018
 definition of, 1012
 F, 1013, 1013f
 formation of, 1013–1014, 1013f
 G, 1013
 myosin and, 1016–1017. *See also* Myosin
 polymerization of, 1013–1014
 structure of, **183**, 183–184, 1012–1013,
 1013f
 in thin filaments, 1016
 Actin–myosin complex, 1014, 1014f
 Actinomycin D, 861, 862, **862**
 Action potentials, 382, 382f
 equilibrium, 391–392, 391f
 generation of, 392, 392f
 ion channels and, 382, 382f, 391–392, 391f
 Activated carriers, in metabolism, 438–442,
 438f, 439f
 Activated methyl cycle, 717–718, 717f
 Activating enzymes, in translation,
 893–897. *See also* Aminoacyl-tRNA
 synthetases
 Activation energy, 222, 226
 Active sites, 185–186, 227–228,
 227f, 228f
 convergent evolution of, 185–186
 definition of, 185–186
 Active transport, 371, 373. *See also*
 Membrane transport
 Acute intermittent porphyria, 731
 Acyl adenylate
 in asparagine synthesis, 713
 in fatty acid metabolism, 644–645, **645**
 in translation, 893–895
 Acyl carnitine, **645**, 645–646, 646f
 Acyl carnitine translocase, 646f
 Acyl carrier proteins (ACPs), in fatty acid
 metabolism, 657–658, **658**
 Acyl CoA, 440, **440, 645**
 in fatty acid metabolism, 645, 646f
 Acyl CoA dehydrogenase, 646, 647
 Acyl CoA synthetase, 644–645
 Adaptive control, 667
 Adaptive immunity, 977. *See also under*
 Immune
 Adaptor proteins, in signal transduction,
 414, 417
 Adenine, 4, **4**, 111, **111**
 deamination of, 838, 838f
 methylation of, 277–278, 277f, 278f
 Adenine nucleotide translocase, 552–553,
 553f, 554f
 inhibition of, 558
 Adenine phosphoribosyltransferase, 744
 Adenosine, 111
 degradation of, 752–753, 753f
 Adenosine 5'-triphosphate. *See* ATP
 (adenosine triphosphate)
 Adenosine diphosphate. *See* ADP
 (adenosine diphosphate)
 Adenosine monophosphate. *See* AMP
 (adenosine monophosphate)
 cyclic. *See* cAMP
 S-Adenosylhomocysteine
 in activated methyl cycle, 717, 717f
 in amino acid synthesis, 717, **717**
 S-Adenosylmethionine (SAM), 693, **693**
 in amino acid synthesis, 716–718
 S-Adenosylmethionine, in phospholipid
 synthesis, 763
 Adenylate cyclase, 474
 in signal transduction, 406, **406**, 406f
 Adenylate kinase
 P-loop NTPase domains in, 284, 284f
 structure of, **284**
 Adenylate, synthesis of, 743–744, 743f
 Adenylation, in amino acid synthesis,
 725–726, 725f
 Adenylsuccinate synthase, 744
 Adenyl transferase, 725, 726f
 Adipokines, 796
 Adiponectin, 796
 Adipose cells (adipocytes), 640f, 641
 in appetite regulation, 795–796
 metabolism in, in starvation, 809–810
 Adipose tissue
 brown, 556–557, 557f
 white, 556
 Adipose triacylglyceride lipase (ATGL),
 643, 643f
 Adler, Julius, 1022

- ADME properties, of drugs, 1031–1036, 1032f
- A-DNA helix, 115–116, 116t
- ADP (adenosine diphosphate)
in activated carriers, 447, 447f
ATP synthesis from, 430–431, 434, 435, 435f
in citric acid cycle, 508, 555–556, 556f
energy charge and, 446–447, 446f
in kinesin movement, 1021, 1021f
in membrane transport, 380
in oxidative phosphorylation, 552, 555–556
in starch synthesis, 597
structure of, **431**
- ADP ribosylation, 298t
- ADP–ATP cycle, energy exchange in, 430–431, 435, 435f
- ADP–VO₄³⁻ complex, 1011, 1012f
- Adrenaline. *See* Epinephrine
- Adrenodoxin, 782
- Advance glycosylation end products, 326
- Aerobic glycolysis, 478–479
- Affinity chromatography, 70–71, 70f, 75, 75t, 78
- Affinity maturation, 989
- Affinity tags, 78, 241–242
- Aflatoxin B₁, 838, **838**
- Aggreccan, 332
- Agonists, 948
- Agouti-related peptide, 796
- Agre, Peter, 394
- Agrobacterium tumefaciens*, tumor-inducing plasmids in, 166–167, 167f
- Akt, in signal transduction, 414, 799
- Alanine
in gluconeogenesis, 490
in glucose–alanine cycle, 684–685, 685f
in muscle contraction, 490
in nitrogen transport, 684–685, 685f
pyruvate formation from, 691, 691f
structure of, 28, 29f
synthesis of, 712–713
transamination of, 691, 691f
- Alanine aminotransferase, 680
- Alanyl-tRNA sequence, 889, 890f
- Albinism, 698t
- Albumin, in drug distribution, 1033, 1033f
- Alcaptonuria, 697
- Alcohol(s)
fermentation of, 453, 466–467, 467f
formation from pyruvate, 466–467
formation of from pyruvate, 467f
metabolism of, 232, 810–813
monosaccharides and, 326
in phospholipid synthesis, 763
toxicity of, 811–813
- Alcohol dehydrogenase, 466–467, 467f, 810–811
in ethanol metabolism, 232
NAD⁺ binding sites in, 469, 469f
- Alcoholic fermentation, 453
- Alcoholic hepatitis, 811–812
- Alcohol-related disorders, 811–813
- Aldehyde(s). *See also* Monosaccharides
oxidation of, in glycolysis, 461, 462f
- Aldehyde dehydrogenase, 811
in ethanol metabolism, 232
- Aldimine, 682, **682**
in amino acid degradation, 682, 682f
in amino acid synthesis, 712–713, 712f
- Aldolase
in Calvin cycle, 595, 595f
in glycolysis, 456f, 458
- Aldose(s), 320, 320f
in Calvin cycle, 595
in transaldolase reaction, 605, 606f
- Aldosterone, 780
synthesis of, 780f, 783, **784**
- Alkali cations, properties of, 386t
- Allolactose, 926, **926**
- Allopurinol, 754
- Allosteric effector, 204–205
- Allosteric enzymes, 237, 237f, 289, 290–296.
See also Aspartate transcarbamoylase (ATCase)
definition of, 291
kinetics of, 291
heterotropic effects on, 296
homotropic effects on, 294
kinetics of, 291f, 293–295
substrate binding by
concerted mechanism in, 294–296
sequential model of, 294
subunits of
catalytic, 291–292
interaction of, 292–295, 294f–296f
regulatory, 291–292
T-to-R state equilibrium in, 294–296, 294f, 295f, 296f
T-to-R state transition in, 294–296, 294f, 295f
- Allosteric inhibitors, 291, 446
- Allosteric interactions, 291, 446
- Allosteric sites, 291
- α chains, 982, 983f
of class I MHC proteins, 992–993, 993f
of hemoglobin, 199, 199f, 211
- α helix, 38–40, **39**, **40**, 40f
amino acid residues in, 50–51, 51t
destabilization of, 40
of α -keratin, **43**, 43–44, 44f
of membrane proteins, 356, 358, 359–360, 360f, 360t
of myosin, 1009–1010, 1010f
- α -hemoglobin, 199, 199f, 211, **211**. *See also* Hemoglobin
- α -hemoglobin stabilizing protein, 211, **211**
- α_1 -antitrypsin, 307
abnormalities of, 312
- $\alpha\beta$ dimers, of hemoglobin, 199, 199f, 202, 202f
- α -tubulin, 1018–1019, 1018f, 1019f
- Alternative splicing, 133, 133f, 878–879, 878f. *See also* Splicing
- Altman, Sidney, 852, 863
- Altrose, 321f
- Alu sequences, 160
- Alzheimer disease, amyloid in, 55–56, 57
- α -Amanitin, **865**, 865–866
- Ames test, 843, 843f
- Amethopterin, 750
- Amidation, in amino acid synthesis, 713
- Amide bonds. *See* Peptide bonds
- Amiloride, **965**
salty taste and, 965
- Amiloride-sensitive sodium ion channels, 965, 965f
- Amines, monosaccharides and, 326
- Amino acid(s), 18–19. *See also* Protein(s)
abbreviations for, 32–33, 32t
acetyl groups of, 57
alpha, 27
aromatic, 28
degradation of, 695–696
synthesis of, 719–722, 720f, 721f
as biomolecular precursors, 726–731
branched-chain, degradation of, 693–695
chirality of, 27, 29f, 713
classification of, 28
D isomer of, 27, 27f
definition of, 18
dipolar form of, 27–28, 27f
elution volume of, 80, 80f
essential, 674, 674t, 711, 711t, 712f
synthesis of, 711–712, 719–723. *See also* Amino acid synthesis
evolutionary favorability of, 33
glucogenic, 690
hydrophilic, 30
protein folding and, 46, 47
hydrophobic, 28, 29f
protein folding and, 45–46, 46f, 47
hydroxyl groups of, 30, 30f, **57**, 57–58
identification of, 80–82, 80f
ionization state of, 27–28, 27f
ketogenic, 690
L isomer of, 27, 27f
metabolic fates of, 673
metabolism of, 437f, 673–698. *See also* Amino acid degradation; Amino acid synthesis
modifications of, 57–59, 57f
negatively charged, 31–33
nonessential, 711, 711t, 712f
synthesis of, 712–713
peptide bonds of, 33, 33f
polar, 30
positively charged, 30–31
properties of, 33
reactive, 30, 33f
in secondary structures, 38–45, 50–52, 51t
sequences of. *See* Amino acid sequences
side chains of. *See* Amino acid side chains
translational activation of, 893–895
zwitterionic form of, 27–28, 27f
- Amino acid composition, determination of, 80–82, 80f

- Amino acid degradation, 437f, 673–700
 acetoacetate in, 694
 acetyl CoA in, 694
 S-adenosylmethionine in, 693, **693**
 aminotransferases in, 680–682
 of aromatic amino acids, 695–696
 of branched-chain amino acids, 694–695
 carbon skeletons from, metabolic fates of, 690–696, 691f
 deamination in, 680–684
 dehydration in, 684
 digestive enzymes in, 255–260, 303–307, 303t, 304f, 674, 674f
 disorders of, 697–698, 698t
 glucose–alanine cycle in, 684–685, 685f
 glutamate dehydrogenase in, 680–681
 glutamate oxidative deamination in, 680–681
 homocysteine in, 693, **693**
 intermediates in, 690–696
 isoleucine in, 694–695
 α -ketobutyrate in, 693, **693**
 α -ketoglutarate in, 692
 leucine in, 693–694
 liver in, 680
 in muscle, 685
 one-carbon units in, 716
 overview of, 673–674
 oxaloacetate in, 692
 oxygenation in, 695–696
 propionyl CoA in, 693, **693**, 694
 proteasomes in, 677, 677f, 678f
 in protein turnover, 675
 pyruvate in, 684–685, 685f, 691, 691f
 rate of, 675, 676t
 regulatory functions of, 678–679, 679t
 Schiff-base intermediates in, 681–682
 serine dehydratase in, 684, 691
 in starvation, 809
 succinyl coenzyme A in, 693
 tetrahydrofolate in, 716
 threonine dehydratase in, 684
 transamination in, 680–685
 ubiquitination in, 298t, 675–678
 urea cycle in, 685–690
 valine in, 694–695
- Amino acid residues, 34
 definition of, 34
 molecular weight of, 34
 in secondary structures, 38–45, 50–52, 51t
- Amino acid sequences, 18–19, 19f, 25, 27–38
 alignment of, 175–181, 176f–182f
 alternative conformations of, 51–52, 51f
 of collagen, 44, 44f
 databases of, in sequence homology analysis, 181, 182f
 determination of, 79–84
 DNA sequencing in, 79–84
 Edman degradation in, 81–83, 81f
 genetic, 35
 protein cleavage for, 82–83, 82f, 83f
 uses of, 79–80
- directionality of, 34, 34f
 in disease, 35–36
 DNA-derived, 84
 evolution of, 36, 79, 174–181
 in genetic code, 129–130, 129t. *See also*
 Genetic code
 glycosylation sites in, 330
 homologous, 175–181. *See also* Sequence homologies
 identification of, 65–66
 internal repeats in, 79
 protein structure and, 18–19, 19f, 25, 35–36, 49–59
 shuffled, 177–178, 177f
 substitutions in, 178–181, 179f–181f
- Amino acid side chains, 27, 28–32
 acidic, 31–33, 32f
 aliphatic, 28, 29f
 aromatic, 28
 basic, 30–31, 31f
 carboxamide-containing, 30, 30f
 charge of, 30–33, 31f, 32f
 definition of, 27
 hydrophilic, 30f, 46, 46f, 47, 47f
 hydrophobic, 28, 45–46, 46f, 47, 47f
 hydroxyl-containing, 30, 30f
 ionizable, 32, 32t
 sulfhydryl-containing, 30, 30f
 thiol-containing, 30, 30f
- Amino acid synthesis, 705–732
 activated methyl cycle in, 717–718, 717f
 adenylation in, 725–726, 725f
 ammonia in, 706–710
 branched pathways in, 723
 chorismate in, 719–720, 720f
 committed step in, 723
 enzymatic cascades in, 725–726, 725f, 726f
 enzyme multiplicity in, 724, 724f
 of essential amino acids, 711–712, 719–723
 feedback inhibition/activation in, 723–724, 726f
 hydroxyethyl-TPP in, 723, 723f
 metabolic precursors in, 711, 711f
 methylation in, 716–718, 717f
 nitrogen fixation in, 706–710
 of nonessential amino acids, 712–719
 one-carbon units in, 715–716, 715t, 716f
 overview of, 705–706
 phosphorylation in, 724
 rate of, 723
 regulation of, 723–726
 regulatory domains in, 724, 724f
 reversible covalent modification in, 725–726, 725f
 S-adenosylmethionine in, 716–718
 shikimate in, 719, 720f
 in starvation, 809
 substrate channeling in, 722–723, 722f
 tetrahydrofolate in, **715**, 715–716, 716f
 threonine deaminase in, 723–724, 723f
 vitamin B₁₂ in, 650–652, 650f, 651f, 717
- Amino acid-binding regulatory domains, 724, 724f
- Amino sugars, 330
- 2-Amino-3-carboxymuconate-6-semialdehyde, 696, **696**
- Aminoacrylate, Schiff base of, 722, **722**, 722f
- Aminoacyl adenylate, in translation, **893**, 893–895, 894f
- Aminoacyl-AMP, 893–895, 894f
- Aminoacyl-tRNA, 128, 128f, **893**, 893–894
- Aminoacyl-tRNA synthetases, 128, 888, 893–897
 activation sites of, **894**, 894–895
 classes of, 897, 897t
 editing sites of, 895, **895**
 proofreading by, 895
 specificity of, 894–895
 tRNA recognition by, 896–897
- Aminoglycosides, **909**, 909–910, 909t
- 5-Aminoimidazole ribonucleotide, **742**, 742f
- 5-Aminoimidazole-4-carboxamide ribonucleotide, 741t, 742f
- 5-Aminoimidazole-4-(*N*-succinylcarboxamide) ribonucleotide, **742**, 742f
- δ -Aminolevulinic synthase, in porphyrin synthesis, 728, 729f
- Aminopterin, 750
- Aminotransferases
 in amino acid degradation, 680–682
 evolution of, 713
 pyridoxal phosphate-dependent, 712–713
- Ammonia
 in amino acid degeneration, 680–681, 685–690
 in amino acid synthesis, 706–710
 conversion to urea, 685–690
 formation of, 680–681, 684, 713
 in glucose-alanine cycle, 684–685, 685f
 in glutamate synthesis, 709
 in glutamine synthesis, 709–710
 neurotoxicity of, 689
 in purine synthesis, 741
 in pyrimidine synthesis, 737, 738
 transport of, 684–685
 in urea cycle defects, 689
- AMP (adenosine monophosphate)
 in adenylation, 725, 725f
 degradation of, 752–753, 753f
 energy charge and, 446–447, 446f
 in fatty acid metabolism, 644–645, 646f
 in glycogen metabolism, 626
 in reversible covalent modification, 725
 structure of, **431**
 synthesis of, 743–744, 743f, 751, 751f
- AMP-dependent protein kinase, 666–667
- Amphibolic pathways, 429
- Amphipathic molecules, 351
- α -Amylase, 328, 454
 in glycogen branching, 629
- Amyloid fibers, in neurodegenerative diseases, 55–56, 56f, 57

- Amyloid plaques, in Alzheimer's disease, 55–56, 57
- Amyloid precursor protein (APP), 57
- Amyloidoses, 55–57
- Amylopectin, 328
- Amylose, 328
- Amyotrophic lateral sclerosis, 147–148, 157
 animal models of, 164
 mutations in, 157, 163
- Amytal, 558
- Anabolic steroids, 785, 948
- Anabolism, 428–429
 definition of, 706b
 electron carriers in, 439
- Anaerobes, obligate, 468–469
 pathogenic, 468, 469t
- Anaplerotic reaction, 516–517
- Anchor residues, 993, 993f
- Ancient DNA, amplification and
 sequencing of, 147, 188–189, 189f
- Andersen disease, 634t
- Androgen(s). *See also* Sex hormones; Steroid hormones
 functions of, 784–785
 reduction of, 785
 synthesis of, 780, 780f, 784, **784**
- Androstenedione, 784, **784**, **948**
- Anemia
 Cooley, 210
 erythropoietin for, 331
 hemolytic, G6PD deficiency and, 609–610, 611
 sickle-cell, 209–210, 209f, 210f
- Anfinsen, Christian, 49–50
- Angiogenin, sequence comparison for, 173, **174**
- Angstrom (Å), 7
- Animal testing, in drug development, 1037
- Anion exchange, 70
- Ankyrin repeats, 972–973, 972f
- Annealing, of DNA strands, 120–121
- Anomers, 321f, 323
- Anosmia, 958
- ANT (adenine nucleotide translocase). *See* ATP-ADP translocase
- Antagonists, 948
- Anthranilate, 720, **721**
- Anthrax, 831
- Antibiotics. *See also* Drug(s) and specific antibiotics
 protein synthesis inhibition by, 909–910
 transcription termination by, 862–863
 translocation inhibition by, 909–910, 909t
- Antibodies, 979–980. *See also* Immunoglobulin(s)
 antigen binding by, 984–986, 985f, 986f
 antigen interaction with, 83–86, 85f
 antigen-binding units of, 981–983
 binding sites of, 984–985, 984f, 985f
 catalytic, production of, 243–244, 243f
 class switching in, 990–991, 991
 constant domains of, 984, 984f
 definition of, 84–85, 979
 diversity of, 980–981
 effector units of, 981–983
 formation of, 988–989, 990–991
 gene recombination in, 987–991, 988f
 class switching and, 990–991, 991f
 hypervariable loops of, 984, 984f
 monoclonal
 for cancer treatment, 420–421
 preparation of, 86–88, 87f
 number of, 980
 oligomerization of, 989–990
 polyclonal, 86, 86f
 production of, 86–88, 87f
 secretion of, 950, 989–990
 structure of, 85f, 981–982
 variable domains of, 983, 984, 984f, 985f
- Antibody diversity, 987–991
- Anticipation, in genetic disease, 842
- Anticoagulants, 310, 312
- Anticodon loop, 890f, 891
- Anticodons, 128, 889, 890f, 891–893, 891f, 892f, 896. *See also* Codons
- Antidiuretic hormone, 96
- Antielastase, 307
- Antigen(s), 85–86
 ABO blood group, 335–336, 335f
 antibody binding of, 85, 85f, 981–986, 985f, 986f
 cross-linking of, 982, 982f
 definition of, 979
 self, 1001
- Antigen–antibody interactions, 83–86, 85f, 981–986, 985f, 986f
- Antigenic determinants, 85, 85f, 980
- Antigen-presenting cells, 996–998, 996f
- Antihemophilic factor, 311, 311f
- Antimalarial drugs, hemolytic anemia and, 609–610
- Antimycin A, 558
- Antioxidants
 vitamin C as, 813
 vitamin E as, 542
- Antiporter, 380, 380f
- Antisense strand, 854
- Antiserum, 86
- Antithrombin III, 312
- Antitransporters, 380–381, 380f, 381f
- α_1 -Antitrypsin, 304–307
 abnormalities of, 312
- Antituberculosis drugs, 679
- AP endonuclease, 840
- Apoenzymes, 221
- Apolipoprotein B-48, 642, 773, 773t, 774, 872–873
- Apolipoprotein B-100, 773t, 774, 774f, 775, 872–873
- Apolipoprotein E, 773t, 774
- Apolipoproteins, 642, 773, 773t, 774, 774f, 775. *See also* Lipoprotein(s)
- Apoproteins, 773
- Apoptosis
 mitochondria in, 559
 T cell, 1000
 zymogens in, 303
- Apoptosome, 559
- Appetite regulation, 794–797, 795f–797f, 795t. *See also* Caloric homeostasis
- Approximation, catalysis by, 254
- Aquaporins, 394, 395f
- Aqueous solutions. *See also* Water
 hydrogen ions in, 13–17
- Arabidopsis*, 783
- Arachidonate, 664–665, 665f
- Arachidonic acid, 358
- Arber, Werner, 141
- Archaea, 3, 3f
 membranes of, 350–351
 proteasomes of, 677–678, 678f
 transcription in, 869
- Arginase, 687
- Arginine, 687
 nitric oxide from, 727–728
 structure of, 30–31, 31f, **687**
 synthesis of, 712, 714, 714f
 in urea cycle, 687
- Argininosuccinase, 687
 deficiency of, 689, 689f
- Argininosuccinate, 686, **686**, 689, **689**
- Argininosuccinate synthetase, 686
- Argonaute-miRNA, 953, 953f
- Aromatase, 785
- Aromatic amino acids, 28. *See also* Amino acid(s)
 degradation of, 695–696
 synthesis of, 719–722, 720f, 721f
- Arrestin, 408, 969
- Arsenite poisoning, 517, 518f
- Arteriosclerosis. *See* Atherosclerosis
- Arthritis, degenerative, 332
- Artificial chromosomes, 151
- Ascorbic acid (vitamin C), 442, 442t, 812–813, **813**
 deficiency of, alcohol-related, 812–813
 forms of, 813, **813**
- Asparaginase
 in amino acid degradation, 692
 in glycoproteins, 330, 331
 structure of, 30, 30f
 synthesis of, 713
- Asparagine
 in amino acid degradation, 692
 carbohydrate units of, 57
 synthesis of, 713, 713f
- Aspartate
 asparagine formation from, 713, 713f
 in catalytic triads, 258–260. *See also* Catalytic triads
 conversion to fumurate, 687, 692
 conversion to oxaloacetate, 692
 in double-displacement reactions, 237
 in purine synthesis, 743
 structure of, 31, 32f, **237**, **290**
 synthesis of, 712–713
 taste of, 962, 965
- Aspartate aminotransferase, **683**
 in amino acid degradation, 680, 682

- Aspartate transcarbamoylase (ATCase), 290–296
active sites of, 293–294
allosteric interactions in, 292–295
cytidine triphosphate inhibition of, 291, 291f, 295–296, 296f
kinetics of, 291, 291f, 294–296, 294f–296f
in pyrimidine synthesis, 290–295, 290f, 738, 751
structure of, **290**, 291–292, **292**
subunits of
catalytic, 291–292
interaction of, 292–295, 294f–296f
regulatory, 291–292
T-to-R state transition in, 294–296, 294f, 295f
ultracentrifugation studies of, 291–292, 292f
- Aspartokinases, 724, 724f
- Aspartyl proteases, in peptide bond cleavage, **263**, 264, 264f
- Aspirin
discovery and development of, 1038–1040
as prostaglandin inhibitor, 358, 665, 1040
- Assays
definition of, 67
of enzyme activity, 67
in protein purification, 67
- ATCase (aspartate transcarbamoylase), **289**
- Atenolol, 1045, **1045**
- Atheroma, 1040
- Atherosclerosis, 759, 774–775, 776–779, 777f
drug therapy for, 1040
HMG-CoA reductase inhibitors for, 779, **779**, **1040**, 1040–1041, **1041**
homocysteine in, 719
- Atkinson, Daniel, 446
- Atorvastatin, 1041, **1041**
- ATP (adenosine triphosphate), 112, **112**, 279, **279**
as activated carrier of phosphoryl groups, 438
ADP units in, 447, 447f
as allosteric effector of ATCase, 296, 296f
binding of
conformational changes and, 280–282, 282f, 284f
by RNA, 190–191, 190f
body requirements for, 525, 554–560
in citric acid cycle, 498, 512, 514–515, 514f
electrostatic repulsion and, 433
energy charge and, 446–447, 446f
during exercise, 805–806, 805t
in fatty acid metabolism, 644–645, 646f
formation of, 430–431
from acetyl CoA oxidation, 437–438
from ADP, 430–431, 434, 435, 435f
binding-change mechanism in, 547, 547f
from carbon oxidation, 434, 435–438, 435f, 437f
chemiosmotic hypothesis for, 544–545, 544f, 545f
creatine phosphate in, 434–435, 805
during exercise, 434–435, 435f, 805–806, 805t
in fatty acid metabolism, 648
from glycolysis, 463–466
ion gradients in, 437–438, 437f
in mitochondria, 526
NADH in, in ATP synthesis, 439
from oxidative phosphorylation, 436–437, 437f, 525, 543–550. *See also* Oxidative phosphorylation
in photosynthesis, 565, 566, 578–581
proton-motive force in, 525–526, 544–545, 544f, 545f
rotational catalysis in, 547–550, 547f–549f
yield in, 554–555, 555t
in gluconeogenesis, 484
in glycolysis
as phosphoryl-group donor, 455, 458
as product, 463–466
in GMP synthesis, 743–744, 743f, 751
high-energy bonds of, 433–434
hydration stabilization in, 433
hydrolysis of
in coupled reactions, 431–433
in DNA replication, 824–825
in DNA supercoiling, 830–831, 830f
free energy from, 429–435
heat generation in, 489
myosin and, 279–282, 281f–283f
in kinesin movement, 1021–1022, 1021f
in muscle contraction, 1009–1012, 1011f, 1012f, 1015, 1016f
rotational motion from, 547–550, 548f, 549f
in splicing, 876–877
in transcription, 876–877
in membrane transport, 374–381. *See also* Ion pumps
in mitochondria, 526
in muscle contraction, 1009–1012, 1011f, 1012f, 1015, 1016f
in myosin movement, 1009–1012, 1011f, 1012f, 1015, 1016f
in nitrogen fixation, 707, 708, 709–710
in oxidative phosphorylation, 525–526
in pentose phosphate pathway, 607f, 608–609
in phosphorylation, 298–301, 432–434, 437–438
phosphoryl-group-transfer and, 434–435, 434t. *See also* Phosphorylation
phosphoryl-transfer and, 434f
in purine synthesis, 742f
as reaction energy source, 429–435
resonance structures of, 433
in signal transduction, 405
structure of, 430, **431**
in substrate cycles, 489
triphosphate moiety of, 430
in ubiquitination, 675–676, 675f
utilization rates for, 435
- ATP synthase (Complex V), 578–579, 579f
a subunit of, 546, 548, 549
 α subunit of, 545, **545**
ATP-driven rotation in, 547–550, 547f–549f
b subunit of, 546
 β subunit of, **545**, 545–547, 547f
binding-change mechanism and, 547, 547f
c ring of, 548–549, 549f
catalytic action of, 546–548
in chloroplasts, 578–579, 583, 583f
F₀ subunit of, **545**, 546
F₁ subunit of, **545**, 545–546
G proteins and, 550
 γ subunit of, **545**, 545–546, 547
rotation of, 547–550, 547f–549f, 1023
inhibition of, 558
in mitochondria, 544–550, 558
in oxidative phosphorylation, 544–550, 558
in photosynthesis, 578–579, 583, 583f
P-loop NTPase domains in, 284, 284f
proton flow through, 546–547
rotational, 547–550, 547f–549f
respiratory chain linkage to, 544–545, 544f, 545f
structure of, **545**, 545–546
in thylakoid membrane, 583
- ATP synthasome, 554
- ATP–ADP cycle, energy exchange in, 430–431, 435, 435f
- ATP–ADP translocase, 552–553, 553f, 554f
inhibition of, 558
- ATPase(s)
AAA
in amino acid degradation, 677
DnaA as, 834
in dynein, 1010, 1011f
mitochondrial. *See* ATP synthase
in motor proteins, 1008–1010, 1011f
P-type, 374–378
evolution of, 374, 378
functions of, 378
in membrane transport, 374–378. *See also* Ion pumps
- ATPase domains, of myosin, 279–280, 280f
- ATP-binding cassettes, 378–380, 379f
- ATP-citrate lyase, 662
- ATP-driven pumps, 371
- ATP-grasp domain, 482, 482f
- ATP-grasp fold, 737
- ATP–magnesium complex, 280
- ATP–myosin complex, 279–280, 280f
- Atrazine, 584, **584**
- Attenuation, 931–932, 932f

- Auditory processing, 971–973
- Autoimmune diseases, 1001
- Autoinducers, 930, 930f
- Autonomously replicating sequence, 151, 151f
- Autoradiography, 73, 143
- Autotrophs, 565, 590
- Axel, Richard, 959
- Axonemes, 1019
- Azathioprine, 1048, **1048**
- B cell, 989–990
memory, 1002
- B cell receptor, 989, 989f
- B vitamins. *See* Vitamin(s)
- Backbone models, 61–62, 62f
- Backbones, in nucleic acids, 110, 110f, 111
- Bacteria, 3, 3f. *See also* *Escherichia coli*
chemotaxis in, 1024–1025, 1024f
DNA replication in, 831–834. *See also*
DNA replication
flagellar movement of, 1022–1025
glyoxylate cycle in, 518–519, 519f
nitrogen fixation in, 706–710
photosynthetic, 584, 584t
reaction center of, 569–572, 570f
proteasomes of, 677–678, 678f
- Bacterial artificial chromosomes, 151
- Bacterial photosynthetic reaction center, 569–572, 570f
- Bacteriochlorophyll, 570, **570**
- Bacteriochlorophyll *b*, 570–571
- Bacteriopheophytin *b*, 570, **570**, 570–571
- Bacteriorhodopsin, 356, 356f
- Baculovirus vectors, 163–164
- BAL (British anti-lewisite), 517, 518f
- Ball-and-chain model, of ion channel
inactivation, 388–389, 389f
- Ball-and-stick models, 22, 23f, 61, 61f
- Band centrifugation, 77–78, 77f
- Basal transcription complex, 941
- Base-excision repair, 840
- Base-pair substitutions, tests for, 843
- Base-paired hairpin. *See* Hairpin turns
- Bases
abbreviations for, 112, 112f
in acid–base reactions, 13–17. *See also*
Acid–base reactions
nucleic acid. *See* Bases/base pairs
sequence of, notation for, 112, 112f
- Bases/base pairs, 110–113, **111**, 114t. *See also* Double helix
adenine, **4**, 111, **111**
adenine–thymine, **5**, **5**
complementarity of, 822, 822f, 823f
cross-linkage of, 838, 839f
cytosine, **4**, 111, **111**
damage to, 838–839
deamination of, 680–684, 838, 841
errors in base pairing and, 117–118, 837–838
repair of, 839–843. *See also* DNA repair
- formation of, 891–893, 901. *See also*
Translation
codon–anticodon interactions in, 891–893
in genetic code, 128–131, 129t. *See also*
Genetic code
guanine, **4**, 111, **111**
guanine–cytosine, **5**, **5**
hydrogen bonds in, **5**, 5f, 10. *See also*
Hydrogen bonds
methylated, in tRNA, 889–890
mismatched, 117–118, 118f, 837–838
nomenclature of, 736t
nonstandard, 117–118, 118f, 837–838
non-Watson–Crick, 837–838
in nucleosides, 111, **111**. *See also*
Nucleoside(s)
in nucleotides, 111–112, **112**. *See also*
Nucleotide(s)
oxidation of, 838
purine, 111, **111**
synthesis of, 740–745, 740f
pyrimidine, 111, **111**
synthesis of, 736–740, 736f
recognition sites and, 141, 141f, 272, 275–277
in recombinant DNA technology, 139. *See also* Recombinant DNA technology
RNA, homologous, 186–187, 187f
rules for, 114
stacking of, 10, 10f, 114–115, 119f
hypochromism and, 120, 120f
thymine, **4**, 111, **111**
in translation, 891–893, 901
uracil, 111, **111**
Watson–Crick, **5**, 113–115, 114f, 186, 187f
wobble in, 891–893
- Basic-leucine zipper, 942
- Bathorhodopsin, 967–968
- Bcr–Abl, in chronic myelogenous leukemia, 421, 421f
- B-DNA helix, 115–116, 116t
- Bennett, Claude, 987
- Benzaldehyde, 958, **958**
- Benzoate, 689
- Berg, Howard, 548, 1023
- Berg, Paul, 148, 644
- Beriberi, 517
- β cells, in diabetes, 802
- β chains, of hemoglobin, 199, 199f, 211
- β sheet, 40–42, 40f–42f
amino acid residues in, 50–52, 51t
- β strands, 41–42, 41f
amino acid residues in, 50–51, 51t
of membrane proteins, 357, 357f
- β turns, 42, 42f
amino acid residues in, 50–51, 51t
- β_2 subunit, of *E. coli*, in DNA replication, 831–832, 831f
- β -adrenergic receptor, 404–405, 404f
- β -adrenergic receptor kinase, 408
- β -arrestin, 408
- β -globin gene. *See also* Hemoglobin transcription and processing of, 131–132, 132f
- β -hemoglobin, 199, 199f, 211. *See also* Hemoglobin
- β -lactam ring, of penicillin, 244, 244f
- β_2 -microglobulin, 992–993, 993f
- β -oxidation pathway, in fatty acid metabolism, 646–647
- β -thalassemia, 210–211, 211
- β -tubulin, 1018–1019, 1018f, 1019f
- Bicarbonate
dehydration of, carbonic anhydrase in, 266–271
in pyrimidine synthesis, 737
- Bicarbonate ion, in oxygen transport, 207–208, 208f
- Bifunctional enzyme, 487
- Bile, in drug metabolism, 1035–1036
- Bile salts, 642, 642f
synthesis of, 779–780, 780f
- Bilirubin, 730, **730**
- Biliverdin, 730, **730**
- Biliverdin reductase, 730, **730**
- Binding energy, 229
definition of, 254
enzyme specificity and, 275–277
- Binding-change mechanism, 547, 547f
- Biochemistry
definition of, 1
unifying concepts in, 1–4, 2f, 3f
- Bioenergetics. *See also* Energy
of coupled reactions, 429–430, 431–433
enzymes and, 222–225
of metabolism, 429–435
thermodynamic principles and, 11–13
- Biofilms, 930–931
- Bioinformatics, 173–192. *See also* Sequence homologies
- Biological diversity, biochemical unity
underlying, 1–4, 2f
- Biological macromolecules, 2
- Biopterin, 695
- Biotin, 441t
in fatty acid synthesis, 657
in gluconeogenesis, 482–483, 483f
- 1,3-Bisphosphoglycerate, **434**
in glycolysis, 464, 484
oxidation of, 436–437
phosphoryl-transfer potential of, 434, 434t
- 2,3-Bisphosphoglycerate
in glycolysis, 464
oxygen affinity of hemoglobin and, 204–205
- Bisubstrate reactions, 235–236
- Bitter taste, 962, 963–964
- Bjorkman, Pamela, 992
- Blackburn, Elizabeth, 837
- BLAST search, 181, 182f
- Bleach, urine as, 687b
- Bleeding disorders, 311–312, 312
- The Blind Watchmaker* (Dawkins), 53
- Blood clotting. *See* Clotting

- Blood groups, glycosyltransferases in, 335–336
- Blood–brain barrier, 1033
- Blow, David, 257
- Blue photoreceptors, 969–970, 970f
- Boat form, 324, 325f
- Body mass index (BMI), 792, 793f
- Body weight, regulation of, 791–798. *See also* Caloric homeostasis
- Bohr, Christian, 206
- Bohr effect, 206–208, 207f
- Bombardment-mediated transformation, 167
- Bonds
- covalent, 7
 - cleavage of, 13
 - disulfide, 35, 35f
 - cleavage of, 49
 - reduction of, 83
 - electrostatic interactions, 7–8
 - in antigen-antibody binding, 984, 985, 985f
 - ATP and, 433–434
 - in enzyme-substrate complex, 228, 229f
 - glycosidic
 - in disaccharides, 327
 - in monosaccharide alcohol/amine complexes, 326, 326f
 - high-energy, 433–434
 - hydrogen. *See* Hydrogen bonds
 - hydrophobic effect and, 9–10, 9f
 - hydrophobic interactions and, 10
 - isopeptide, 675, 675f
 - noncovalent, 7–11. *See also* Noncovalent bonds
 - peptide. *See* Peptide bonds
 - phosphodiester, 110, **110**, 111
 - hydrolysis of, 272–274
 - in resonance structures, 7
 - surface complementarity and, 11
 - units of measure for, 7
 - van der Waals interactions. *See* Van der Waals interactions
- Bonitus, Jacob, 517b
- Bordetella pertussis*, 422
- Bortezomib (Velcade), **678**, 679
- Bovine spongiform encephalopathy, 56–57, 56f
- Boyer, Herbert, 148
- Brain
- glucose metabolism in, in starvation, 809–810, 810t
 - sensory processing in. *See* Sensory systems
 - vanishing white matter in, 908–909, 909f
- Branched-chain amino acids. *See also* Amino acid(s)
- degradation of, 693–695
- Branched-chain ketoaciduria, 697
- Branching enzyme, in glycogen metabolism, 629
- Brenner, Sydney, 128
- Briggs, George, 231
- British anti-lewisite (BAL), 517
- 3-Bromoacetyl phosphate, 242, **242**
- Bromodomains, 949–950, 950f
- Brown fat, 556–557
- Brown, Michael, 767b, 775, 776
- Bubble boy disease, 753
- Buchner, Eduard, 454
- Buchner, Hans, 454
- Buck, Linda, 959
- Buffers, 15–17, 15f, 16f
 - in carbon dioxide hydration, 270, 270f
- Burkitt lymphoma, 869
- t*-Butyloxycarbonyl amino acid, 97, **97**
- Butyryl ACP, 658t, 659, **659**
- bZip, 942
- C genes, 987
 - in antibody switching, 991
- C₃ plants, 600
- C₄ pathway, in photosynthesis, 599–600, 600f
- Ca²⁺ pump, 374–378, 375f, 376f
- CAAT box, 127, 867, 867f
- CAD, 688
- Caenorhabditis elegans*
 - genome of, 159
 - RNA interference in, 166
- Caffeine, metabolism of, 783
- Calciferol (vitamin D), 442, 442t
 - deficiency of, 786
 - sources of, 786
 - synthesis of, 785, 785f
- Calcineurin, 990, **990**
- Calcitriol, 785, **785**
- Calcium ATPase, in phosphoinositide cascade, 409
- Calcium ATPase, 375–377
- Calcium ion(s)
- in calmodulin activation, 410–411
 - in insulin secretion, 802
 - in phosphorylase kinase activation, 624, 624f
 - prothrombin binding of, 310–311
 - in pyruvate dehydrogenase complex activation, 514
 - in signal transduction, 409–411, 409f–411f, 802
 - structure of, **403**
 - in vision, 969
- Calcium ion channels, 367, 384f. *See also* Ion channels
- sequence homologies of, 367, 384, 384f, 386
- Calcium ion pump, 374–378, 375f, 376f
 - evolution of, 378
- Calmodulin, 79, **79**, 624
 - in glycogen metabolism, 624
 - in signal transduction, 410–411
- Calmodulin-dependent protein kinases, 411
- Calnexin, 339
- Caloric homeostasis, 791–798
 - definition of, 791
 - in diabetes, 799–802
 - dieting and, 797–798
 - evolution and, 792–793
 - exercise in, 803–806
 - fasting and, 796
 - food intake and, 793–794
 - insulin in, 796
 - melanocyte-stimulating hormone in, 796
 - obesity and, 792–803. *See also* Obesity
 - satiating signals in, 795–797, 796f
 - signaling in, 794–797, 794t, 795f–797f
 - suppressors of cytokine signaling in, 797, 797f
- Calorie (cal), 223b
- Calreticulin, 339
- Calvin cycle, 590–601
 - C₄ pathway and, 599–600
 - energy expenditure in, 597
 - evolution of, 600
 - hexose sugar formation in, 594–597, 594f
 - oxygenase reaction in, 593, 593f
 - pentose phosphate pathway and, 609
 - 3-phosphoglycerate formation in, 591–592, 592f
 - reactions in, 590–597, 590f, 596f
 - regulation of, 598–600
 - ribulose 1,5-bisphosphate regeneration in, 594–597, 596f
 - salvage pathway in, 593–594, 593f
 - stages of, 590–591, 590f, 596f
 - thioredoxin in, 598–599, 598t, **599**
- CaM kinase, 411
- cAMP
- in glycogen metabolism, 625–626, 625f, 626
 - in protein kinase A activation, 301, 301f
 - as second messenger, 402–403
 - in signal transduction, 405, 406–407
 - structure of, **301**, **403**
- cAMP receptor protein (CRP), 927–928, 927f
- Camptothecin, 831
- Cancer
- aerobic glycolysis in, 478–479
 - breast, taxol for, 1019–1020
 - carcinogen testing and, 843–844
 - citric acid cycle defects in, 515
 - colorectal, 842–843
 - cytochrome P450 and, 783
 - defective DNA repair in, 842–843
 - drug resistance in, 1050–1051
 - enhancers in, 869
 - fatty acid synthase in, 663
 - glycolysis in, 478–479, 479f
 - hypoxia inducible factor 1 in, 515
 - immune response in, 1001
 - leukemia, 421
 - in Li-Fraumeni syndrome, 843
 - metabolic derangements in, 515
 - mutagens and, 838
 - myc* gene in, 869
 - oncogenes and, 420
 - protein kinase inhibitors for, 421
 - proto-oncogenes and, 420
 - signal transduction defects in, 420

- Cancer—(continued)
 skin, in xeroderma pigmentosum, 842
 telomerase inhibitors for, 837
 thymidylate inhibitors for, 749–750
 tumor hypoxia in, 478–479
 tumor-suppressor genes and, 420
 Warburg effect in, 478
- CAP (catabolite activator protein), 927–928, 927f
- CAP–cAMP complex, 927–928
- Capsaicin, 973–974, 973f
- Captopril, 264
- Carbamate, 208, **208**
 in Calvin cycle, 592–593
- Carbamic acid, 737, **737**, 738, 738f
- Carbamoyl phosphate, **290**, **686**
 in pyrimidine synthesis, 737
 in urea cycle, 685–687, 685f
- Carbamoyl phosphate synthetase, 689f
 active sites on, 737–738, 738f
 deficiency of, 689, 689f
 isozymes of, 688
 in pyrimidine synthesis, 737, 751
 structure of, **737**, 737–738, **738**
 synthesis of, 737
 in urea cycle, 685–686
- Carbamoylaspartate, **290**, 738, **738**. *See also* Aspartate transcarbamoylase (ATCase)
 biosynthesis of, 290–296
- Carbohydrate–asparagine adduct, **57**
- Carbohydrates, 319–340
 abbreviations for, 330b
 disaccharides, 327–329. *See also* Disaccharides
 in glycoproteins, 57, 329–337
 lectins and, 337–339, 339f
 metabolism of, 454
 monosaccharide, 320–327. *See also* Monosaccharides
 N-linked, 330, 330f, 334, 336
 oligosaccharides, 327. *See also* Oligosaccharides
 O-linked, 330, 330f, 334
 overview of, 319–320
 peptide bond cleavage in, 337
 polysaccharides, 328, 328f, 329f. *See also* Polysaccharides
 in red blood cells, 335
 sequencing of, 336–337
 starch, 328–329, 329f
 in viral infections, 339–340
- Carbo-loading, 806
- Carbon dioxide
 activated, biotin carrier for, 483, 483f
 in Calvin cycle, 591–597
 from carbon oxidation, 435
 hydration of, 206
 carbonic anhydrase in, 266–271
 in oxygen release by hemoglobin, 207–208, 207f, 208f
 transport of, C₄ pathway for, 599–600, 600f
- Carbon fuels
 body reserves of, 809
 definition of, 498
 for exercise, 805–806, 805t
 for glucose metabolism, 808, 809
 oxidation of. *See also* Catabolism
 in citric acid cycle, 498. *See also* Citric acid cycle
 free energy of, 434, 435–438, 435f
- Carbon monoxide, in oxidative phosphorylation inhibition, 558
- Carbon monoxide poisoning, 213
- Carbon skeletons, of amino acids, metabolic fates of, 690–696, 691f
- Carbonic acid, biosynthesis of, 266–271
- Carbonic anhydrases, 207, 207f, 266–271
 alpha-type, 271
 beta-type, 271
 catalytic activity of, 266–271
 evolution of, 271
 gamma-type, 271, **271**
 structure of, **267**, 267–268, 271, **271**
 zinc site in, 267–269, 267f–269f
- Carboxamides, 30, 30f
- 2-Carboxy-3-keto-D-arabinitol 1,5-bisphosphate, 592f
- Carboxyaminoimidazole ribonucleotide, **742**, 742f
- Carboxybiotin, 483, **483**
- Carboxyglutamate, **57**, 58, 310, **310**
 biosynthesis of, 310–311
 in prothrombin, 310–311
 in vitamin K deficiency, 57, 310
- Carboxyhemoglobin, 213–214
- γ-Carboxylation, 298t
- Carboxyl-terminal domain (CTD), 865, 868, 877, 877f
- 1-Carboxyphenylamino-1-deoxyribulose 5-phosphate, **721**, 722
- Carcinoembryonic antigen, 1001
- Carcinogens, tests for, 843–844
- Cardiac muscle, H and M isozymes in, 297, 297f
- Cardiolipin, 349, **349**
 functions of, 762
 synthesis of, 762–763
- Cardiotonic steroids, 377, 377f
- Cardiovascular disease, 744–745, 759, 776–779
 homocysteine in, 719
- Cargo receptors, 913–914
- Carnitine, 645, **645**
 deficiency of, 646
- Carnitine acyltransferase I, 645, 666
- Carnitine acyltransferase II, 646
- Carotenoids, 582–583
- Carriers, 371
- Cartilage, 332, 332f
- Carvone, 958, **958**
- Caspases, 303, 559
- Cassette mutagenesis, 157, 157f
- Catabolism, 428
 definition of, 706b
 electron carriers in, 438–439, 438f, 439f
 energy from, 435–438
 free energy of, 434, 435–438, 435f, 437f
 stages of, 437–438, 437f
- Catabolite activator protein (CAP), 927–928, 927f
- Catabolite repression, 927–928
- Catalase, 542
- Catalysis
 by approximation, 254
 in carbon dioxide hydration, 266–271
 Circe effect in, 235b
 covalent, 254, 255–260. *See also* Covalent catalysis
 in DNA cleavage, 272
 in double-displacement (ping-pong) reactions, 237
 efficiency of, 235, 235t
 electrophilic, 683
 enzyme activity in
 assays for, 67. *See also* Protein purification
 specific, 67
 enzyme–substrate complex formation in, 226–227
 general acid-base, 254
 in metabolic regulation, 446
 metal ion, 221, 221t, 254–255
 in carbon dioxide hydrolysis, 267–269, 267f–269f
 in DNA cleavage, 274, 277
 Michaelis constant (K_M) for, 231–235
 in peptide bond cleavage, 258–260, 259f
 rate of, 231–235. *See also* Enzyme kinetics; Reaction rates
 reaction equilibrium and, 224–225
 reaction rate acceleration and, 206, 220t, 225–229, 226f
 by RNA, 879–881
 in selective binding of transition state, 225–226, 225f, 227–228, 243–244
 in sequential reactions, 236–237
 site-detected mutagenesis and, 262–263, 262f
- Catalytic antibodies, production of, 243–244, 243f
- Catalytic groups, 227
- Catalytic RNA, 879–881, 900
- Catalytic strategies, 254–286
 of carbonic anhydrases, 253, 266–271
 covalent, in chymotrypsin, 255–260
 of myosins, 253–254
 overview of, 253–254
 of restriction endonucleases, 253, 271–279
 of serine proteases, 253, 255–266
- Catalytic triads, 257–260
 in chymotrypsin, 257–260, 261f
 in elastase, 261, 261f
 site-directed mutagenesis and, 262–263, 262f
 in subtilisin, 261, 261f
 in trypsin, 260–261, 261f

- Catalytically perfect enzymes, 234, 235, 460
Cataracts, 472
Cation exchange, 70
CCA terminal region, 891
CCA terminus, of tRNA, 890f, 891
CD3, 995, 995f
CD4, 997
CD8, 994–995, 995f
cDNA (complementary DNA), 154–155, 154f, 162f
 in quantitative polymerase chain reaction, 162, 162f
cDNA library, 154
CDP, hydrolysis of, 431
CDP-diacylglycerol, 761, **761**
CDP-ethanolamine, synthesis of, 763
CDRs (complementarity-determining regions), 984, 984f, 985–986
Cech, Thomas, 852, 879
Celecoxib, 1044, **1044**
Celecoxib (Celebrex), 1044
Cell cycle, 836, 836f
Cell types, in eukaryotes, 938, 939t
Cell-mediated immunity, 991
Cell-to-cell ion channels, 372, 393–394, 393f, 394f
Cellular energy. *See* Energy
Cellular immune response, 980
Cellular respiration, 498, 499f, 593f, 594.
 See also Respiratory chain
 definition of, 526b
 in photosynthesis, 593f, 594
 regulation of, 554–560
Cellulase, 313
Cellulose, 328–329
Centrifugation
 band, 77–78, 77f
 density-gradient equilibrium, 119–120, 119f
 differential, 67–68, 68f
 gradient, 77–78, 77f
 homogenate in, 67, 68f
 sedimentation coefficients in, 76, 76t, 77f
 supernatant in, 67, 68f
 zonal, 77–78, 77f
Ceramide, **764**
 sphingolipids from, 763–764
 synthesis of, 764, 764f
Cerebroside, 350, **350**
 synthesis of, 764
Cetuximab, 421
CF₁–CF₀ complex, 578–579. *See also* ATP synthase (Complex V)
cGMP
 structure of, **403**
 in vision, 968f, 969
cGMP phosphodiesterase, in vision, 968
cGMP-gated Ca²⁺ channel, in vision, 968
Chain, Ernest, 1037
Chain-terminated fragments, in DNA sequencing, 143
Chair form, 324, 325f
Changeux, Jean-Pierre, 202
Channels
 ion. *See* Ion channels
 water, 394
Charcot-Marie-Tooth disease, 1018
Chargaff, Erwin, 114
Charge separation, photoinduced, 569, 569f
Charged tRNA, 891f, 893
Chemical modification reaction, 256
Chemical protons, 540f
Chemical reactions. *See* Reaction(s)
Chemical shifts, in NMR spectroscopy, 101, 101f
Chemiosmotic hypothesis, 544–545, 544f, 545f
Chemistry, combinatorial
 in drug development, 1041. *See also* Drug development
 in evolution studies, 188–189
Chemoattractants, 1024
Chemorepellants, 1024
Chemotaxis, 1024–1025, 1025f
Chemotherapy, cancer, resistance in, 1050–1051
Chemotrophs, 428
Cheng–Prusoff equation, 1031
CheY, 1024
ChIP (chromatin immunoprecipitation), 945
Chirality, 27
 of amino acids, 28, 29f, 713
Chitin, 333, 333f
Chloramphenicol, 909t, 910
Chlorobium thiosulfatophilum, 584, 584t
Chlorophyll *a*, **568**, 568–572, 568f, 569f
 in photosystem II, 573, 573f
Chlorophyll *b*, **582**, 582–583, 582f
Chloroplasts, 567–568, 567f
 ATP synthesis in, 578–581, 578f
 evolution of, 568
 genome of, 568
 starch in, 597
 structure of, 567, 567f
Chlorpromazine, **1038**
 discovery of, 1038
 mechanism of action of, 1038, 1039f
Cholecalciferol, 785, **785**
Cholecystokinin, in caloric homeostasis, 794–795, 795f
Cholera, 421–422, 765
Cholesterol, 350, **350**
 “bad,” 744
 bile salts from, 779–780
 elevated levels of, 744–745, 759, 776–779, 777f
 “good,” 744–745, 776
 labeling of, 767f
 in lipid membrane, 363
 metabolic fates of, 775–776
 metabolism of, 775–779
 properties of, 767, 767b
 receptor-mediated endocytosis and, 385f
 steroid hormones from, 780–782
 transport of, 773–774, 774–775
 reverse, 778–779
Cholesterol synthesis, 767–779
 condensation mechanism in, 769, 769f
 hepatic, 770, 774f
 isopentenyl pyrophosphate in, 768
 mevalonate in, 767–768
 rate of, 770–773
 regulation of, 770–779
 site of, 773, 774f
 squalene in, 768–770
 stages of, 767
 sterol regulatory element binding protein in, 770–771, 771f
Choline, in phospholipids, 349
Chondroitin 6-sulfate, **331**, 332
Chorismate, in amino acid synthesis, 719–720, 720f
Chromatin, 937–941, 938–941
 definition of, 938–939
 structure of, 938f
 DNA packing in, 941
 in gene regulation, 944–951
 remodeling of, 944–951, 949–951, 950f
 structure of, 939
 transcription factors and, 946–947
Chromatin immunoprecipitation (ChIP), 945
Chromatin-remodeling engine, 950, 950f
Chromatography
 affinity, 70–71, 70f, 75, 78
 gel-filtration, 69, 69f, 75
 high-pressure liquid, 71, 71f
 ion-exchange, 69–70, 69f, 75, 75t
 in amino acid identification, 80–81, 80f
Chromogenic substrate, 256
Chromophores, 967
Chromosomes
 bacterial artificial, 151
 yeast, 937, 938f
 yeast artificial, 151, 151f
Chronic myelogenous leukemia, treatment of, 421
Chylomicron remnants, 773
Chylomicrons, 642, 642f, 773, 773t
Chymotrypsin, **186**, 255–260
 active sites of, 185–186, 186f, 257–258
 catalytic triad in, 257–260
 covalent catalysis in, 255–260
 acyl-enzyme intermediate in, 257, 259f
 tetrahedral intermediate in, 258–259, 259f
 as two-stage process, 256–257, 257f, 259f
 homologs of, 260–261, 261f
 inhibition of, 53f, 241–242, 241f
 in peptide bond cleavage, 259f
 serine residue of, 255–256, 256f
 specificity of, 256f, 260, 260f
 structure of, **256**, 257–258, **258**, 260, 261f
 substrate preferences of, 234–235, 235t
 trypsin and, 260–261, 261f
Chymotrypsin inhibitor, structure of, 53f
Chymotrypsinogen, 257–258, 303–305

- Cilia
 cochlear, 971–973, 971f, 972f
 microtubules in, 1019
- Ciprofloxacin, 831, **831**
- Circadian rhythms, 974
- Circe effect, 235, 235b
- Circular DNA, 117, 117f
- Cirrhosis, 811–812
- Cis configuration, of peptide bonds, 36–37, 36f, 37f
- Citrate
 in fatty acid metabolism, 662, 662f, 666, 667f
 isomerization of, in citric acid cycle, 506, 506f
- Citrate synthase, in citric acid cycle, 504, 505f
- Citric acid cycle, 497–520
 acetyl coenzyme A in, 497, 500–501, 501, 503–505, 514–515, 653, 656
 aconitase in, 506, **506**
 ATP in, 498, 512, 514–515, 514f, 554–555, 555t
 in cancer, 515
 in cellular respiration, 499f
 citrate isomerization in, 506, 506f
 citrate synthase in, 503–505, 505f
 citryl coenzyme A in, 505
 definition of, 497
 electron-transport chain in, 498, 512
 enol intermediate in, 504
 enzyme complexes in, 512
 evolution of, 518
 function of, 498
 glycolysis and, 499–503, 499f
 intermediates in, from amino acid degradation, 690–696
 isocitrate dehydrogenase in, 506, 514, 514f
 isocitrate in, 506–507, 507f
 α -ketoglutarate dehydrogenase complex in, 499, 507, 514–515, 514f
 α -ketoglutarate in, 506–507, 507f, 692
 ketone bodies in, 810, 810f
 malate in, 510
 in mitochondria, 498, 498f
 net reaction of, 510
 nucleoside diphosphokinase in, 508
 overview of, 497–499
 oxaloacetate in, 498, 498f, 504, 505f, 509–510, 515, 653
 oxalosuccinate in, 506, 507f
 pyruvate carboxylase in, 516
 pyruvate dehydrogenase complex in, 499–503, 499f, 499t, 502f, 503f
 pyruvate dehydrogenase in, 500
 rate of, 556f
 reaction rate in, 556
 reactions of, 510–512, 511f, 511t
 regulation of, 512–516, 555–556, 556f
 as source of biosynthetic precursors, 516–518
 stoichiometry of, 510–512, 511f, 511t
 substrate channeling in, 512
 succinate dehydrogenase in, 509–510
 succinyl coenzyme A in, 507–508, 507f, 514
 succinyl coenzyme A synthetase in, 507–508
- Citrulline, 686, **686**, 689
- Citrullinemia, 698t
- Citryl coenzyme A, in citric acid cycle, 505
- Clamp loaders, 832
- Class I MHC proteins, 991–996, 993f, 998–999. *See also* Major histocompatibility complex proteins
- Class II MHC proteins, 996–999, 996f
- Class switching, 990–991, 991f
- Clathrin, 775, 776f
- Cleavage
 DNA. *See* DNA, cleavage of
 protein, 82–83, 82f
- Cleland notation, 236, 237
- Cleland, W. Wallace, 236
- Clinical trials, 1048–1049, 1049f
- Clones, DNA, 154–155
- Cloning, 87–88
 expression, 154–155, 155f
 plasmid vectors in, 149–151, 149f, 150f
- Cloning vectors, 148, 149
- Clotting, 307–313
 extrinsic pathway of, 308, 308f
 impaired, 310–313, 311–313
 in hemophilia, 311
 intrinsic pathway of, 308, 308f
 regulation of, 311–312
 zymogen activation in, 307–312
- Clotting factors, 312
- CMP (cytidine monophosphate), 762
- Coactivators, 947–948, 948f, 949–951
- Coagulation. *See* Clotting
- Coat proteins, 914
- Coated pits, 775, 776f
- Cobalamin (vitamin B₁₂), 441t, 649
 in amino acid synthesis, 650–652, 650f, 651f, 717
 as coenzyme, 650–652, 650f, 651f, 717
 in fatty acid metabolism, 649–652
 structure of, **650**, 650–651
- Cobratoxin, 390
- Cochlear hair cells, 971–973, 971f, 972f
- Coding strand, 854
- Codons, 19, 109–110, 128. *See also* Anticodons
 definition of, 128
 in genetic code, 129–130, 129t
 initiation, 900–901
 in translation, 889, 891–893, 892f
- Coenzyme(s), 221, 221t
 vitamin, 441t
- Coenzyme A, 440, **440**, 441t
 as acyl group carrier, 440
 ADP units in, 447, 447f
 in fatty acid metabolism, 644
- Coenzyme B₁₂, 650–652, 650f, 651f
- Coenzyme Q (ubiquinone), 532–533, 533f
 in fatty acid metabolism, 646
- Cofactors, enzyme. *See* Coenzyme(s)
- Cognate DNA, 272
 cleavage of, 275–277
- Cohen, Stanley, 148
- Cohesive-end method, 148–149, 149f
- Coiled-coil proteins, 43, 44f
- Collagen, 303
 amino acid sequences of, 44, 44f
 ascorbate and, 813
 in cartilage, 332
 helix of, 44–45, 44f
- Collagenase, 303
- Color blindness, 970–971
- Color vision, 966, 969–971. *See also* Vision
 in animals, 970, 970f
 defective, 970–971
 evolution of, 970, 970f
- Colorectal cancer, 842–843
- Combinatorial association, antibody diversity and, 988–989
- Combinatorial chemistry, in evolution studies, 188–189
 in drug development, 1041. *See also* Drug development
- Combinatorial control, 943
- Committed step, 474, 723
- Compactin, 1040, **1040**
- Comparative genomics, 160–161, 160f
- Compartments, drug target, 1033, 1033f
- Competitive inhibition, 238–240, 238f, 239f, 240f
- Complement cascade, 981
- Complementarity-determining regions (CDRs), 984, 984f, 985–986
- Complementary DNA (cDNA), 154–155, 154f
 in quantitative polymerase chain reaction, 162, 162f
- Complementary single-stranded ends, 148
- Computer databases, for amino acids, 65–66, 181, 182f
- Concentration gradient, 373–374
 in ATP synthesis, 437–438, 437f
- Concerted mechanism, in substrate binding, 294–296
- Concerted (MWC) model
 of allosteric enzyme kinetics, 296, 296f
 of hemoglobin oxygen binding, 202–203, 203f, 214–216, 216f
- Cones, 966, 969–970, 969f
- Congenital erythropoietic porphyria, 730–731
- Congestive heart failure, digitalis for, 377
- Conjugation, in drug metabolism, 1034–1035
- Connexin, 394
- Connexon, 394, 394f
- Consensus sequences, 126b, 126f, 299
 in phosphorylation, 299
 in promoters, 857, 857f
 in splicing, 132f, 133, 873–874, 873f
- Conservative substitutions, 178
- Constant (C) genes, 987
 in class switching, 991

- Constant regions, 984, 984f
Constitutional isomers, 321, 321f
Continuous genes, 131, 132
Controlled termination of replication, 143–144, 143f
Convergent evolution, 185–186
Cooley anemia, 210–211
Cooperative binding, 200–201, 201f, 203f, 294
Cooperative transition, in protein folding, 52
Cooperativity, 289
Coprotophyrinogen III, 729, **729**
Cordycepin, 872
Core enzyme, 856
Core promoter, 857
Corepressors, 927
Corey, Robert, 38
Cori, Carl, 454
Cori cycle, 490, 490f, 685
Cori disease, 634t
Cori, Gerty, 454, 634
Coronary artery disease. *See* Atherosclerosis
Corrin ring, 650–651, 650f
Corticosteroids. *See also* Steroid hormones synthesis of, 783
Corticosterone, **784**
Cortisol, synthesis of, 780, 780f, 783, **784**
Corynebacterium diphtheriae, 910
Cotransporters, 380, 380f
Coulomb's law, 7–8
Covalent bonds, 7. *See also* Bonds cleavage of, 13
Covalent catalysis, 254, 255–260 acyl-enzyme intermediate in, 257, 259f chymotrypsin and, 255–260 tetrahedral intermediate in, 258–259, 259f as two-stage process, 256–257, 257f, 259f
Covalent modification, of proteins, 57–58, 57f, 297–302, 298t mechanisms of, 298t. *See also* Phosphorylation
COX2 inhibitors, **1044** development of, 1043–1045
CpG islands, 946
CpG, methylation of, 945–946
Crassulacean acid metabolism, 600–601, 600f
Cre recombinase, 845–846
Creatine kinase, 236–237 in sequential reactions, 236–237, 236f
Creatine phosphate, **434** during exercise, 434–435, 435f, 805, 805t phosphoryl-transfer potential of, 434, 434t
Creutzfeldt–Jakob disease, 56–57, 56f
Crick, Francis, 5, 114, 127, 128, 891
Cristae, 526, 527f
Critical concentration, 1014
Crixivan (indinavar), development of, 1043, 1043f
Cro, λ repressor and, 929
Cross-links, 838, 839f
Crotonyl ACP, 658t, 659, **659**
Crown gall, 166–167, 166f
CRP (cAMP receptor protein), 927–928, 927f
Crystallography, X-ray, 98–100, 98f–100f of enzyme-substrate complexes, 227, 227f
c-Src, in cancer, 420
CTD (carboxyl-terminal domain), 865, 868, 877, 877f
CTP. *See* Cytidine triphosphate (CTP)
Cumulative feedback inhibition, 725
Cupric ion, 325
Cyanide, 558
Cyanobacteria, 568, 568f
Cyanogen bromide, in protein cleavage, 82, 82f
Cyclic adenosine monophosphate. *See* cAMP
Cyclic hemiacetals, 322
Cyclic photophosphorylation, 580–581, 580f
Cyclin, 836 ubiquitination of, 298, 298t
Cyclin B, degradation of, 673f
Cyclin destruction boxes, 676
Cyclin-dependent protein kinases, 836
Cycloheximide, 909t, 910 in taste, 963–964
Cyclooxygenase 2, 1044
Cyclooxygenase inhibitors, development of, 1044–1045
Cyclophosphamide-glutathione conjugate, 1034, **1034**
Cyclosporin, 990, **990**
Cystathionine, 718–719, **719**
Cysteine molecular models of, 23f pyruvate formation from, 691, 691f structure of, 30, 30f synthesis of, 714–715, 718–719
Cysteine proteases, in peptide bond cleavage, **263**, 263–264, 264f
Cystine, 35, 35f
Cytidine, 111 synthesis of, 739–740
Cytidine diphosphodiacylglycerol (CDP-diacylglycerol), 761, **761**
Cytidine monophosphate (CMP), 762
Cytidine triphosphate (CTP), 761 ATCase inhibition by, 291, 291f, 295–296, 296f hydrolysis of, 431 in pyridine synthesis, 291, 291f, 295–296, 296f structure of, **290**, 291 synthesis of, 739–740
Cytidine triphosphate synthetase, 739
Cytochrome definition of, 535 in photosynthetic reaction center, 572, 572f
Cytochrome *b₅*, 664, 664f
Cytochrome *bf* complex, 575, 575f location of, 583, 583f
Cytochrome *c*, 533, 535 in apoptosis, 559 evolution of, 543, 543f in oxidative phosphorylation, 531, 532f, 532t
Cytochrome *c* oxidase (Complex IV), 531, 532f, 532t in oxidative phosphorylation, 531 in respiratory chain, 537–540, 538f–540f
Cytochrome *c* oxidoreductase, 535–536
Cytochrome P450, 782–783, 782f in drug metabolism, 1034
Cytochrome P450 monooxygenases, 781
Cytochrome reductase, 531, 532f, 532t, 535–536, 536f
Cytoglobin, 212
Cytokines, 998, 998f
Cytoplasm fatty acid synthesis in, 657 glycolysis in, 498
Cytosine, 4, **4**, 111, **111** deamination of, 838, 841
Cytoskeleton, 1007, 1008f
Cytotoxic T cells, 980, 994–996, 997–998, 997f. *See also* T cell(s)
D amino acids, 27, 27f
D genes, 988 in antibody switching, 991
D stereoisomers monosaccharide, 320 of monosaccharides, 321f, 322f
DAG. *See* Diacylglycerol (DAG)
Dalton, 34
Dark reactions, of photosynthesis, 566, 589, 590–601. *See also* Calvin cycle; Photosynthesis
Darst, Seth, 853
Databases, of amino acid sequences, 65–66, 181, 182f
Dawkins, Richard, 53
DCC (dicyclohexylcarbodiimide), 97, **97**
Deamination, 838, 838f, 841 in amino acid degradation, 680–684
Decarboxylation, 484 in citric acid cycle, 500, 507 in fatty acid synthesis, 659 in gluconeogenesis, 484 in pentose phosphate pathway, 601
Decorated actin, 1014
Degenerative arthritis, 332
Degron, 676
Dehydration, in amino acid degradation, 684
Dehydroascorbic acid, 813, **813**
7-Dehydrocholesterol, 785, **785**
Dehydrogenases, NAD⁺ binding sites in, 469, 469f
3-Dehydroquinate, in amino acid synthesis, 719, **720**
3-Dehydroshikimate, **720**
Deletions, production of, 156

- Denatured proteins, 49–50, 49f, 50f
- Density-gradient equilibrium
sedimentation, 119–120, 119f
- Deoxyadenosine, 111, 872
- 5'-Deoxyadenosyl radical, 651, 651f
- 5'-Deoxyadenosylcobalamin, **650**
- Deoxyadenylate, 111
- 3-Deoxyarabinoheptulosanate 7-phosphatase,
in amino acid synthesis, 719, **720**
- Deoxycycline, 240
- Deoxycytidine, 111
- Deoxycytidylate, 111
- Deoxyguanosine, 111
- Deoxyguanosine 3-monophosphate
(3'-dGMP), 112, **112**
- Deoxyguanylate, 111
- Deoxymyoglobin, 196, **197**. *See also*
Myoglobin
- Deoxyribonucleic acid. *See* DNA
- Deoxyribonucleoside 3'-phosphoramidites,
in DNA synthesis, 144, **144**, 144f
- Deoxyribonucleoside triphosphate, in
replication, 822, 823f
- Deoxyribonucleotide synthesis, 745–750
deoxyuridylate in, 748
dihydrofolate reductase in, 749
regulation of, 752, 752f
ribonucleotide reductase in, **745**,
745–750, 745f, **746**, 752, 752f
thymidylate in, 748, 749f
- Deoxyribose, 110, **110**, 322f
- Dephosphorylation, 300
- (-)-Deprenyl, 242, **242**
- Dermatan sulfate, **331**, 332
- 1-Desamino-8-D-arginine vasopressin, 96, **96**
- Desaturase, 664, 664f
- Designer genes, 157
- Desmolase, 783
- α -Dextrinase, 454
- DHAP. *See* Dihydroxyacetone phosphate
(DHAP)
- DHU loop, 891
of tRNA, 890f
- Diabetes insipidus, 96
- Diabetes mellitus, 325–326, 798–803
as autoimmune disease, 1001
derivation of name, 798b
glucose homeostasis in, 798–800
incidence of, 798
insulin in, 798–800
insulin resistance and, 799–802
ketosis in, 633f, 653, 655, 803
obesity and, 798–803
pancreatic failure in, 801–802
type 1, 798, 802–803
type 2, 798–802
- diabetes mellitus, type 2
pathogenesis of, 800–802
treatment of, 802
- Diabetic ketoacidosis, 803
- Diacylglycerol (DAG), **408**, **642**
in phospholipid synthesis, 761, 761f,
762, 762f
in signal transduction, 408–409, 409f
synthesis of, 761
- Diacylglycerol 3-phosphate, 348, **348**
in membrane lipid synthesis, 760
- Diacylglycerol kinase, 760
- Dialysis, in protein purification, 69, 69f
- Dianabol, **948**
- Diastereoisomers, 321, 321f
- Diazotrophic microorganisms, 707
- 5,5-Dibromo-4,4'-dichloro-indigo, **924**
- Dicarboxylate carrier, 554, 554f
- Dicoumarol, 310, **310**
- Dictyostelium discoideum*, myosin-ATP
complex in, 280, 280f
- Dicyclohexylcarbodiimide (DCC), 97, **97**
- Dideoxy method, 143–144, 143f
- 2,4-Dienoyl CoA reductase, 649, **649**
- Diet, 20, 20f. *See also specific nutrients*
high-protein low-carbohydrate, 798
ketogenic, 656
low-phenylalanine, 674
spicy food in, capsaicin in,
973–974, 973f
starved–fed cycle and, 807–808. *See also*
Starvation
- Dietary fiber, 329
- DiETING, 797–798
- Differential centrifugation, 67–68, 68f
- Diffusion
active, 371, 373
facilitated, 371, 373
lipid
lateral, 361–364, 362f
transverse, 362
simple, 372
- Digestion, 437, 674, 674f. *See also* Amino
acid degradation
chymotrypsin in, 255–260. *See also*
Chymotrypsin
enzymes in, 255–260, 303–307, 303t,
304f, 674, 674f
starved–fed cycle and, 807–808
- Digitalis, Na⁺–K⁺ pump inhibition
by, 377
- Digitoxigenin, 377, **377**
- Diglyceride acyltransferase, 761
- Dihydrobiopterin, 695, **695**
- Dihydroceramide, **764**
- 1,25-Dihydrocholecalciferol, 785, **785**
- Dihydrofolate, in deoxyribonucleotide
synthesis, 748, **749**
- Dihydrofolate reductase, 695, 695f
in deoxyribonucleotide synthesis, 749
- Dihydrolipoyl dehydrogenase, in citric acid
cycle, 499t, 501, 502f
- Dihydrolipoyl transacetylase, in citric acid
cycle, 499t, 501
- Dihydroorotate, 738, **738**
- Dihydropteridine reductase, 695, 695f
- Dihydrosphingosine, **764**
in sphingolipid synthesis, 737
- Dihydrotestosterone, 785
- Dihydrouridine (UH₂), **890**
- Dihydroxyacetone, 320, **320**, 321f
structure of, 321f
in transaldolase reaction, 605–606, 606f
- Dihydroxyacetone phosphate (DHAP), 326,
326f, **458**, 479
in Calvin cycle, 594f, 595, **595**
in fructose metabolism, 469–470, 469f
in gluconeogenesis, 480f
in glycolysis, 456f, 458–459, 458f, 460f,
469–470, 480f
isomerization to glyceraldehyde
3-phosphate, 224, **224**,
458–459, 460f
- Dihydroxycholesterol, 783, **783**
- Diisopropylphosphofluoridate (DIPF),
enzyme inhibition by, 241,
241f, **241**
- 2,2-Dimercaptopropanol (BAL), 517, 518f
- Dimerization arm, 416
- Dimers, 48
- Dimethylallyl pyrophosphate, 742f, 768,
768, 768–769
- Dimethylbenzimidazole, 651
- N,N*-Dimethylpropargylamine, 242, **242**
- 2,4-Dinitrophenol (DNP), 558, **558**
- Dioxygenases, 696
- Dipalmitoyl phosphatidylcholine deficiency,
765–766
- DIPF (diisopropylphosphofluoridate),
enzyme inhibition by, 241, **241**, 241f
- Diphosphatidylglycerol, 349, **349**
functions of, 762
synthesis of, 762
- Diphthamide, 910–911
- Diphtheria, 910–911
- Dipolar ions, 27–28, 27f
- Direct repair, 840
- Disaccharides, 327–329. *See also*
Carbohydrates
abbreviations for, 330b
structure of, 327, 327f
- Discontinuous genes, 131
- Discontinuous (split) genes, 131–132,
132f, 133f
evolutionary advantages of, 133
- Diseases and disorders
albinism, 698t
alcaptonuria, 697
alcohol-related, 811–813
Alzheimer disease, 55–56, 57
amino acid sequences and, 35–36
amyloidoses, 55–57
amyotrophic lateral sclerosis, 147–148
Andersen disease, 634t
anemia, 330–331
anthrax, 831
anticipation in, 842
argininosuccinase deficiency, 689, 689f
arsenite poisoning, 517, 518f
atherosclerosis. *See* Atherosclerosis
autoimmune, 1001
beriberi, 517
bleeding disorders, 310–313, 311–313

- bovine spongiform encephalopathy, 56
 cancer. *See* Cancer
 carbamoyl phosphate synthetase
 deficiency, 689, 689f
 carbon monoxide poisoning, 213
 cardiovascular disease, 719, 759, 774–775,
 776–779. *See also* Atherosclerosis
 carnitine deficiency, 646
 cataracts, 472
 Charcot-Marie-Tooth disease, 1018
 cholera, 421–422, 765
 citrullinemia, 698t
 congenital disorders of glycosylation, 336
 congestive heart failure, 377
 Cooley anemia, 210–211
 coronary artery disease, 759, 774–775,
 776–779, 777f. *See also*
 Atherosclerosis
 Creutzfeldt–Jakob disease, 56
 diabetes insipidus, 96
 diabetes mellitus. *See* Diabetes mellitus
 diagnosis of, polymerase chain reaction
 in, 146–148
 diphtheria, 910–911
 drug-resistant, 1050–1051
 emphysema, 307
 environmental factors in, 19–20
 epilepsy, 656
 familial hypercholesterolemia, 759,
 776–779
 galactosemia, 472
 gargoylism, 332, 332f
 gene therapy for, 167–168
 genetic variations and, 19–20
 glucose 6-phosphate dehydrogenase
 deficiency, 609–610, 611
 glycogen storage diseases, 634–635, 634t
 gout, 753–754
 heart disease, 719
 hemolytic anemia, 609–610, 611
 hemophilia, 311
 Hers disease, 634t
 HIV infection. *See* Human
 immunodeficiency virus infection
 homocystinuria, 698t
 Huntington disease, 55–56, 842
 Hurler disease, 332, 332f
 hyperlysinemia, 698t
 I-cell disease, 336
 inborn errors of metabolism, 697–698, 698t
 infant respiratory distress syndrome,
 765–766
 lactose intolerance, 471
 Leber hereditary optic neuropathy, 559
 Lesch–Nyhan syndrome, 754
 Li–Fraumeni syndrome, 843
 long QT syndrome, 392–393
 mad cow disease, 56
 malaria, 610
 maple syrup urine disease, 697
 mercury poisoning, 517
 misfolded proteins in, 56–57
 mitochondrial, 558–559
 mucopolysaccharidoses, 332
 multidrug resistance in, 378–379
 multiple myeloma, 87–88
 mushroom poisoning, 865, 865–866
 mutations causing, 147–148, 157
 neurological, protein misfolding in,
 56–57, 56f
 ornithine transcarbamoylase deficiency, 689
 osteoarthritis, 332
 osteogenesis imperfecta, 45
 osteomalacia, 786
 Parkinson disease, 55–56, 57, 242, 676
 phenylketonuria, 674, 697–698
 phosphatase deficiency, 514
 porphyrias, 730–731
 predisposition to, 19–20
 prion, 56–57, 56f
 protein aggregates in, 56–57
 recombinant DNA technology and,
 146–148
 retinitis pigmentosa, 877–878
 ricin poisoning, 911
 rickets, 786
 scurvy, 57, 812–813
 seizures, 656
 severe combined immunodeficiency,
 167–168
 sickle-cell anemia, 209–210, 209f, 210f
 smallpox, 1003
 spina bifida, 755
 splicing defects and, 877–878, 879t
 steatorrhea, 642
 Tay–Sachs disease, 765–766
 thalassemia, 210–211
 transmissible spongiform
 encephalopathies, 55–56
 tuberculosis, 679
 tyrosinemia, 698t
 urea cycle defects, 668–669
 vanishing white matter, 908–909, 909f
 vitamin D deficiency, 786
 Wernicke–Korsakoff syndrome, 812
 whooping cough, 422
 Zellweger syndrome, 652
 Dismutation, 541b, 542f
 D isomers, 321f, 322f
 monosaccharide, 320
 Displacement loop, 845, 845f
 Dissociation constant (K_d), 1030–1031
 for ligand binding, 1030–1031, 1030f
 Distal histidine, 198, **198**
 Distributive enzymes, 832b
 Disulfide bonds, 35, 35f
 cleavage of, 49
 Diuron, 584, **584**
 Divergent evolution, 185
 Diversity (D) genes, 988
 in class switching, 991
 D-loop, 845, 845f
 DNA, 110
 A-form, 115–116, 116, 116t
 ancient, amplification and sequencing of,
 147, 188–189, 189f
 annealing of, 120–121
 antisense strand of, 854
 backbone of, 110, 110f, 111
 bases in, 4, **4**, 4f, **5**, 5–6, 110–111, **111**.
 See also Bases/base pairs
 B-form, 115–116, 116, 116t
 in chromatin, 938f, 939–941
 circular, 117, 117f
 cleavage of
 in cognate vs. noncognate DNA,
 275–277, 276f
 in-line displacement of, 272–274
 magnesium in, 274, 275f, 277
 mechanisms of, 272–274
 methylation in, 277–278
 phosphodiester bridge hydrolysis in,
 272–274, 272f
 phosphorothioates in, 273–274, 274f
 restriction enzymes in, 141 42, 271–279
 restriction-modification systems in,
 272, 272f
 sites of, 141, 141f, 271–272, 272,
 275–277. *See also* Recognition sites
 stereochemistry of, 273–274, 274f
 cloned, 154–155
 coding strand of, 845
 cognate, 272
 cleavage of, 275–277
 complementarity with mRNA, 126, 126f
 complementary, 154–155, 154f, 162f
 condensed, 828
 cross-links in, 838, 839f
 damage to
 causes of, 837–839
 repair of, 839–843. *See also* DNA repair
 denaturation of, in acid-base reactions,
 14–15, 14f
 directionality of, 112
 double helix of, 5–15, 6f, 26f, 109,
 113–115. *See also* Double helix
 evolution of, molecular studies of,
 189–191, 190f
 functions of, 2, 18, 19
 hybridization of, 121
 hypersensitive sites in, 944
 junk, 19
 lagging strand of, 823f, 824
 leading strand of, 823f, 824
 length of, 113
 linker, 148–149, 149f, 939
 linking number of, supercoiling and,
 826, 827f
 methylation of, 718, 718f, 945–946
 in amino acid synthesis, 716–718, 718f
 in cleavage, 277–278, 278f
 minor groove in, 822, 822f
 mitochondrial, 527–528
 genetic code of, 131, 131t
 sequencing of, 158
 noncoding, 159–160
 in nucleosome, 939–941
 operator, 922f
 overview of, 4–6, 819–820

- DNA—(continued)
- packing of, 941
 - palindromic, 141
 - phosphodiester bridges of, 110, **110**, 111
 - hydrolysis of, 272–274
 - polarity of, 112
 - primer strand of, 122, 145, 821
 - promoter sites in, 126–127, 126f, 852
 - in bacteria, 852, 856–858, 857f
 - properties of, 4–6
 - in protein encoding, 18–19
 - recombinant. *See* Recombinant DNA
 - relaxed, 117, 117f, 826, 828f
 - renaturation of, 120–121
 - rewinding of, in transcription, 859, 859f
 - sense strand of, 845, 854
 - size of, 113
 - stem-loop motif in, 118f
 - sticky ends of, 148, 149f
 - structure of, 4–6, 4f–6f, **110**, 110–113, **112**
 - sugar-phosphate units of, 4, 4f
 - sugars in, 110–111, 110f
 - supercoiled, 117, 117f. *See also* Supercoiled DNA
 - synthesis of, 5–6, 6f, 113, 119–120, 121–122, 121f, 122f. *See also* Replication
 - recombinant methods of, 139–157. *See also* Recombinant DNA technology
 - telomeric, 836–837, 836f, 837f
 - template strand of, 121–122, 122f
 - in replication, 121–122, 122f, 820–821
 - in transcription, 124, 125f, 126, 126t, 854, 855f
 - topoisomerases and, **828**, 828–831, 829f, 830f
 - topoisomers of, 826, 828f
 - unwinding of, 826–831, 858, 858f
 - in transcription, 858, 858f
 - Watson–Crick model of, 5, 113–115, 114f, 819–820. *See also* Double helix
 - X-ray diffraction patterns of, 110, 113f
 - Z-form, 116, 116f, 116t
- DNA amplification, polymerase chain reaction in, 145–146, 145–147
- DNA blots, 142, 142f
- DNA fingerprint, 141
- DNA fragments
 - amplification of, 145–146
 - joining of, 148–149, 149f
 - production of, 141–142
 - separation and visualization of, 141–142
- DNA gyrase, 831
- DNA ligase, 148–149, 823f, 824, 841
- DNA linker, 148–149, 149f
- DNA microarrays, 162–163, 162f
- DNA mismatch repair, 840, 840f. *See also* DNA repair
- DNA photolyase, 840
- DNA polymerase(s), 121–122, 121f, 821–823
 - bacterial, 835t
 - classification of, 821
 - deoxyribonucleoside triphosphate binding by, 822, 823f
 - error-prone, 835t, 837–838
 - eukaryotic, 835–836, 835t
 - Klenow fragment of, 821, 821f
 - in leading/lagging strand synthesis, 832–833, 832f, 833f
 - metal ions of, 821–822, 821f
 - primer for, 821, 821b, 823, 823f
 - in prokaryotes, 831–834
 - in proofreading, 839–840, 839f
 - reaction mechanism of, 821–822, 821f
 - specificity of, 221, 822
 - structure of, 821, **821**
 - types of, 835t
- DNA polymerase α , 835, 835t
- DNA polymerase β , 835, 835t
- DNA polymerase δ , 835, 835t
- DNA polymerase I, 834
- DNA polymerase II, 835t
- DNA polymerase III, **831**, 831–832, 832–833
 - sliding clamp unit of, 831–832, 831f, 834
- DNA polymerase III holoenzyme, 832–833, 833f, 834
- DNA polymerase switching, 835
- DNA probes, 80, 142, 144–145
 - generation of, 144–145, 151–153
 - solid-phase approach in, 144–145, 144f
 - for genomic library, 151–153, 152f
- DNA recombination, 844–846
 - definition of, 844
 - functions of, 844
 - Holliday junctions in, 845–846, 845f
 - initiation of, 844–845
 - mechanisms of, 844–846, 845f
 - RecA* in, 845
 - recombinases in, 845–846
- DNA recombination synapse, 846
- DNA repair, 122, 820, 837–844
 - base-excision, 840
 - defective, in cancer, 842–843
 - direct, 840
 - double-strand, 841
 - enzyme complexes in, 840, 840f
 - glycolases in, 840, 841
 - ligase in, 824, 841
 - mismatch, 840, 840f
 - nonhomologous end joining in, 841
 - nucleotide-excision, 840–841, 841f
 - proofreading in, 839–840
 - single-strand, 839–841
 - tumor-suppressor genes in, 842
 - uracil DNA glycolase in, 841, 841f
- DNA replication, 5–6, 6f, 119–121, 819, 820–837
 - in bacteria, 831–834
 - base complementarity in, 822, 822f, 823f
 - cell cycle and, 836, 836f
 - clamp loaders in, 832
 - controlled termination, 143–144, 143f
 - coordinated processes in, 831–837
 - cross-linkage in, 838, 839f
 - definition of, 113
 - directionality of, 112, 122, 823, 832
 - DNA polymerase III holoenzyme in, 832–833, 833f, 834
 - DNA polymerases in, 121–122, 121f, 821–823, 835–836, 835t. *See also* DNA polymerase(s)
 - DNA probes in, 145
 - DnaA* in, 834, 834f
 - in *E. coli*, 831–834
 - errors in, 837–838
 - repair of, 837–844. *See also* DNA repair
 - in eukaryotes, 835–836
 - helicases in, 120, **824**, 824–825, 824f, 825f, 832
 - initiation of, 823, 834–836
 - in bacteria, 834, 834f
 - in eukaryotes, 835–836
 - sites of, 834–836
 - lagging strand in, 823f, 824
 - synthesis of, 823f, 824, 832–833, 833f
 - leading strand in, 823f, 824
 - synthesis of, 823f, 824, 832–833, 833f
 - licensing factors in, 835
 - ligase in, 823f, 824
 - Okazaki fragments in, 823–824, 823f, 833
 - origin of, 834, 834f
 - origin of replication complexes in, 835
 - prepriming complex in, 834, 834f
 - primer in, 122, 145, 821, 821b, 823, 823f
 - processivity in, 831–832, 831f
 - proofreading in, 839–840, 839f
 - rate of, 831–832
 - recombinant DNA technology in, 145. *See also* Recombinant DNA technology
 - replication fork in, 823, 823f, 832–833, 833f
 - RNA polymerase in, 823, 823f
 - semiconservative, 118–120, 120f
 - sites of
 - in bacteria, 834, 834f
 - in eukaryotes, 835–836
 - sliding DNA clamp in, 831–832, 831f
 - specificity of, 822, 822f, 823f
 - strand joining in, 823f, 824
 - strand separation in, 120, 824–825, 825f
 - telomeres in, 836–837, 836f, 837f
 - template in, 121–122, 122f, 820–821
 - trombone model of, 833, 833f
- DNA sequencing, 143–144, 143f
 - in amino acid sequencing, 84
 - chain-termination method in, 143, 143f
 - fluorescence detection in, 143–144, 143f
 - in forensics, 147, 147f
 - for Neanderthals, 188–189, 189f
 - Sanger dideoxy method in, 143–144, 143f
- DNA transfer. *See also* Recombinant DNA technology
 - by electroporation, 167, 167f
 - gene guns for, 167

- by microinjection, 163, 163f
- vectors for, 149–151, 149f, 150f, 154–155
- DNA vectors, 149–151, 149f–151f
- DnaA, assembly of, 834, 834f
- DNA-binding domains, 941–942, 943
 - in eukaryotes, 943
 - in prokaryotes, 942. *See also* DNA-binding proteins
- DNA-binding proteins. *See also* Transcription factors
 - basic-leucine zipper in, 942
 - homeodomains in, 942
 - match with regulatory site, 922–923
 - in prokaryotes, 922–928, 922f, 923–928, 923f
 - transcription inhibition by, 924–927
- DNA-binding sites
 - chromatin and, 941–942, 943
 - evolution of, 927
 - hypersensitive, 944
- Dolichol phosphate, 334, 334
- Domains
 - DNA-binding, 941–942, 943
 - homeodomains, 943
 - immunoglobulin, 981–982
 - of living organisms, 3, 3f
 - protein, 47, 47f
 - exon encoding of, 133, 133f
- Dopamine, 1038
- Double helix, 5, 5f, 26f, 109, 113–121
 - A, 115–116, 116t
 - B, 115–116, 116t
 - base pairing in, 5, 5f, 10–11, 10f, 113–115, 114, 114t. *See also* Bases/base pairs
 - discovery of, 5, 113–114
 - disruption of, in acid-base reactions, 14–15, 14f
 - formation of, 6, 6f
 - electrostatic interactions in, 10
 - heat released in, 12–13, 13f
 - hydrogen bonds in, 10
 - hydrophobic interactions in, 10
 - van der Waals forces in, 10
 - hydrogen bonds in, 5, 5f, 10, 114, 118f
 - left-handed, in Z-DNA, 116, 116t
 - melting of, 120–121, 120f, 824–825, 825f
 - in replication, 118–121
 - unwinding of, 826, 828–829
 - supercoiling and, 826
 - topoisomerases in, 828–831, 829f, 830f
 - in transcription, 858, 858f
 - Z, 116, 116t
- Double-displacement reactions, 237
- Double-reciprocal plots, 233, 233f, 240, 240f
- Dreyer, William, 987
- Drosophila melanogaster*
 - alternative splicing in, 879
 - sensory bristles in, 972
 - Toll receptor in, 978–979
- Drug(s). *See also specific drugs*
 - absorption of, 1031–1033, 1032f
 - ADME properties of, 1031–1036, 1032f
 - agonist, 948
 - antagonist, 948
 - concentration of, 1031
 - distribution of, 1033, 1033f
 - excretion of, 1035–1036
 - immune-modulating, 990
 - metabolism of, 1034–1036
 - cytochrome P450 in, 783
 - receptors for, 948, 949f
 - resistance to, 1050–1051
 - response to, genetic variations in, 1047–1048
 - routes of administration for, 1032
 - side effects of, 1031, 1036
 - genetic variations in, 1047–1048
 - therapeutic index of, 1036
- Drug development, 1001–1052
 - animal testing in, 1037
 - candidate drugs in
 - absorption of, 1031–1033, 1032f
 - ADME properties of, 1031–1036, 1032f
 - distribution of, 1003f, 1033
 - effective concentrations of, 1031, 1031f
 - essential characteristics of, 1030–1037
 - ligand binding and, 1030–1031, 1030f
 - metabolism and excretion of, 1034–1036
 - number of, 1041–1042
 - oral bioavailability of, 1032–1033, 1032f
 - potency of, 1030–1031
 - routes of administration for, 1032
 - side effects of, 1031, 1036–1037
 - target compartments of, 1003f, 1033
 - therapeutic index of, 1036
 - clinical trials in, 1048–1049, 1049f
 - combinatorial chemistry in, 1041
 - drug resistance and, 1050–1051
 - dual pathways for, 1029–1030, 1030f
 - genetic variations and, 1047–1048
 - genomics in, 1045–1048
 - high-throughput screening in, 1041
 - phases of, 1048–1049
 - screening libraries in, 1039–1042, 1042f
 - serendipitous observation in, 1037–1038
 - 7TM receptors in, 404, 1045
 - split-pool synthesis in, 1041, 1042f
 - structure-based, 1042–1045, 1043f, 1044f
- Dynamic instability, 1019
- Dynein, 1008
 - ATP binding to, 1010, 1011f
 - structure of, 1010, 1011f
- E. coli*. *See Escherichia coli*
- E site, ribosomal, 900, 900f, 904
- E'_0 (oxidation-reduction potential), 528–531
- Ear, hair cells of, 971–973, 971f, 972f
- Early humans, DNA sequencing for, 188–189, 189f
- EcoRI* endonuclease, 278
- EcoRV* endonuclease, 272, 273–277, 274f–277f
 - binding affinity of, 275
 - recognition site of, 275–277, 275f
- Editing, RNA, 852
- Edman degradation, 81–83, 81f, 82f, 93
 - protein cleavage for, 82–83, 82f
- Edman, Pehr, 81
- EF hand, 410–411, 411f
- Effector functions, 981
- EGF. *See* Epidermal growth factor (EGF)
- Eicosanoids, 664–665, 665, 665f
- Elastase, catalytic triad in, 261, 261f
- Elastase inhibitor, 307
- Electrochemical potential. *See* Membrane potential
- Electrocyclic reactions, 720
- Electromagnetic spectrum, 966f
- Electron carriers. *See also* Transporters
 - in metabolism, 438–439, 438f, 439f
 - in oxidative phosphorylation, 438–439, 438f, 439f, 531–543, 532t, 551f, 552–553, 552f, 554f. *See also* Respiratory chain
 - in photosynthesis, 568–572, 569f, 571f, 572f
- Electron sink, 605, 683
- Electron transfer. *See also* Electron-transport chain
 - in oxidative phosphorylation, 528–531, 542–543. *See also* Respiratory chain
 - rate of, 542f
 - in photosynthesis, 568–572, 569f, 571f, 572–577, 572f
- Electron-density maps, 99–100, 100f
- Electronic nose, 961–962, 962f
- Electron-transfer potential, 528
 - in oxidative phosphorylation, 528–530
- Electron-transferring flavoprotein (ETF), 646
- Electron-transport chain, 498, 512, 528
 - electron flow through, 540f
 - inhibition of, 558, 582f
 - rate of, 555–556
 - in oxidative phosphorylation, 438–439, 438f, 439f, 531–543, 532t, 540f. *See also* Respiratory chain
 - in photosynthesis, 568–572
- Electrophilic catalyst, 683
- Electrophoresis
 - gel, 71–73, 72f, 73f, 141–142, 142f
 - in restriction fragment separation, 141–142, 142f
 - SDS, 73, 78
 - SDS–polyacrylamide, of membrane proteins, 355, 355f
 - two-dimensional, 74, 74f
- Electroporation, 167, 167f
- Electrospray ionization (ESI), 91–92
- Electrostatic interactions, 7–8. *See also* Bonds
 - in antigen–antibody binding, 984, 985, 985f
 - ATP and, 433
- ELISA (enzyme-linked immunosorbent assay), 88–89, 89f
- Elongation factor(s), 902–903, 903f
 - G, 904–905, 904–906, 904f
 - Ts, 903
 - Tu, 902–903, 903f

- Embden, Gustav, 454
- Embden–Meyerhof pathway, 454. *See also* Glycolysis
- Emphysema, 307
- Enantiomers, 321, 321f
- Endergonic reactions, 222
- Endocytosis, receptor-mediated, 365f, 366, 775–776, 776f
- Endonucleases. *See* Restriction enzymes (endonucleases)
- Endoplasmic reticulum, 365, 979f
in diabetes, 802
fatty acid synthesis in, 664
protein glycosylation in, 333–334, 333f
protein synthesis in, 911–914
protein targeting from, 911–914
ribosome binding to, 911–914
rough, 911
smooth, 911
- Endoplasmic reticulum (ER) stress, 802
- Endosymbiosis, 365, 527
- Endotoxin, 978
- End-product inhibition. *See* Feedback inhibition
- Enediol intermediate, in glycolysis, 459, 460f
- Energy. *See also* Bioenergetics; Thermodynamics
activation, 222, 226
from ATP hydrolysis, 429–435
binding, 229
definition of, 254
enzyme specificity and, 275–277
body requirements for, 549b
from carbon oxidation, 435–437, 435–438, 435f, 437f
from catabolism, 434, 435–438, 435f, 437f
enzymatic transformation of, 221–222
free. *See* Free energy
glycogen storage of, 328, 615, 629–630
kinetic, 11
laws of thermodynamics and, 11–13, 222
lipid storage of, 641–642
from oxidative phosphorylation, 437–438
potential, 11
of reactions, 222–225
units of, 7, 223b
- Energy charge, 446–447, 446f
- Energy homeostasis. *See* Caloric homeostasis
- Enhancers, 127, 868–869, 943–944, 943f
in cancer, 869
- Enol phosphate, 465
- Enolase, in glycolysis, 465
- 5-Enolpyruvylshikimate 3-phosphate, **720**
- Enoyl CoA, 646–647, **647**, **648**, 649
- Enoyl CoA hydratase, 646–647
- Ensemble studies, 246, 246f
- Enterohaptic cycling, 1036, 1036f
- Enteropeptidase, in trypsin activation, 305, 306f
- Enthalpy, 11–12
- Entropy, 11–12
- Envelope, nuclear, 365
- Enzymatic cascades, 307
in amino acid synthesis, 725–726, 725f, 726f
in blood clotting, 307–308, 308f
- Enzymatic cleavage, of proteins, 82–83, 82f
- Enzyme(s), 219–248
active sites of, 185–186, 227–228, 227f, 228f
convergent evolution of, 185–186
definition of, 185–186
mapping of, 241–242
affinity tags for, 241–242
allosteric, 237, 237f, 289, 290–296. *See also* Allosteric enzymes
amounts of, regulation of, 446
apoenzymes, 221
bifunctional, 487
catalytic activity of, 205–208. *See also* Catalysis
assays for, 67. *See also* Protein purification
specific, 67
catalytic efficiency of, 235, 235t
catalytically perfect, 234, 235, 460
classification of, 248–249
coenzymes. *See* Coenzyme(s)
cofactors for, 221, 221t
core, 856
covalent modification of, 57–58, 57f, 297–302, 298t
definition of, 26, 219
denatured, 49–50, 49f, 50f
digestive, 255–260, 303–307, 303t, 304f, 674, 674f
distributive, 832b
energy-transducing, 221–222
holoenzymes, 221
inhibition of, 238–245
affinity tags in, 241–242, 241f
competitive, 238–240, 238f, 239f, 240f
feedback, 291, 446. *See also* Feedback inhibition
group-specific agents in, 241f
group-specific reagents in, 241
irreversible, 238, 238f, 241–242
noncompetitive, 230–240, 238, 238f, 239–240, 239f, 240f
reversible, 238, 238f
suicide (mechanism-based), 242, 750, 754
transition-state analogs in, 243, 243f
uncompetitive, 238, 238f, 239, 239f, 240, 240f
isozymes, 289–290, 296–297, 297f
kinetic properties of, 229–237. *See also* Enzyme kinetics
kinetically perfect, 234, 235, 460
in linked pathways, 744. *See also* Metabolic pathways
in multienzyme complexes, 660–661
nomenclature for, 248–249
overview of, 220–222
- processive
definition of, 832b
in DNA replication, 831–832
- prosthetic groups of, 221
- proteolytic, 220–221, 302–313. *See also* Proteolytic enzymes
- reaction equilibrium and, 224–225
reaction rate acceleration by, 220, 220t, 225–229, 226f
- restriction, 141–142, 141f, 253, 271–279. *See also* Restriction enzymes
- specificity of, 220–221, 221f, 275–277
binding energy and, 275–277
substrate binding by. *See also* Enzyme-substrate complex
concerted mechanism in, 294–296
cooperative, 200–201, 201f, 294
energy for, 229, 254, 275–277. *See also* Binding energy
sequential model of, 294
specificity of, 220–221, 221f, 275–277
substrates of, 220. *See also* Enzyme-substrate complex
in transition state formation, 225–226, 225f, 227–228
turnover number of, 234, 234t
- Enzyme cofactors. *See* Coenzyme(s)
- Enzyme kinetics, 229–237
definition of, 229
in first-order reactions, 229–230
fraction of active sites filled (f_{ES}) in, 234
initial velocity and, 230, 230f
 k_{cat}/K_M , 234–235
kinetic perfection and, 234, 235, 460
Lineweaver–Burk plot of, 233, 233f
Michaelis constant (K_M) in, 231–235, 233t
Michaelis–Menten, 229–237, 231f
in pseudo-first-order reactions, 230
in second-order reactions, 230
sigmoidal, 200, 291, 291f, 294, 295f
- Enzyme multiplicity, 724, 724f
- Enzyme regulation, 289–314
allosteric, 289, 290–296
dephosphorylation in, 300
isozymes in, 289–290, 296–297, 297f
phosphorylation in, 298–301
protein kinases in, 298–301
proteolytic activation in, 290, 302–313
reversible covalent modification in, 290, 297–392
zymogens in, 303–313
- Enzymes
ensemble studies of, 246, 246f
single molecule studies of, 246, 246f
- Enzyme–substrate complex, 226–227, 227, 227f
attractive forces in, 228, 228f
cooperative binding and, 200–201, 201f, 203f, 294
dissociation constant for, 233–234
in double-displacement (ping-pong) reactions, 237

- induced-fit model of, 228, 228f, 254, 457, 457f
 lock-and-key model of, 228, 228f
 in sequential reactions, 236–237
- Epidermal growth factor (EGF), in signal transduction, 402f, 415–418, 416f–418f
- Epidermal growth factor receptor, 415–418, 416f–418f
 in cancer, 421
- Epigenetic factors, 20
- Epigenome, 938
- Epilepsy, ketogenic diet for, 656
- Epimers, 321f, 322
- Epinephrine, **403**
 in fatty acid metabolism, 643, 666–667
 in glycogen metabolism, 624–626
 in signal transduction, 402f, 403–410, 406f. *See also* Signal transduction synthesis of, 726, 726f
- Epitopes, 85, 85f, 980
- EPO (erythropoietin), 331, 331f
- ϵ chains, 982, 983f
- Equilibrium constant
 for dissociation of water, 14
 free-energy change and, 222–225, 224t
- Equilibrium potential, 391–392, 391f
- Erbix, 421
- Error-prone DNA polymerase, 835t, 838
- Erythrocytes. *See* Red blood cells
- Erythromycin, 909t, 910
- Erythropoietin (EPO), 331, 331f
- Erythrose 4-phosphate, **603**
 in amino acid synthesis, 719, 720f
 in Calvin cycle, **595**
 in pentose phosphate pathway, 602f, 603, 604f
- Escherichia coli*. *See also* Bacteria
 DNA cloning and expression in, 154–155
 DNA repair in, 839–840
 DNA replication in, 831–834. *See also* DNA replication
 flagella of, 1022–1025
 gene expression in, 922–928, 923–928. *See also* Gene expression/regulation, in prokaryotes
 genome of, 113, 113f, 182f, 928, 937
 lac operon of, 922, 925–928, 925f, 926f
 lactose permease symporter in, 381, 381f
 pyruvate dehydrogenase complex in, 499f, 499t
 replication in, 831–834
 restriction enzymes of, 272–279, 274f–277f
- ESI (electrospray ionization), 91–92
- Essential amino acids, 674, 674t, 711, 711t, 712f
 synthesis of, 719–723. *See also* Amino acid synthesis
- Essential fatty acids, 664
- Estradiol, **784**
 synthesis of, 785
- Estrogen(s). *See also* Sex hormones; Steroid hormones
 regulation of, 946
 synthesis of, 780, 780f, **784**, 785
- Estrogen receptors, 946
 drug binding to, 948, 949f
- Estrogen response elements (EREs), 946
- Estrone, synthesis of, 780, 780f, **784**, 785
- ETF (electron-transferring flavoprotein), 646
- ETF : ubiquinone reductase, 646
- Ethanol. *See also* Alcohol(s)
 fermentation of, 466–467, 467f
 formation of from pyruvate, 466–467, 467f
 in glycolysis, 453
 metabolism of, 232, 783, 810–813
 toxicity of, 811–813
- Ethanolamine, 349, 763, 763f
- Ethylene, synthesis of, 718, 718f
- Eukarya, 3
- Eukaryotes, 3, 3f
 cell types in, 938, 939t
- Eversion, 376
- Evolution, 3, 3f
 of amino acid sequences, 36, 79, 174–181
 of blood types, 335–336
 caloric homeostasis and, 792–793
 of Calvin cycle, 600
 of carbonic anhydrases, 271
 of chloroplasts, 568
 of citric acid cycle, 518
 convergent, 185–186, 185f
 of cytochrome c, 543, **543**, 543f
 of cytochrome P450, 783
 divergent, 185
 of DNA binding sites, 927
 endosymbiotic events in, 527, 568
 essential elements of, 189
 experimental studies of
 ancient DNA amplification and sequencing in, 188–189
 combinatorial chemistry in, 188–189
 molecular, 188–191
 of feedback inhibition, 724
 of glucose metabolism, 490–491
 of glycogen metabolism, 627
 horizontal gene transfer in, 278–279
 of immune system, 978–981, 984
 of immunoglobulin fold, 984
 of introns and exons, 133
 of ion pumps, 374, 378–379
 of metabolic pathways, 447
 of microRNA, 954
 of mitochondria, 527
 obesity and, 792–793
 of olfaction, 959–960, 959f
 of photoreceptors, 970, 970f
 of photosynthesis, 568, 584, 600
 of proofreading, 895
 of proteasomes, 677–678, 678f, 679
 of protein degradation pathways, 677–678
 of proteins, 133
 of P-type ATPases, 374, 378–379
- of restriction enzymes, 278–279
 of ribosomes, 900
 RNA catalysis and, 881
 of rubisco, 600
 sequence homology and, 174–181, 176f–182f. *See also* Sequence homologies
 signal transduction pathways, 419
 split genes in, 133
 of succinyl coenzyme A, 509
 tertiary structure and, 183–184
 time line for, 3f
 of transaminases, 713
 of transcription, 869
 of urea cycle, 688
 of vision, 970, 970f
- Evolutionary trees, 187–188, 187f
- Exercise. *See also* Muscle contraction
 ATP in, 434–435, 435f, 805–806, 805t
 caloric homeostasis and, 803–806
 carbo-loading for, 806
 citric acid cycle during, 514
 creatine phosphate in, 434–435, 435f, 805, 805t
 fatty acid metabolism in, 804, 804f, 806
 fuel sources for, 805–806, 805t
 gene expression and, 804
 gluconeogenesis during, 489–490, 490f
 glycolysis during, 473–474, 475f, 478–479, 489–490
 lactate in, 489–490, 490f, 805
 mitochondrial biogenesis and, 804, 804f
 oxidative phosphorylation in, 805–806
 superoxide dismutase and, 542
- Exergonic reactions, 222
- Exon(s), 110, 132, 133
 evolution of, 133
- Exon shuffling, 133, 133f
- Exonuclease(s), 821
 in DNA polymerase III holoenzymes, 832, 833f
 in proofreading, 839–840, 839f
- Expression cloning, 154–155, 155f
- Expression vectors, 149, 154–155
- External aldimine, 682, **682**
 in amino acid degradation, 682, 682f
 in amino acid synthesis, 712f, 713
- Extrinsic pathway, coagulation, 308, 308f
- F_0F_1 -ATPase. *See* ATP synthase
- F_{ab} fragments, 981–982, 982f
 in antigen–antibody binding, 985f, 986, 986f
- Facilitated diffusion, 371, 373
- F-actin, 1013, 1013f
- Factor VIII, 311, 311f
- Factor XIII_a, 309
- FAD (flavin adenine dinucleotide)
 ADP units in, 447, 447f
 in catabolism, 438–439, **439**, 439f
 in citric acid cycle, 498, 498f, 501–502, 509–510, 512
 in fatty acid oxidation, 646, 647f

- FADH₂ (flavin adenine dinucleotide reduced)
 in catabolism, 438–439, **439**
 in citric acid cycle, 498, 503, 510, 512
 in fatty acid oxidation, 646–647
 in oxidative phosphorylation, 505, 535
 electron-transfer potential of, 530–531
 reduction potential of, 528–530
- Familial hypercholesterolemia, 759, 776–779
- Farnesyl pyrophosphate, 769, **769**
- Farnesylation, 298t
- 5-Farnesylcysteine methyl ester, 359, **359**
- Fasting, 796
- Fat
 body, energy storage in, 641
 brown, 556–557, 557f
 fecal, 642
 neutral. *See* Triacylglycerol(s)
 white, 556
- Fat cells, 641
 energy storage in, 641
- Fatty acid(s), 346–348, 347f, 347t
 carbon atoms in, 347–348, 347f
 chain length in, 437–438
 covalent attachment of, 639
 essential, 664
 examples of, 347t
 functions of, 639
 in lipid membrane, 362–363, 363f
 in muscle
 during exercise, 804, 804f, 806
 in obesity, 800–801
 odd-chain, 649–650, 650f
 polyunsaturated, eicosanoids from,
 664–665, **665**, 665f
 saturation of, 348
 storage form of, 648–649
 structure of, 346–348, **347**, 362–363, 363f
 synthesis of, 643–644, 643f, 644f
 unsaturated, 648–649, 664–665
- Fatty acid metabolism, 437f, 639–669
 acetyl CoA carboxylase in, 657, 658t,
 666–667, 666f
 acetyl CoA in, 646–647, 657
 activation in, 644–645
 acyl carnitine in, 645–646, 646f
 acyl carrier proteins in, 657–658, **658**,
 658t, 659f
 in animals vs. plants, 656
 β -oxidation pathway in, 646–647
 chylomicrons in, 642, 642f
 citrate in, 662, 662f, 666, 667f
 coenzyme A in, 644–645
 coenzyme B₁₂ in, 651–652
 cytoplasmic, 657
 degradation in, 640f, 646–657, 666–667
 reactions in, 647f, 647t
 vs. synthesis, 657, 658t
 diet and, 667
 in endoplasmic reticulum, 664
 energy yield from, 641, 647–648
 enoyl CoA hydration in, 646–647,
 647f, 647t
 epinephrine in, 643, 666–667
 ethanol and, 811
 during exercise, 804, 804f, 806
 fatty acid synthase in, 658–659, 660f,
 661f, 663
 fatty acid unsaturation in, 664–665
 glucagon in, 643, 666–667
 in glucose homeostasis, 808
 hormones in, 643, 666–667
 ketone bodies in, 653–656
 lipases in, 641–642, 642f, 643
 lipid mobilization and transport in,
 642–644, 642f, 643f
 lipolysis in, 643–644, 644f
 malonyl CoA in, 657, 658t, **659**, 666
 in muscle, 804, 804f
 oxidation in, 642–656, 647f, 647t
 palmitoyl CoA in, 647–648, 666
 pancreatic lipases in, 641–642, 642f
 peroxisomal, 652, 653f
 reactions of, 640–641, 640f
 regulation of, 666–667
 in starvation, 809, 809f, 810
 synthesis in, 640–641, 640f, 643–644,
 643f, 644f, 656–657
 in animals, 659–661
 citrate carriers in, 662, 662f
 condensation in, 658–659, 658t, 659f
 coordinated metabolic pathways in,
 654f, 663, 666f
 dehydration in, 658t, 659, 659f
 elongation in, 658, 658t, 659f, 664–665
 insulin in, 667
 key features of, 657
 NADPH sources for, 662–663
 reactions in, 658–659, 658t, 659f
 reduction in, 658t, 659, 659f
 of unsaturated fatty acids, 664–665, 665f
 vs. degradation, 657, 658t
 thiolysis in, 647–648, 647f, 647t
 triacylglycerol hydrolysis in,
 643–644, 643f
 of unsaturated fatty acids, 648–649, 648f,
 664–665
- Fatty acid synthase, 656–663, 660f
 in animals, 659–661, 660f, 661f
 in cancer, 663
- Fatty acid synthase inhibitors, 663
- Fatty acid thiokinase, 644–645
- Fatty acyl CoA dehydrogenase, 646
 in oxidative phosphorylation, 535
- F_c fragments, 981
- FDA (Food and Drug Administration), 1049
- Fe protein, in nitrogen fixation, 707, **707**
- Feedback inhibition, 291, 446
 in amino acid synthesis, 723–726
 in cholesterol synthesis, 770
 cumulative, 725
 enzyme multiplicity and, 724, 724f
 evolution of, 724
 in nucleotide synthesis, 751
- Feedforward stimulation, 476
- Fehling's solution, 325
- FeMo cofactor, **708**, 708–709
- Fermentation, 466–468
 to alcohol, 453, 466–467, 467f
 as anaerobic process, 468–469
 in glycolysis, 453
 to lactic acid, 453, 467–468
 start/end points for, 469t
- Ferredoxin, 575–577, **576**
 in nitrogen fixation, 707
- Ferredoxin–NADP⁺ reductase, **576**,
 576–577, 577f
- Ferredoxin–thioredoxin reductase, 599
- Ferritin, 730, **951**, 951–952
- Ferrochelatase, 730
- Fetal alcohol syndrome, 812
- Fetal hemoglobin. *See also* Hemoglobin
 oxygen affinity of, 205, 205f
- Fiber, dietary, 329
- Fibrin clot
 formation of, 308–309, 308f
 lysis of, 312
- Fibrin, structure of, 309, 309f
- Fibrinogen
 conversion to thrombin, 308–309
 structure of, 308, 308f
 sulfation of, 298t
- Fibrinopeptides, 308
- Fibrous proteins, 43–45
- 50S subunit, of ribosome, 897–898
- Fight or flight response, 301
- Filters, selectivity, 385–386
- Fingerprint, DNA, 141
- First Law of Thermodynamics, 11. *See also*
 Thermodynamics
- First-order reactions, rate of, 229–230
- First-pass metabolism, 1035
- Fischer, Emil, 228, 1042
- Fischer projections, 21, 22f, 23f
- 5' cap, 870–871, 871f
- 5' splice sites, 870–871, 871f, 873–874, 873f
- Flagella
 microtubules in, 1019
 rotary movement of, 1022–1025
 structure of, 1022, 1022f, 1023f
- Flagellin, 1022, 1022f
- Flavin adenine dinucleotide. *See* FAD
- Flavin mononucleotide, 533–534, 534f, 860f
- Flavoproteins, 502
 electron-transferring, 646
- Fleming, Alexander, 1037
- FliG, 1023, 1023f
- FliM, 1023
- FliN, 1023
- Flip-flop, 362, 362f
- Flippases, 378
- Florey, Howard, 1037
- Fluconazole, **1033**
 distribution of, 1003f, 1003f
- Fluid mosaic model, 362
- Fluorescamine, in Edman degradation,
 81, **81**
- Fluorescence detection, in DNA
 sequencing, 143–144, 143f
- Fluorescence microscopy, 90–91, 90f

- Fluorescence recovery after photobleaching (FRAP), 361, 361f
- Fluorouracil, 749–750
- fMET. *See* Formylmethionine (fMet)
- fMRI. *See* Functional magnetic resonance imaging
- Folding funnel, 54f
- Folding, protein. *See* Protein(s), folding of
- Folic acid, 441t
- deficiency of, spina bifida and, 755
- Food and Drug Administration (FDA), 1049
- Food intake. *See also* Diet; Starvation starved–fed cycle and, 807–808
- Food Pyramid, 20f
- Food, spicy, capsaicin in, 973–974, 973f
- 5-Foraminoimidazole-4-carboxamide ribonucleotide, 742f
- Forensics, polymerase chain reaction in, 147, 147f
- Formamide, molecular models of, 23f
- N^5 -Formiminotetrahydrofolate, 715, **716**
- Formylglycinamide ribonucleotide, 741, 742, **742**, 742f
- Formylkynurenine, 696, **696**
- Formylmethionine (fMET), 130, **130**, 901–902
- Formylmethionyl-tRNA, 901–902, 902, 902f
- N^{10} -Formyltetrahydrofolate, 715–716, 742f
- Fourier transform, 99–100
- Frameshift mutations, tests for, 843
- Franklin, Rosalind, 113
- FRAP (fluorescence recovery after photobleaching), 361, 361f
- Free energy, 12, 222–225, 226. *See also* Energy
- of activation, 222, 226
- ATP and, 430–431
- binding, 229, 254
- from carbon oxidation, 435–437, 435–438, 435f
- in concentration gradients, 373–374, 437
- equilibrium constant and, 222–225, 224t
- Gibbs, 12, 226
- in membrane transport, 373–374, 373f
- in metabolism, 429–430
- from proton gradients, 559–560, 560f
- in redox reactions, 530
- reduction potential and, 528–530
- of translation, 893–894
- Free radicals. *See* Reactive oxygen species (ROS)
- Fructofuranose, 323, 323f, 324f
- Fructokinase, 469
- Fructopyranose, 324f
- Fructose, 322, 322f
- in glycolysis, 469–470, 469f, 470f
- metabolism of, 469–470, 470f
- open-chain form of, 323f
- ring form of, 323, 324f
- structure of, 322f
- Fructose 1,6-bisphosphatase, in gluconeogenesis, 482
- Fructose 1,6-bisphosphate, **458**
- in Calvin cycle, 594, 594f
- in gluconeogenesis, 482, 484
- in glycolysis, 456f, 458, 460
- Fructose 1-phosphate, in glycolysis, 469–470, 469f, 487
- Fructose 2,6-bisphosphate, 487, 488f
- Fructose 6-phosphate, **457**
- in Calvin cycle, 594, 594f, 595f, 596f
- in gluconeogenesis, 482, 484–485, 487
- in glycolysis, 455f, 456f, 458, 458f, 459, 470, 487
- in pentose phosphate pathway, 602f, 603, 604f
- in sucrose synthesis, 597, **598**
- Fructose bisphosphatase 2, 487
- FtsZ, 1019
- Fuels. *See* Carbon fuels
- Fumarase, 510
- Fumarate, **510**, 687, 687f
- in citric acid cycle, 510
- from phenylalanine, 696, 696f
- in purine synthesis, 742f, 743, 743f
- in urea cycle, 687
- 4-Fumarylacetoacetate, 696, **696**
- Functional groups, of proteins, 26
- Functional magnetic resonance imaging, 197–198, 198f
- Furanose, 323–325, 323f
- envelope forms of, 325, 325f
- Futile cycles, 489
- $G_{(olf)}$, 959, 960
- G elongation factor, 904–905, 904–906, 904f
- G protein(s), 405–406
- activation of, 406
- ATP synthase and, 550
- in cholera, 421–422
- definition of, 405
- in glycogen metabolism, 624–626
- heterotrimeric, 405–406
- in olfaction, 959
- P-loop NTPases in, 405
- resetting of, 407–408
- in signal transduction, 405–411. *See also* Signal transduction
- small, 418, 418t
- structure of, 405, **405**
- subunits of, 405
- in taste, 963–965
- of bitterness, 962, 963–964
- of sweetness, 965–966
- in translation, 902–903
- in vision, 968, 968f
- in whooping cough, 422
- G6PD. *See* Glucose 6-phosphate dehydrogenase (G6PD)
- G-actin, 1013
- GAL4 binding sites, 945, 945f
- Galactitol, 472
- Galactokinase, 470
- Galactolipids, in thylakoid membrane, 567
- Galactose, 321–322, 322f
- in blood groups, 335
- disorders of, 471–472
- in glycolysis, 469f, 470–471
- Galactose 1-phosphate, 470, **470**
- Galactose 1-phosphate uridylyl transferase, 470
- Galactose 6-phosphate, 470
- Galactose-glucose interconversion pathway, 470–471
- Galactosemia, 472
- β -Galactosidase, 328, **924**, 926
- in lactose metabolism, 924–925
- Galactoside permease, 924
- Galacturonic acid, 329, 329f
- γ chain(s), 982, 983f
- γ chain(s), of fetal hemoglobin, 205
- Gangliosides, 350
- disorders of, 765–766
- structure of, 738, 765f
- synthesis of, 764–765
- GAP. *See* Glyceraldehyde 3-phosphate
- Gap junctions, 372, 393–394, 393f, 394f
- GAPs (GTPase activating proteins), 418
- Gargoylism, 332, 332f
- Garrod, Archibald, 697
- Gastric enzymes, 674, 674f
- Gastric H^+ – K^+ ATPase, 374
- Gastric zymogens, 303t
- GC box, 867, 867f
- GDP (guanosine diphosphate)
- in citric acid cycle, 508
- hydrolysis of, 431
- in olfaction, 959, 960
- in signal transduction, 405, 418, 418f
- in translation, 902–903, 908
- in tubulin, 1019
- in vision, 968, 968f
- GEF (guanine-nucleotide-exchange factor), 417
- Gel electrophoresis, 71–73, 72f, 73f, 141–142, 142f
- in restriction fragment separation, 141–142, 142f
- SDS, 73, 78
- SDS–polyacrylamide, of membrane proteins, 355, 355f
- Gel-filtration chromatography, 69, 69f, 75, 75t
- Gellert, Martin, 828
- Gene(s)
- comparative analysis of, 160–161, 160f
- continuous, 131, 132
- definition of, 19
- designer, 157
- discontinuous, 131
- discontinuous (split), 131–132, 132f, 133f
- horizontal transfer of, 278–279
- identification of, in genome sequencing, 17–18
- number in genome, 159
- protein-encoding, 19
- synthetic, 157
- tumor suppressor, 420

- Gene chips (microarrays), 162–163, 162f
- Gene disruption, 164–165, 165f
- Gene expression studies, 161–167
 cDNA in, 154–155
 DNA microinjection in, 163, 163f
 expression vectors in, 154–155
 gene disruption, 164–165
 gene-expression analysis in, 161–162, 162f
 recombinant DNA technology in. *See* Recombinant DNA technology
 RNA interference in, 165–166, 167f
 transgenic animals in, 164, 164f
 viral vectors in, 163–164
- Gene expression/regulation, 109–110, 123–128
 basic-leucine zipper in, 942
 constitutive, 921
 definition of, 921
 in eukaryotes, 937–955
 chromatin remodeling in, 944–951, 949–951
 coactivators in, 947–948, 948f, 949–951
 DNA methylation and, 945–946
 enhancers in, 127, 868–869, 943–944
 histones in, 939–941, 940f, 949–951, 950f
 in liver, 939t
 methylation in, 945–946
 nuclear hormone receptors in, 946
 nucleosomes in, 939–941, 940f
 overview of, 937–938
 in pancreas, 939t
 tissue-specific, 939t
 transcription factors in, 946–947.
See also Transcription factors
 vs. in prokaryotes, 937–938
 in prokaryotes, 921–933
 attenuation in, 931–932, 932f
 biofilms and, 930–931
 catabolite activator protein in, 927–928, 927f
 catabolite repression in, 927–928
 corepressors in, 927
 DNA-binding proteins in, 922–923, 922–928
 match with regulatory site, 922–923
 in prokaryotes, 922–928
 genetic switching and, 928–931
 helix-turn-helix motif in, 923, 923f
lac operon in, 925–928, 925f, 926f. *See also under lac*
 levels of, 161–162
 ligand binding in, 926
 operon model of, 924–928
 posttranscriptional, 931–933
pur repressor in, 927
 quorum sensing in, 930–931, 930f
 regulatory sites in, 922–928, 922f
 RNA in, 123–128
 signaling in, 929–930
 social interactions in, 929–930
 symmetry matching in, 922
- transcriptional, 921–928. *See also* Transcription
 translational, 951–953
 vs. in eukaryotes, 937–938
 regulated, 921
 transcriptional
 in eukaryotes, 941–944
 in prokaryotes, 921–928
 translational, 951–953. *See also* Translation
- Gene guns, 167
- Gene knockout, 164–165, 165f
- Gene therapy, 167–168
- Gene-expression analysis, 161–162, 162f, 163–164. *See also* Gene expression studies
- General acid–base catalysis, 254
- Genetic code, 19, 128–131
 definition of, 128
 degeneracy of, 129, 130, 892
 major features of, 129–130
 of mitochondrial DNA, 131, 131t
 universality of, 131
 variations of, 131
- Genetic engineering. *See* Recombinant DNA technology
- Genetic imprinting, 20
- Genetic information, flow of, 109–110
- Genetic mutations. *See* Mutations
- Genetic switch, 928–931
- Genetic variation, 19–20
- Genome, 157–161, 159f–161f
 analysis of, 159–161
 comparative, 160–161, 160f
 of *Caenorhabditis elegans*, 159
 of chloroplasts, 568
 definition of, 66
 of *Escherichia coli*, 113, 113f, 928, 937
 of *Haemophilus influenzae*, 158, 158f, 181
 of Indian muntjak, 113, 113f
 mitochondrial, 527–528, 527f, 528f
 noncoding DNA in, 159–160
 number of genes in, 159
 proteome and, 66
 of puffer fish, 161, 161f
 of *Reclinomonas americana*, 528
 of *Rickettsia prowazekii*, 527–528
 of *Saccharomyces cerevisiae*, 158, 937, 938f
 sequencing of, 17–18, 157–161, 158f
 next-generation methods for, 160
 size of, 113
- Genomic libraries, 151–153, 152f, 153f
- Genomics
 comparative, 160–161, 160f
 in drug development, 1045–1048
- George III (King of England), porphyria in, 731
- Geraniol, **958**
- Geranyl pyrophosphate, 769, **769**
- Geranyl transferase, 769, **769**
- Gerhart, John, 291
- Ghrelin, 796
- Gibbs free energy, 12, 226
- Gibbs, Josiah Willard, 12
- Gigaseal, 383
- Gla domain, in prothrombin, 310, 310f
- Gleevec, 421
- Globin(s). *See also* Hemoglobin; Myoglobin
 evolution of, 187–188, 187f
 sequence alignment in, 175–181, 176t–182t
 structure of, 48, 48f, **183**, 183–184
 types of, 211–212
- Globin fold, 199
- Globin genes, 211–212
- Globins, 175
- Glomeruli. *See also* Kidney
 drug metabolism in, 1035
- Glucagon, 488
 in fatty acid metabolism, 643, 666–667, 808
 in glucose homeostasis, 807–808, 808
 in glycogen metabolism, 624–626, 807–808, 808
- Glucagon-like peptide 1 (GLP1), in caloric homeostasis, 795, 795f
- Glucocorticoids. *See also* Steroid hormones
 synthesis of, 780, 780f, 783
- Glucogenic amino acids, 690. *See also* Amino acid(s)
- Glucokinase, 807
- Gluconeogenesis, 479–491
 carboxybiotin in, 483
 definition of, 453, 479
 in diabetes, 803, 803f
 evolution of, 490–491
 fructose 1,6-bisphosphate in, 480f, 482, 484
 fructose 6-phosphate in, 480f, 482, 484–485
 glucose 6-phosphatase in, 480f, 484, 485f
 glucose 6-phosphate in, 480f, 484–485, 485f, 807
 in glucose homeostasis, 807–810
 glycolysis and, 481–482, 486–491
 historical perspective on, 454
 in kidney, 481
 in liver, 481
 orthophosphate in, 484
 oxaloacetate in, 480f, 481, 482, 483–484
 phosphoenolpyruvate in, 480f, 481, 482, 483–484
 phosphorylation in, 485
 reactions in, 479–485, 480f, 481–485
 coupled, 485
 regulation of, 486–491, 803, 803f
 sites of, 481
 in starvation, 809
 in starved–fed cycle, 807–810
 stoichiometry of, 485
 urea cycle and, 687
- Glucopyranose, 323, 323f
 boat form of, 324, 325f
 chair form of, 324, 325f
- Glucose
 body stores/requirements for, 479
 as cellular fuel, 455

- in Cori cycle, 490, 490f
 in glycogen, 328, 328f, 615, 629–630
 metabolism of, 437f. *See also*
 Gluconeogenesis; Glycolysis
 carbon fuels for, 808, 809
 in diabetes mellitus, 798–800
 evolution of, 490–491
 historical perspective on, 454
 homeostatic mechanisms in, 798–800.
See also Glucose homeostasis
 in liver, 806
 in muscle, 805–806
 reactions in, 428f, 454f
 in starvation, 809
 starved–fed cycle in, 807–808
 open-chain form of, 323, 323f
 overview of, 453–454
 properties of, 455
 regulated release of, 616–617. *See also*
 Glycogen metabolism
 ring form of, 323, 323f
 storage forms of, 328, 328f, 329f, 615,
 629–630
 structure of, 321–322, 321f–323f
 synthesis of
 from dietary carbohydrates, 454
 from non carbohydrate precursors,
 453–454, 454f, 479–491. *See also*
 Gluconeogenesis
 taste of, 962, 964–965
 Glucose homeostasis, 807–810. *See also*
 Glucose, metabolism of
 in diabetes, 798–803, 803f
 in starvation, 809–810
 starved–fed cycle in, 807–808
 Glucose 1-phosphate, **617**
 in glycogen metabolism, 617–618
 Glucose 6-phosphate, 326, 326f, **457**
 deficiency of, 634–635
 in gluconeogenesis, 484–485, 485f, 807
 in glycolysis, 456f, 457–458, 607–609, 807
 metabolic fates of, 616f
 in pentose phosphate pathway, 601,
 607–609
 reactive oxygen species and, 609
 Glucose 6-phosphate dehydrogenase
 (G6PD)
 antioxidant properties of, 609
 deficiency of, 609–610, 611
 in pentose phosphate pathway, 601, 603f
 Glucose 6-phosphate transporter, 635
 Glucose 6-phosphatase, **455**
 in gluconeogenesis, 484, 485f
 in glycogen metabolism, 621
 in glycolysis, 455–457, 456f
 Glucose transporters (GLUTs), 372, 477,
 477t, 485, 799
 in cancer, 479
 insulin secretion and, 801–802
 Glucose-alanine cycle, 684–685, 685f
 Glucose-stimulated insulin secretion,
 801–802
 α -Glucosidase, 454
 α -1,6-Glucosidase, 620, 620f
 Glucuronic acid, conjugation of,
 1034–1035, **1035**
 Glutamate
 in amino acid degeneration, 680–681
 arginine synthesis from, 714, 714f
 chirality of, 709, 710f
 conversion to ammonia, 680–681
 glutamine synthesis from, 709–710, 710f
 in nitrogen fixation, 709
 in nitrogen transport, 685, 685f
 oxidative deamination of, 680–681
 proline synthesis from, 714, 714f
 structure of, 31, 32f, **237, 680**
 synthesis of, 685, 709, 709f, 712–713
 taste of, 962, 962f, 965
 Glutamate dehydrogenase, 710
 in amino acid degradation, 680–681
 in glutamate synthesis, 709
 in nitrogen fixation, 709
 Glutamate synthase, 710
 Glutamate synthetase, in nitrogen fixation,
 709–710
 Glutamic γ -semialdehyde, **714**
 in arginine synthesis, 714
 in proline synthesis, 714
 Glutamine
 in ammonia formation, 714
 in nitrogen fixation, 709
 in nitrogen transport, 685
 in pyrimidine synthesis, 737
 structure of, 30, 30f
 synthesis of, 709–710, 710f, 725–726
 Glutamine phosphoribosyl
 aminotransferase, 741, 751
 Glutamine synthetase, 709–710
 regulation of, 725–726, 725f
 structure of, 725
 Glutathione, **727, 727**
 antioxidant properties of, 609
 conjugation of, 1030, **1035**
 Glutathione peroxidase, 542, 610,
 727, **727**
 Glutathione reductase, 610, 727
 Glutathione–drug conjugates, **1034**,
 1034–1035
 GLUTs. *See* Glucose transporters
 (GLUTs)
 Glycan-binding proteins, 337–338
 Glyceraldehyde, 320, **320**, 321f
 in glycolysis, 461, 462f, 470
 Glyceraldehyde 3-phosphate (GAP), **224**,
 326, 326f, **603**
 in Calvin cycle, 594
 dihydroacetone phosphate isomerization
 to, 224, **224**, 458–459, 458f, 460f
 in glycolysis, 224, 456f, 458–459, 458f,
 460, 460f, 470
 in lipolysis, 644
 oxidation of, energy from, 436
 in pentose phosphate pathway, 602, 602f,
 603f, 604, 604f
 in sucrose synthesis, 597, **598**
 Glyceraldehyde 3-phosphate
 dehydrogenase, **481**
 in Calvin cycle, 594
 in glycolysis, 461, 462f, 463f, 464
 NAD⁺ binding sites in, 469, 469f
 Glycerol, **644**
 in gluconeogenesis, 481
 metabolism of, 437f, 643–644, 644
 in phospholipids, 348
 Glycerol 3-phosphate, in membrane lipid
 synthesis, 760
 Glycerol 3-phosphate shuttle, 551, 551f
 Glycerol phosphate acyltransferase, 760
 Glycerol phosphate dehydrogenase, 551
 in oxidative phosphorylation, 535
 Glycinamide ribonucleotide, **742**, 742f
 Glycine
 in Calvin cycle, 594
 in collagen, 44–45, 44f
 heme labeling with, 728, 728b
 porphyrins from, 728–730, 729f
 serine formation from, 691
 structure of, 28, 29f
 synthesis of, 714–715, 716
 Glycine cleavage enzyme, 716
 Glycine synthase, 716
 Glycoaldehyde, in pentose phosphate
 pathway, 605, 605f
 Glycobiology, 320
 Glycocholate, 642, **642**
 synthesis of, 780, 780f
 Glycoforms, 330
 Glycogen, 328, 328f, **617**
 branching in, 615, 616f, 629
 glucose storage in, 328, 328f, 615,
 629–630
 as homopolymer, 328
 storage sites for, 616, 616f
 structure of, 328, 328f, 615, 616f, 629f
 Glycogen metabolism, 615–636
 branching enzyme in, 629
 carbonium ion intermediate in, 619
 degradation in, 616–627
 cAMP in, 626
 initiation of, 624–626
 regulatory cascade in, 624–626, 625f
 termination of, 626–627
 degradative, 630–631
 disorders of, 634–635, 634t
 epinephrine in, 624–626
 evolution of, 627
 during exercise, 805–806
 G proteins in, 624–626
 glucagon in, 624–626
 α -1,6-glucosidase in, 620, 620f
 glycogen phosphorylase in, 617–624, **618**,
 620f, 633–634, 633f. *See also*
 Glycogen phosphorylase
 glycogen synthase in, 627–629,
 632–633, 633f
 glycogen synthase kinase in, 629, 630f,
 631, 632–633, 632f
 glycogenin in, 628

- Glycogen metabolism—(*continued*)
 hormones in, 624–626, 632–633, 632f
 insulin in, 632–633, 632f
 overview of, 615–617
 phosphoglucomutase in, 620, 643
 phosphoglycerate mutase in, 620
 phosphorolysis in, 617–621
 phosphorylase in, 617–624. *See also*
 Glycogen phosphorylase
 phosphorylase kinase in, 623–624, 624f,
 629, 630f
 protein kinase A in, 629, 630f
 protein phosphatase 1 in, 626–627,
 631–634, 631f
 pyridoxal phosphate in, 618–619, 619f
 pyrophosphate hydrolysis in, 627–628
 as regulated release of glucose, 616–617
 regulation of, 629–634
 in liver, 621, 633–634, 633f
 in muscle, 631–633
 signaling in, 624–626
 synthesis in, 616–617, 627–635
 transferase in, 620, 620f
 uridine diphosphate glucose in, 627–630
- Glycogen phosphorylase, 617–624, 620f,
 633–634, 633f
 a, 622–623, **644**, 644f
 amino-terminal domain of, 618–619, 618f
 b, 622–623, **644**, 644f
 carboxyl-terminal domain of,
 618–619, 618f
 catalytic mechanism of, 618–619
 evolution of, 627
 glycogen binding site of, 618–619, 618f
 regulation of, 621–624
 structure of, **618**, 618–619
 T and R states of, 621–623
- Glycogen storage diseases, 634–635, 634t
- Glycogen synthase, 627–629, 632–633, 633f
- Glycogen synthase kinase, 629, 630f, 631,
 632–633, 632f, 799
- Glycogen transferase, 620, 620f
- Glycogenin, 628
- Glycolases, in DNA repair, 840, 841
- Glycolate, in Calvin cycle, 593–594, 593f
- Glycolate oxidase, 594
- Glycolipids, 350, **350**
- Glycolysis, 444, 453–479
 aerobic, 478–479
 aldehyde oxidation in, 461, 462f
 ATP formation in, 463–466
 yield in, 554–555, 555t
 1,3-bisphosphoglycerate in, 484
 in cancer, 478–479
 citric acid cycle and, 499–503, 499f
 committed step in, 474
 definition of, 453
 in diabetes, 803, 803f
 dihydroxyacetone phosphate in, 456f,
 458–459, 458f, 460f, 469–470
 enolase in, 465
 evolution of, 490–491
 during exercise, 478–479, 805–806
 feedforward stimulation in, 476
 fermentation in, 466–468
 fructose 1,6-bisphosphate in, 456f,
 457–458, 458f, 460
 fructose 6-phosphate in, 456f, 458,
 458f, 459
 fructose in, 469–470, 469f
 galactose in, 469f, 470
 gluconeogenesis and, 481–482, 486–491
 glucose 6-phosphate in, 456f, 457–458,
 459, 807
 in glucose homeostasis, 807–810
 glucose transporters in, 477, 477t
 glucose trapping in, 455–457, 456f
 glyceraldehyde 3-phosphate dehydrogenase
 in, **460**, 461, 462f, 463f
 glyceraldehyde 3-phosphate in, 224,
 456f, 458–459, 458f, 460, 460f,
 461, 462f
 hexokinase in, 455–457, 456f
 in liver, 476
 in muscle, 473–474
 historical perspective on, 454
 hypoxia-inducible transcription factor in,
 479, 479f, 479t
 isomerization of three-carbon
 phosphorylated sugars in, 456f,
 458–460, 458f
 in liver, 475–477, 487
 in muscle, 473–474, 475f
 NADH in, 466–468
 pentose phosphate pathway and,
 601–609
 phosphoenolpyruvate in, 464f, 465
 phosphofructokinase in
 in liver, 474–477, 475f, 476f, 487, 488
 in muscle, 473–474, 473f
 phosphoglycerate kinase in, 463–464
 phosphoglycerate mutase in, 464, 464f
 phosphoryl group transfer in, 444, 444f
 pyruvate formation in, 464–466,
 464f–466f
 pyruvate kinase in, 465
 in liver, 476–477, 476f
 in muscle, 474
 reactions of, 445, 456f, 466t–467t
 regulation of, 472–479, 486–491,
 802–803, 803f
 reversal of, stoichiometry of, 485
 stages of, 456f
 in starvation, 809, 809f
 in starved-fed cycle, 807–810
 thioester intermediate in, 461–463, 462f
 transaldolase in, 601–604, 605, 606f
 transketolase in, 601–605, 605f
 triose phosphate isomerase in, 456f,
 458–460, 459f
- Glycomics, 320
- Glycopeptide transpeptidase, penicillin
 inhibition of, 244, 245f
- Glycoproteins, 329–337
 sequencing of, 336–337
- Glycosaminoglycans, 329–330, **331**
- Glycosides, 326
- Glycosidic bonds
 in disaccharides, 327
 in monosaccharide-alcohol/amine
 complexes, 326, 326f
- Glycosyl phosphatidylinositol, 359, **359**
- Glycosylated hemoglobin, 325–326
- Glycosylation, 329–337
 congenital disorders of, 336
 proteases in, 337
 sites of, 330, 333–334, 337
- Glycosyltransferases, 335, **335**
 in blood groups, 335
- Glyoxylate cycle, 518–519, 519f
- Glyoxylate, in Calvin cycle, 593–594
- Glyoxysomes, 519
- Glyphosate, 719–720
- GMP (guanosine monophosphate),
 synthesis of, 743–744, 743f,
 744, 751, 751f
- GMP synthetase, 744
- Goldstein, Joseph, 767b, 775, 776
- Golgi complex
 protein glycosylation in, 333–334,
 333f, 334f
 protein modification in, 913–914, 914f
- Gout, 751, 753–754
- G-protein receptor kinase 2 (GRK2), 408
- G-protein-coupled (7TM) receptors,
 404–406
- Gradient centrifugation, 77–78, 77f
- Graft rejection, 998
- Granum, 567
- Granzymes, 996
- Grb-2, 417
- Green fluorescent protein, 58, 58f, 90
- Green photoreceptors, 969–970, 969f, 970f
- Greider, Carol, 837
- GRK2 (G-protein receptor kinase 2), 408
- Group-specific reagents, 241
- Group-transfer reactions, 444. *See also*
 Phosphoryl group transfer
 activated carriers in, 438–442
 active carriers in, 438f, 439f
- GTP (guanosine triphosphate)
 in AMP synthesis, 743f, 744, 751
 hydrolysis of, 431
 in translation, 902–903, 905f
 in olfaction, 959, 960
 in protein targeting, 913
 in signal transduction, 405–406, 407–408,
 407f, 418, 418f
 in translation, 902–903, 908, 913
 in tubulin, 1019
 in vision, 968, 968f
- GTPase(s)
 in protein targeting, 912
 in signal transduction, 407, 407f
- GTPase activating proteins (GAPs), 418
- GTPases, in signal transduction, 298, 298t
- Guanidinium, 31, **31**
- Guanidinium chloride, in bond cleavage,
 49, **49**

- Guanine, 4, 4, 111, 111
 deamination of, 838
 degradation of, 753f
- Guanine-nucleotide exchange factor (GEF), 417
- Guanosine, 111
- Guanosine diphosphate. *See* GDP (guanosine diphosphate)
- Guanosine monophosphate. *See* GMP (guanosine monophosphate)
- Guanosine triphosphate. *See* GTP (guanosine triphosphate)
- Guanylate. *See* GMP (guanosine monophosphate)
- Guanylate cyclase, in vision, 969
- Guanylate kinase, structure of, 284
- Gustation, 962–966. *See also* Taste
- Gustducin, 963, 963f
- Gyrase inhibitors, 831
- H chains. *See* Heavy (H) chains
- H isozyme, 297, 297f
- H zone, 1016, 1016f
- Haber, Fritz, 707
- Haemophilus influenzae*, genome of, 158, 158f, 181
- Hair cells, 971–973, 971f, 972f
- Hairpin turns, 42, 43f
 amino acid residues in, 50–51, 51t
 in mRNA, 42, 43f, 127, 127f
 in transcription termination, 859–860, 859f
- Haldane, John, 231
- Half-life
 of drugs, 1036
 of proteins, 675, 676t
- Haptenic determinant, 990
- Haptens, 990
- HAT (histone acetyltransferase), 949, 950
- Hatch, Marshall Davidson, 599
- Haworth projections, 323
- Hayaishi, Omar, 696
- HDLs (high-density lipoproteins), 773, 773t, 774–775, 776, 778–779.
See also Lipoprotein(s)
- Hearing, 971–973
- Heart disease, homocysteine in, 719
- Heart failure, digitalis for, 377
- Heart, H and M isozymes in, 297, 297f
- Heat, from oxidative phosphorylation, 556–557
- Heat shock protein 70, 183, 183–184
- Heat-shock promoter, 858, 858f
- Heat-shock response element, 868
- Heat-shock transcription factor, 868
- Heavy (H) chains, 981–982, 981f, 987–989, 988f
 in class switching, 991
 formation of, 991
- Heavy meromyosin, 1009, 1009f
- Heimiacetals, 322
- Heinz bodies, 610, 610f
- Helicases, 120, 824–825, 824f, 825f
 in DNA replication, 120, 824–825, 825f, 832
 in splicing, 876–877
 structure of, 824, 824–825, 824f, 825f
- Helix
 alpha, 38–40, 39, 40, 40f
 amino acid residues in, 50–51, 51t
 of α -keratin, 43, 43–44, 44f
 of kinesin, 1012
 of membrane proteins, 356, 358, 359–360, 360f, 360t
 of myosin, 1009–1010, 1010f, 1012f
 of collagen, 44–45, 44f
 double. *See* Double helix
 recognition, 923
 relay, 1012, 1012f
 screw sense of, 39, 40f
- Helix-loop-helix, in EF hand, 410–411, 411f
- Helix-turn-helix motif, 47, 47f, 923, 923f
- Helper T cells, 980, 996–998, 998f.
See also T cell(s)
 in HIV infection, 999–1000
- Hemagglutinin, 339, 340f
- Heme, 45, 196, 196–198
 in cytochrome *c* oxidase, 538–539
 degradation of, 730, 730f
 labeling of, 728, 728b, 728f
 in Q-cytochrome *c* oxidoreductase, 535–536, 536f
 synthesis of, 728–730, 729f
- Hemiacetals, 322
 cyclic, 323
- Hemichannels, 394, 394f
- Hemiketals, 322–323
- Hemoglobin, 195–216
 α chains of, 199, 199f, 211, 211
 $\alpha\beta$ dimers of, 199, 199f, 202, 202f
 β chains of, 199, 199f, 211
 β -globin gene of, transcription and processing of, 131–132, 132f
 evolution of, 175–181, 187–188, 187f
 fetal, oxygen affinity of, 205, 205f
 glycosylated, 325–326
 Hill plot for, 213–214, 214f
 leghemoglobin and, 180, 180f, 181f, 183, 183f. *See also* Leghemoglobin
 overview of, 195–196
 oxygen affinity of, 204–205, 204f
 pH and, 206–207, 206f
 oxygen binding by, 196–199
 allosteric effectors for, 206
 concerted (MWC) model of, 202–203, 203f, 214–216, 216f
 cooperative nature of, 200–201, 201f, 203f
 quantitative models of, 213–216, 214f, 216f
 sequential model of, 203, 203f, 216
 structural changes in, 201–202, 202, 204, 204f
 oxygen release by, 200, 201f, 206–208
 Bohr effect and, 206–208, 207f
 carbon dioxide in, 207–208, 208f
 in oxygen transport, 200–201, 207–208, 208f
 oxygen-binding curve for, 199–200, 200f, 201f
 with concerted model, 214–216, 216f
 for Hill coefficients, 214, 214f
 R state of, 202–204, 203f
 sequence homology with myoglobin, 175–181, 176f–182f, 199
 structure of, 48, 48f, 199
 oxygen-binding-induced changes in, 201–202, 202, 204f
 oxygen-binding-induced changes in, 204
 quaternary, 201–202, 202
 tertiary, 183, 183f
 T state of, 202–204, 203f, 207–208, 207f
 vs. myoglobin, 195–196
- Hemoglobin A, 199
- Hemoglobin gene, introns in, 131–132, 132f
- Hemoglobin H, 210
- Hemoglobin S, 209, 209–210, 209f
- Hemolytic anemia, G6PD deficiency and, 609–610, 611
- Hemophilia, 311
- Henderson–Hasselbalch equation, 16–17
- Henseleit, Kurt, 685
- Heparin, 312, 331, 332
- Hepatic gluconeogenesis, 481
- Hepatic glycolysis, 475–477
- Hepatitis, alcoholic, 811
- Hepatotoxicity, of acetaminophen, 1036, 1037f
- Heptad repeats, in coiled-coil proteins, 43, 44f
- Heptoses, 320
- Her2 receptor, 417, 421
- Herbicides, mechanism of action of, 584, 584, 719–720
- Hereditary nonpolyposis colorectal cancer, 842–843
- Hers disease, 634t
- Heterolytic cleavage, 651
- Heterotrophs, 566, 590
- Heterotropic effect, 296
- Hexokinase
 in glycogen metabolism, 620
 in glycolysis, 455–457, 456f, 457f
 in liver, 476
 in muscle, 473–474
 induced fit in, 457, 457f
- Hexose monophosphate pathway. *See* Pentose phosphate pathway
- Hexose monophosphate pool, 594
- Hexose sugars, formation of, in Calvin cycle, 594–597, 594f
- Hexoses, 320–321
- High-density lipoproteins, 773, 773t, 774–775, 776, 778–779. *See also* Lipoprotein(s)

- High-energy bonds, 433–434
- High-pressure liquid chromatography, 71, 71f
- High-protein–low-carbohydrate diets, 798
- High-throughput screening, 1041
- Hill, Archibald, 213
- Hill coefficients, 214
- Hill plot, 213–214, 214
- Histamine, synthesis of, 726, 726f
- Histidine
 in carbon dioxide hydration, 269, 270, 270f
 in catalytic triads, 258–260. *See also* Catalytic triads
 conversion to glutamate, 692, 692f
 distal, 198, **198**
 histamine from, 726, 726f
 in oxygen release from hemoglobin, 207, 207f
 proximal, 197
 structure of, 31, 31f
- Histidine operon, 932–933, 932f
- Histone acetyltransferase (HAT), **949**, 950
- Histone deacetylase, 950
- Histones, 939–941, 940f
 acetylation of, 298t, 949–951, 950f
 amino-terminal tails of, coactivator modification of, 949–951, 950f
 in gene regulation, 939–941, 940f, 949–951, 950f
 sequence homology of, 940–941, 940f
 structure of, 940–941, 940f
- HIV infection. *See* Human immunodeficiency virus infection
- H⁺–K⁺ pump, 374
- HMG-CoA (3-hydroxy-3-methylglutaryl CoA), 653, **653**, 654
 in cholesterol synthesis, 767–768, 770–771
 metabolic fates of, 768f
 regulation of, 770–771
- HMG-CoA reductase, in cholesterol synthesis, 767–768
- HMG-CoA reductase inhibitors, 779, **779**, **1040**, 1040–1041, **1041**
- Hodgkin, Alan, 382
- Hoffmann, Felix, 1039–1040
- Hogness box, 126f, 127
- Holliday junctions, 845–846, 845f
- Holliday, Robin, 845
- Holoenzymes, 221
- Homeostasis, caloric, 791–798. *See also* Caloric homeostasis
- Homocysteine
 in activated methyl cycle, 717–718, 717f
 in amino acid degradation, 693, **693**
 in amino acid synthesis, 717–718
 in cysteine synthesis, 719
 synthesis of, 717
 in vascular disease, 719
- Homocysteine methyltransferase, 717
- Homocystinuria, 698t
- Homogenate, centrifugation of, 67, 75t
- Homogentisate, 695, **696**
- Homogentisate oxidase, 696
 in alcaptonuria, 697
- Homologous recombination, 970b
 in color blindness, 970
 in gene knockout, 164–165
- Homologs, 174–175, 175f
- Homology, 174–181, 175f
 sequence, 175–181, 176f–182f. *See also* Sequence homologies
- Homolytic cleavage, 651, 651f
- Homopolymers, 328
- Homotropic effects, 294
- Hood, Leroy, 987
- Horizontal gene transfer, 278–279
- Hormone(s). *See also specific hormones*
 in citric acid cycle regulation, 514
 eicosanoid, 664–665, **665**, 665f
 in fatty acid metabolism, 643–644, 666–667
 in gene expression, 946–949
 in gluconeogenesis, 488
 in glucose metabolism, 488
 in glycogen metabolism, 624–626, 632–633, 632f
 local, 665
 metabolic functions of, 446–447
 sex
 regulation of, 946
 synthesis of, 780, 780f
 in signal transduction, 405–406. *See also* Signal transduction
- steroid, 780–782
 anabolic, 785, 948
 cardiogenic, 377, 377f
 hydroxylation of, 781–782
 structure of, 781, **781**
 synthesis of, 780, 780f, 783
- Hormone receptor(s), 946–948, 947f–949f, 948f, 949f
 DNA-binding domains of, 946, 947f
 drug binding to, 948–949, 949f
 ligand-binding domains of, 946–947, 947f
 nuclear localization of. *See* Nuclear hormone receptors
- Hormone–receptor complexes, in signal transduction, 405–406
- Human immunodeficiency virus, 999–1000, 999f
- Human immunodeficiency virus infection
 aspartyl protease in, 264, 264f
 helper T cells in, 996–998
 immune system in, 999–1000, 999f
 protease inhibitors for, 264–265, **265**, 266f
 development of, 1043, 1043f, 1044f
 resistance to, 1050
 vaccine for, 1003
- Humoral immune response, 979–980
- Huntingtin, 842
- Huntington disease, 55–56, 842
- Hurler disease, 332, 332f
- Huxley, Andrew, 382
- Hyaluronate, **331**, 332
- Hybridization, DNA, 121
- Hybridoma cells, in monoclonal antibody production, 87–88, 87f
- Hydrogen bonds, 5, 8, 9, 9f, 11, 38–40. *See also* Bonds
 in α helix, 38–40, 39f
 in antigen–antibody binding, 984, 985, 985f, 986
 in β sheet, 40–42, 40f, 41f
 in double helix, 5, 5f, 10, 114, 118f
 in enzyme–substrate complex, 228, 228f
 in water, 9–10, 9f
- Hydrogen ion(s). *See also* Acid(s)
 in aqueous solutions, 13–17
 oxygen affinity of hemoglobin and, 206–207, 206f
 pH and, 13–14. *See also* pH
 sour taste of, 962, 962f, 965–966
- Hydrogen ion channels, in taste, 965–966
- Hydrogen-potassium ion pump, 374
- Hydrolases, 249t. *See also* Enzyme(s)
- Hydrolysis
 in metabolism, 444–445
 of peptide bonds. *See* Peptide bonds, cleavage of
- Hydronium ions, 13
- Hydropathy plot, 360, 361f
- Hydrophilic side chains, 30, 30f. *See also* Amino acid side chains
 protein folding and, 46, 46f, 47
- Hydrophobic effect, 9–10, 9f, 28
- Hydrophobic interactions, 10
- Hydrophobic side chains, 28, 29f. *See also* Amino acid side chains
 protein folding and, 45–46, 46f, 47
- Hydroxide ions, pH and, 13–14
- 3-Hydroxy-3-methylglutaryl CoA. *See* HMG-CoA (3-hydroxymethylglutaryl CoA)
- L-3-Hydroxyacyl CoA dehydrogenase, 647
- 3-Hydroxyanthranilate, 696, **696**
- D-3-Hydroxybutyrate, **653**, 653–655. *See also* Ketone bodies
- D-3-Hydroxybutyrate ACP, 658t, 659, **659**
- Hydroxyethyl-TPP
 in amino acid synthesis, 723–724, 723f
 in citric acid cycle, 500, **500**
- Hydroxyl groups, 30, 30f, 44, 57–58
- Hydroxylation
 cytochrome P450 in, 782–783, 782f
 protein, 30, 30f, 57–58
 steroid, 781–782
- p-Hydroxymercuribenzoate, 291, **291**, 293
- Hydroxyphenylpyruvate, **696**
 in amino acid degradation, 695, 696f
 in amino acid synthesis, 720, 721f
- Hydroxyphenylpyruvate hydroxylase, 696
- 17 α -Hydroxyprogesterone, 784, **784**
- Hydroxyproline, 44, **57**
 synthesis of, 812f, 813
- Hyperbaric oxygen therapy, 206
- Hypercholesterolemia, 759, 774–775
 familial, 759, 776–779

- Hyperlysinemia, 698t
 Hypersensitive sites, 944
 Hyperuricemia, 753–754
 Hypervariable loops, 984, 984f
 Hypochromism, 120, 120f
 Hypomethylation, 945
 Hypoxanthine, 838, **838**
 degradation of, 752, 753f
 Hypoxanthine-guanine
 phosphoribosyltransferase
 (HGPRT), 744
 deficiency of, 754
 Hypoxia inducible factor 1 (HIF-1), in
 cancer, 515
 Hypoxia, tumor, 479
 Hypoxia-inducible transcription factor
 (HIF-1), 479, 479f, 479t
- I band, 1016, 1016f
 Ibuprofen, 358
 I-cell disease, 336
 Ig. *See* Immunoglobulin(s)
 Ig- α -Ig- β , 989, 989f
 Imatinib mesylate, 421
 Imidazole, 31, **31**
 4-Imidazolone 5-propionate, 692, **692**
 Immune response, 977–1004. *See also*
 Antibodies; Antigen(s)
 antigen binding in, 984–986
 in autoimmune diseases, 1001
 B cells in, 989–990. *See also* B cell
 in cancer, 1001–1002
 cellular, 980
 class switching in, 990–991, 991f
 evolution of, 978–981
 humoral, 979–980
 overview of, 977–978
 selectins in, 339, 339f
 to self-antigens, 1001
 self-tolerance in, 1001
 signaling in, 989–990, 998
 T cells in, 980–981. *See also* T cell(s)
 Immune-modulating drugs, 990
 Immunity
 adaptive, 977, 978, 979–981
 cell-mediated, 961
 innate, 978–979
 Immunization. *See* Vaccine(s)
 Immunodeficiency, gene therapy for,
 167–168
 Immunoelectron microscopy, 91, 91f
 Immunogens, 980
 Immunoglobulin(s). *See also* Antibodies
 cleavage of, 982, 982f
 constant regions of, 984, 984f
 definition of, 83
 heavy chains of, 981–982, 981f,
 987–989, 988f
 in class switching, 991
 formation of, 991
 light chains of, 981–982, 981f, 987–989,
 987f, 988f
 in class switching, 991
 properties of, 982t
 segmental flexibility of, 982, 982f
 sequence diversity in, 983f, 984
 variable regions of, 983, 984f
 Immunoglobulin α , 989
 Immunoglobulin A (IgA), 982t, 983
 Immunoglobulin β , 989
 Immunoglobulin D (IgD), 982t, 983, 983f
 Immunoglobulin domains, 981–982
 Immunoglobulin E (IgE), 982t, 983, 983f
 Immunoglobulin fold, 984, 984f
 Immunoglobulin G (IgG), 981f–983f, 982,
 982t, 983f
 Immunoglobulin M (IgM), 982t, 983, 983f
 B cells and, 989, 989f
 Immunologic techniques
 antibody production for, 86–88, 87f
 hybridoma cells in, 87–88, 87f
 monoclonal antibodies in, 86–88,
 86f–88f
 polyclonal antibodies in, 86, 86f
 for protein study, 84–91
 Immunological memory, 1002
 Immunoreceptor tyrosine-based activation
 motif (ITAM), 989
 Immunosuppressants, 990
 Immunotoxins, genetically engineered, 157
 IMP. *See* Inosine monophosphate (IMP)
 Inactivated vaccines, 1002
 Inborn errors of metabolism, 697–698, 698t
 Indian muntjac, genome of, 113, 113f
 Indinavir, 264–265, **265**, 266f
 development of, 1043, 1043f
 Indirect ELISA, 88, 89f
 Indole, substrate channeling and, 722–723
 Indole-3-glycerol phosphate, **721**, 722
 Induced pluripotent stem cells, 944
 Induced-fit model, of enzyme–substrate
 complex, 228, 228f, 254, 457, 457f
 Infant respiratory distress syndrome,
 765–766
 Influenza virus, 339–340
 Information science, 17
 Inhibition constant (K_i), 1031
 Initiation factors, 902
 Initiator tRNA, 907
 In-line displacement, 272–274
 Innate immunity, 977. *See also* Immune
 response
 Inosinate. *See* Inosine monophosphate (IMP)
 Inosine
 in anticodons, 891
 degradation of, 752, 753f
 Inosine monophosphate (IMP), 742f, 743
 AMP from, 743–744, 743f
 GMP from, 743–744, 743f
 synthesis of, 743, 743f, 744, 751
 Inositol 1,4,5-trisphosphate (IP₃), **403**,
 408–409, 409f
 Inositol, in phospholipids, 349
 Insertional inactivation, 1494
 Insertions, production of, 157
 Insig, 771, 772f
- Insulin
 amino acid sequence of, 35, 35f
 in appetite regulation, 796, 797
 biosynthesis of, 303
 in diabetes, 798–803. *See also* Diabetes
 mellitus
 exercise and, 803
 in fatty acid synthesis, 667
 in glucose metabolism, 488, 798–800
 glucose-stimulated secretion of, 801–802
 in glycogen metabolism, 632–633, 632f
 mass spectrometry of, 91–95, 93f
 in obesity, 798, 800–802
 regulation of, 798–800
 secretion of, 799, 799f, 801–802
 in signal transduction, 411–415,
 412f–415f, 798–800, 799f
 structure of, 35, 35f, 412, **412**
 Insulin receptor, 412–415, 412f–415f,
 799, 799f
 Insulin receptor substrates, 412–415, 414f,
 799, 800
 Insulin receptor tyrosine kinase, 412–415
 Insulin resistance, 798–802, 799–802
 Insulin-dependent diabetes mellitus,
 802–803. *See also* Diabetes mellitus
 Integral membrane proteins, 355, 355f
 Intercalation, 862
 Intermediate-density lipoproteins, 773,
 773t, 774. *See also* Lipoprotein(s)
 Internal aldimine, 682, **682**
 in amino acid degradation, 682, 682f
 in amino acid synthesis, 712, 712f
 Internal guide sequence, 881, 881f
 Internal repeats
 in amino acid sequences, 79
 sequence homology of, 184, 185f
 Internet databases, of amino acid sequences,
 65–66, 181, 182f
 Intestinal microvilli, 328f
 Intestines, protein digestion and absorption
 in, 674, 674f
 Intrinsic pathway, coagulation, 308, 308f
 Intrinsically unstructured proteins, 54–55
 Introns, 110, 131–132, 132f, 869
 evolution of, 133
 group I, 880
 removal of, 132–133, 132f. *See also*
 Splicing
 Inverted repeats, as recognition sites, 275
 Ion channels, 372, 382–393
 acetylcholine receptor as, 389–390,
 390f, 391f
 action potentials and, 382, 382f,
 391–392, 391f
 calcium, 367, 384f, 386
 cell-to-cell, 393–394, 393f, 394f
 definition of, 382
 equilibrium potential and, 391–392, 391f
 gap junction, 372, 393–394, 393f, 394f
 in hearing, 972–973
 inactivation of, 388–389, 389f, 392
 ligand-gated, 389–390, 391f

- Ion channels—(*continued*)
 nerve impulses and, 382
 opening and closing of, 389–390, 391f, 392
 patch-clamp studies of, 383, 383f
 potassium, 364–393, 382. *See also* Potassium ion channels
 rate of transport in, 387
 responsive to mechanical impulses, 972–973
 selectivity filter in, 385–386, 386f, 387f
 sequence homologies of, 384, 384f, 386
 sodium, 382, 383–384, 384f, 387–392.
See also Sodium ion channels
 specificity of, 385–387
 in taste, 965–966, 965f
 TRP, 973
 voltage-gated, 387, 388f
- Ion, dipolar, 27–28, 27f
- Ion gradients, 373–374
 in ATP synthesis, 437–438, 437f
- Ion pumps, 371–372, 374–381
 Ca^{2+} , 374–377, 375f, 376f
 evolution of, 374, 378–379
 $\text{H}^+ - \text{K}^+$, 374
 $\text{Na}^+ - \text{K}^+$, 374, 377
- Ion-exchange chromatography, 69–70, 70f, 75, 75t
 in amino acid identification, 80–82, 80f
- IP_3 (inositol 1,4,5-trisphosphate), 408, 408–409, 409f
- IPGT (isopropylthiogalactoside), 926, 926
- IRE (iron-response element), 951–952, 952f
- IRE-binding protein, 951–952
- Iron
 in heme, 730. *See also* Heme
 oxygen binding to, 196–198, 197f
 metabolism of, 951–953
- Iron center, of ribonucleotide reductase, 746
- Iron protein, in nitrogen fixation, 707, 708–709
- Iron-molybdenum cofactor, 708, 708–709
- Iron-response element (IRE), 951–952
- Iron-response element-binding protein (IRP), 951–952, 953f
- Iron-sulfur proteins, 506
 in nitrogen fixation, 708–709
 in oxidative phosphorylation, 534, 536
- IRP (iron-response element-binding protein), 951–952, 953f
- Isocitrate dehydrogenase, in citric acid cycle, 506, 514, 514f
- Isocitrate, in citric acid cycle, 506–507, 507f
- Isocitrate lyase, in glyoxylate cycle, 518–519, 519f
- Isoelectric focusing, 73, 73f
 with SDS-PAGE, 74, 74f
- Isoelectric point, 73
- Isoenzymes, 289–290, 296–297, 297f
- Isoleucine
 degradation of, 694–695
 in maple syrup urine disease, 697
 structure of, 28, 29f
 synthesis of, 723–724
- Isomerases, 249t. *See also* Enzyme(s)
- Isomerization, in metabolism, 443t, 444
- Isomers, 27
 carbohydrate, 321
 constitutional, 321, 321f
- 3-Isopentenyl pyrophosphate, 742f, 768, 768
- Isopeptide bonds, 675, 675f
- Isopropylthiogalactoside (IPTG), 926, 926
- Isovaleryl CoA, 694, 694
- Isozymes, 289–290, 296–297, 297f
- ITAM (immunoreceptor tyrosine-based activation motif), 989
- J genes, 987–988
 in antibody switching, 991
- Jacob, François, 924
- Jagendorf, André, 577
- Jenner, Edward, 1002
- Joining (J) genes, 987–988
 in class switching, 991
- Joule (J), 7, 223b
- K^+ ions. *See* Potassium
- κ chains, 982, 983f, 987, 989
- k_{cat} (turnover number), 234, 234t
- k_{cat}/K_M ratio, 234–235
- K_d (dissociation constant), 1030–1031
 for enzyme-substrate complex, 233–234
 for ligand binding, 1030–1031, 1030f
- Kendrew, John, 196
- Kennedy, Eugene, 526, 644
- Keratan sulfate, 331, 332
- α -Keratin, α helices of, 43–44, 44, 44f
- Ketimine, 682, 682, 712
- Ketoacidosis, in maple syrup urine disease, 697
- 3-Ketoacyl CoA, 647
- α -Ketobutyrate, 719
 in amino acid degradation, 693, 693
 in amino acid synthesis, 719, 723
- Ketogenic amino acids, 690. *See also* Amino acid(s)
- Ketogenic diet, 656
- α -Ketoglutarate, 692
 in amino acid degradation, 692
 in amino acid synthesis, 709–710, 712
 in citric acid cycle, 507, 507f, 692
 in double-displacement reactions, 237
 in glutamate synthesis, 709, 710
 in 4-hydroxyproline synthesis, 812f, 813
 in nitrogen fixation, 709
- α -Ketoglutarate dehydrogenase complex
 in citric acid complex, 499–500, 507
 in citric acid cycle, 507, 514–515, 514f
- α -Ketoisocaproate, 693–694, 694
- Ketone bodies, 653–656
 acetyl CoA formation from, 633f, 653–655
 in citric acid cycle, 810, 810f
 in diabetes, 633f, 653, 655, 803
 in ethanol metabolism, 811
 as fuel source, 654–655, 654f
 in starvation, 809f, 810
 synthesis of, 810, 810f
- Ketose, 320, 320f
 in Calvin cycle, 594
 in transaldolase reaction, 605, 606f
 in transketolase reaction, 605, 605f
- Ketosis, diabetic, 633f, 653, 655
- 3-Ketosphinganine, 764
 in sphingolipid synthesis, 737
- β -Ketothiolase, 647, 647t
- Keyhole limpet hemocyanin, 990
- Khorana, Har Gobind, 128
- K_i (inhibition constant), 1031
- Kidney
 drug metabolism in, 1035
 gluconeogenesis in, 481
- Killed vaccines, 1002
- Killer T cells, 980, 994–995, 997–998, 997f.
See also T cell(s)
- Kilobase (kb), 124b
- Kilocalorie (kcal), 7, 223b
- Kilojoule (kJ), 7, 223b
- Kinase(s). *See also specific types*
 activity and properties of, 457
 definition of, 457
 induced fit in, 457, 457f
 magnesium and, 457
 in phosphorylation, 457
 substrate-induced cleft closing in, 457, 457f
- Kinase cascade, in signal transduction, 406–407, 408–409, 409f, 418
- Kinesin, 1008, 1018–1022
 ATP binding to, 1012, 1012f, 1021, 1021f
 conventional, 1010
 disorders of, 1018
 movement along microtubules, 1020–1022, 1020f, 1021f
 myosin and, 1008
 relay helix of, 1012, 1012f
 structure of, 1010, 1010f
- Kinetic energy, 11. *See also* Energy
- Kinetic perfection, 235
- Kinetically perfect enzymes, 234, 235, 460
- Kinetics. *See also* Bioenergetics; Energy;
 Reaction rates
 definition of, 229
 enzyme, 229–237. *See also* Enzyme kinetics
- Kirschner, Marc, 1019
- Klenow fragment, 821, 821f
- Klug, Aaron, 939
- K_M (Michaelis constant), 231–235
 calculation of, 233
 definitions of, 232, 234
 for selected enzymes, 233t

- Köhler, Georges, 87
 Kornberg, Arthur, 121
 Kornberg, Roger, 853
 Koshland, Daniel E., Jr., 228
 Krebs cycle. *See* Citric acid cycle
 Krebs, Hans, 437, 518b, 685
 Kringle domain, in prothrombin, 310, 310f
 Kynurenine, 696, **696**
- L amino acids, 27, 27f
 L chains. *See* Light (L) chains
 Laborit, Henri, 1038
 lac operator, 926, 926f, 927f
 lac operon, 925–928, 925f, 926f
 lac regulatory site, nucleotide sequence of, 922f
 lac repressor, 922f, 923, 925–928, 926f, 927
 lac repressor–DNA complex, 922f
 Lactase, 328, 454
 deficiency of, 471
 Lactate, **236**
 in Cori cycle, 490, 490f
 formation of, 236, 489–490, 490f
 from pyruvate, 467–468
 in gluconeogenesis, 453, 479
 in glycolysis, 453
 in muscle contraction, 489–490, 490f, 806
 Lactate dehydrogenase, 236
 evolution of, 490–491
 in gluconeogenesis, 479
 in glycolysis, 467–468
 isozymes of, 297, 297f, 490–491
 Lactic acid fermentation, 453, 467–468
Lactobacillus, 471f
 β -Lactoglobulin, mass spectrometry of, 93, 93f
 Lactose, 328
 metabolism of, 923–924
 Lactose intolerance, 471
 Lactose operon. *See* lac operon
 Lactose permease, in membrane transport, 381, 381f
 Lagging strand, 823f, 824, 832–833, 833f
 λ chains, 982, 983f
 λ phage, 150–151, 150f, 151f
 λ repressor, 928–929, 928f, 929f
 Cro protein and, 929
 genetic switching and, 928–931
 self-regulation by, 928–929
 Lanosterol, 769–770, **770**
 Lansoprazole, 1046, **1046**
 Lariat, in splicing, 874, 874f, 875f
 Lateral diffusion, of membrane lipids, 361–364, 362f
 Laws of thermodynamics, 11–13. *See also* Thermodynamics
 LDLs. *See* Low-density lipoprotein(s)
 Leader sequences, 931, 932, 932f
 Leading strand, 823f, 824, 832–833, 833f
 Leber hereditary optic neuropathy, 559
 Lectins, 337–339, **338**
 Leder, Philip, 987
 Leghemoglobin, 180, 181f, 183, 183f, 707.
See also Hemoglobin
 evolution of, 187–188, 187f
 tertiary structure of, 183, 183f
 Lehninger, Albert, 526, 644
 Leloir, Luis, 627
 Leptin, 795–797, 796f
 Leptin resistance, 797
 Lesch–Nyhan syndrome, 754
 Leucine
 degradation of, 693–695
 in maple syrup urine disease, 697
 structure of, 28, 29f
 synthesis of, 723–724
 Leucine-rich repeats, 978, 978f
 Leukemia, chronic myelogenous, treatment of, 421
 Leukotrienes, 664–665, 665f
 Lever arm, of myosin, 1011–1012, 1011f, 1018, 1018f
 Levinthal, Cyrus, 52
 Levinthal's paradox, 53
 Libraries
 cDNA, 154
 genomic, 151–153, 152f, 153f
 screening, in drug development, 1039–1042, 1042f
 Licensing factors, 835
 Li-Fraumeni syndrome, 843
 Ligand, 402, 1030
 Ligand binding
 dissociation constant for, 1030–1031, 1030f
 in drug development, 1030–1031, 1030f
 in gene expression, 926, 946–947
 Ligand-binding curve, 1030, 1030f
 Ligand-gated ion channels, 389–390, 391f.
See also Ion channels
 Ligase, 249t, 824, 841. *See also* Enzyme(s)
 Ligation reactions, in metabolism, 443–444, 443t
 Light (L) chains, 981–982, 981f, 987–989, 987f, 988f
 in class switching, 991
 Light, electromagnetic spectrum of, 966, 966f
 Light meromyosin, 1009, 1009f
 Light perception. *See* Vision
 Light reactions, 566–567, 566f, 572–584, 589. *See also* Photosynthesis
 in photosystem I, 567, 572, 572f, 574f, 575–577, 575f, 583, 583f
 in photosystem II, 567, 572–577, 572f–575f, 583, 583f
 Light-harvesting complexes, 583, 583f
 Limit dextrin, 454
 LINES, 160
 Lineweaver–Burk plot, 233, 233f, 240, 240f
 Linker DNA, 148–149, 149f, 939
 Linking number, 826, 827f
 Linoleate, 664, **664**
 oxidation of, 648–649, 649f
 Linolenate, 664, **664**
 Linoleoyl CoA, 648–649, **649**
 Lipases, 641–642, 642f, 643–644
 Lipid(s)
 dietary, solubilization of, 779–780
 energy storage in, 641–642
 fatty acids in, 346–348, 347f, 347t. *See also* Fatty acid(s)
 hydrolysis of, 643–644, 643f
 membrane. *See* Membrane(s); Membrane lipids
 metabolism of. *See* Fatty acid metabolism
 mobilization of, 643–644, 643f
 transport of, 642, 642f
 Lipid A, 978, 978f
 Lipid bilayer. *See* Membrane(s), lipid bilayer of
 Lipid diffusion
 lateral, 361–364, 362f
 transverse, 362
 Lipid kinases, in insulin signaling, 414
 Lipid phosphatases, in signal transduction, 415
 Lipid rafts, 363
 Lipid vesicles, 353–354, 353f
 Lipin 1, 766–767
 Lipinski's rules, 1032–1033, 1032f
 Lipoamide, in citric acid cycle, 501, **501**, 502–503
 Lipoic acid, in citric acid cycle, 500
 Lipolysis, 643–644, 644f. *See also* Fatty acid metabolism
 in starvation, 809, 809f, 810
 Lipophilic molecules, 372
 Lipopolysaccharide (LPS), 978–979, 978f
 Lipoprotein(s)
 classification of, 773, 773t
 high-density, 773, 773t, 774–775, 776, 778–779
 intermediate-density, 773, 773t, 774
 low-density, 559, 744–748, 773–774, 773t, 775–778
 in familial hypercholesterolemia, 776–778
 receptor-mediated endocytosis of, 775–776, 776f
 metabolism of, 775f
 transport function of, 773–774
 very-low-density, 773, 773t
 Lipoprotein lipases, 773
 Lipoprotein particles, 773
 Liposomes, 353–354, 353f
 Lipoxxygenase, 665
 Liquid chromatography, high-pressure, 71, 71f
 L isomers, monosaccharide, 320
 Live attenuated vaccines, 1002
 Liver
 acetaminophen-related injury of, 1036, 1037f
 alcoholic injury of, 811–812
 in amino acid metabolism, 680
 cholesterol synthesis in, 770, 774f
 cirrhosis of, 811–812
 drug metabolism in, 1035–1036, 1036f
 ethanol metabolism in, 811–812

- Liver—(continued)
 fatty, 811
 fatty acid metabolism in, 761
 gene expression in, 939t
 glucose metabolism in, 621, 633–634, 633f, 806
 gluconeogenesis in, 490, 490f
 glycolysis in, 475–477, 487, 807
 ketone body synthesis in, 654–655, 654f, 810, 810f, 810t
 metabolism in
 interchanges with muscle in, 490, 490f, 684–685
 in starvation, 810, 810t
 triacylglycerol synthesis in, 761, 773, 774f
- Local hormones, 665
- Lock-and-key model, of enzyme–substrate complex, 228, 228f
- Long interspersed elements (LINES), 160
- Long QT syndrome, 392–393
- Loops, 42, 43f
- Lou Gehrig's disease, 147–148
- Lovastatin, 779, **779**, **1040**, 1040–1041
- Low-carbohydrate–high-protein diets, 798
- Low-density lipoprotein(s), 773–774, 773t, 774f–777f, 775–778, 779. *See also* Lipoprotein(s)
 in familial hypercholesterolemia, 776–778
 receptor-mediated endocytosis of, 775–776, 776f
- Low-density lipoprotein receptor, 777–778, 777f
- Low-phenylalanine diet, 674
- Lungs, oxygen transport to, 200–201, 208, 208f
- LuxR, 930
- Lyase-catalyzed reactions, 445
- Lyases, 662b. *See also* Enzyme(s)
- Lymphocytes. *See* B cell; T cell(s)
- Lymphotoxin, 55, **55**
- Lynch syndrome, 842–843
- Lysine
 structure of, 30–31, 31f
 synthesis of, 724, 724f
- Lysophosphatidate, 760, **760**
- Lysosomal proteins, 911
- Lysosomes
 definition of, 336
 function of, 336
 in I-cell disease, 336
 in receptor-mediated endocytosis, 776
- Lysozyme, **227**
 antibody binding of, 986, 986f
 molecular models of, 61–62, 61f, 62f
- M isozyme, 297, 297f
- MacKinnon, Roderick, 384, 388
- Macromolecules, biological, 2
- Mad cow disease, 56–57, 56f
- MADLI-TOF mass spectrometry, in oligosaccharide sequencing, 337
- Magnesium ions
 in ATP hydrolysis, 280
 in Calvin cycle, 592–593, 598, 598f
 in DNA cleavage, 274, 277
 kinases and, 457
- Magnetic resonance imaging, functional, 187f, 197–198
- Main olfactory epithelium, 958
- Major facilitator superfamily, 477–478
- Major histocompatibility complex (MHC), 961–1000, 980–981
- Major histocompatibility complex proteins, 961–1000
 class I, 961–996, 993f, 998–999
 class II, 996–999, 996f
 diversity of, 998–999
 peptide presentation by, 992–994, 992f, 993f
 structure of, 992–994, 994f
 T-cell receptors and, 994–998, 994f. *See also* T-cell receptors
 in transplant rejection, 998
- Malaria
 G6PD deficiency and, 611
 infectious mechanisms in, 340
 sickle-cell trait and, 210, 210f
- Malate, **510**
 in Calvin cycle, 599, 600f
 in citric acid cycle, 510
- Malate dehydrogenase, 510
- Malate synthase, in glyoxylate cycle, 519, 519f
- Malate–aspartate shuttle, 552, 552f
- MALDI (matrix-assisted laser desorption/ionization), 91–92, 92f, 93f
- MALDI-TOF mass spectrometry, 92, 92f, 93f
- 4-Maleylacetoacetate, 696, **696**
- Malonyl ACP, 658–659, 658t, **659**
- Malonyl CoA, 657, 666
- Maltase, 328, 454
- Maltose, 327, 328
- Manganese
 in ATP hydrolysis, 280
 in photosystem II, 574, 574f
- Manganese center, 574, 574f
- Mannose 6-phosphate, 336, **336**
- Mannose 6-phosphate receptor, 336, 338
- Mannose, structure of, 321–322, 321f, 322f
- Maple syrup urine disease, 697
- Maps
 active site, 241–242
 electron-density, 99–100, 100f
- Margoliash, Emanuel, 543
- Mass spectrometry, 91–95, 92f, 93f, 95f
 in oligosaccharide sequencing, 336–337, 337f
 tandem, 93–94, 94f
 vs. Edman degradation, 93
- Mast cells, heparin in, 312, 312f
- Matrix-assisted laser desorption/ionization (MALDI), 91–92, 92f, 93f
- McArdle disease, 634t, 635
- MDR (multidrug-resistance) protein, 378, 378f
- Mechanism-based (suicide) inhibition, 242, 750, 754
- Megabase (Mb), 937b
- Melanin, synthesis of, 726
- Melanocyte-stimulating hormone, 796
- Melting, of double helix, 120–121, 120f, 824–825, 825f
- Membrane(s), 345–368
 in Archaea, 350–351, 350f
 asymmetry of, 362, 363–364, 364f
 in bacteria, 363, 364–365
 chloroplast, 567–568, 567f
 cholesterol in, 363
 diffusion across. *See* Membrane diffusion
 in eukaryotes, 363, 364–366, 364f, 365f
 fatty acids in, 362–363, 363f
 flip-flop in, 362, 362f
 fluidity of, 361–364, 362f
 key features of, 346
 lipid bilayer of, 352–355
 formation of, 352–353
 functions of, 362
 noncovalent forces in, 353
 as permeability barrier, 362
 as solvent for membrane proteins, 362
 melting temperature of, 362–363, 362f, 362t
 mitochondrial, 526, 527f
 overview of, 345–346
 permeability of, 354, 354f, 371
 liposomic evaluation of, 353–354, 353f
 phospholipid, 352–355, 352f–354f
 planar bilayer, 354, 354f
 synthetic, 354, 354f
 thylakoid, 567–568, 567f, 574–575
 proton gradient across, 577–581
 stacked vs. unstacked regions of, 583, 583f
 vesicle formation from, 365
 vesicle fusion to, 366, 366f
- Membrane channels
 ion, 371–372, 372f, 382–393. *See also* Ion channels
 water, 394
- Membrane diffusion
 active, 371, 373
 facilitated, 371, 373
 lipid
 lateral, 361–364, 362f
 transverse, 362
 simple, 372
- Membrane lipids. *See also* Membrane(s), lipid bilayer of
 amphipathicity of, 351, 352
 archaeal, 350–351, 350f
 asymmetric distribution of, 362, 363–364
 cholesterol, 350, **350**
 fatty acids in, 346–348, 347f, 347t
 flip-flop of, 362, 362f
 glycolipids, 349–350
 hydrophilicity of, 351, 352

- hydrophobicity of, 351, 352–353
lateral diffusion of, 361–364, 362f
phospholipids, **348**, 348–349, 352–355
 synthesis of, 760–767, 760f
polar head group of, 351
sphingolipids, synthesis of, 763–765
synthesis of, 759–787
in thylakoid membranes, 567–568
transverse diffusion of, 362
triacylglycerols, synthesis of, 760–767, 760f
types of, 348–350
- Membrane polarization, action potential and, 382
- Membrane potential, 373, 382
action, 382, 382f, 391–392, 391f
 generation of, 392, 393f
 current generated by, 392
 Nernst equation for, 391
- Membrane proteins
 α helix of, 356, 358, 359–360, 360f, 360t, 362f
amounts of, 355
bacteriorhodopsin, 356, 356f
 β strands of, 357, 357f
channel. *See* Membrane channels
functions of, 355
hydropathy plots for, 360, 362f
hydrophobicity of, 45–46, 46f, 47f
integral, 355, 355f
interaction with membrane, 357–359
 membrane anchors in, 359f
 peripheral, 355–356, 355f
 prostaglandin H₂, 356, 358f
 pump. *See* Ion pumps
 SDS–polyacrylamide gel
 electrophoresis, 355, 355f
 solubility of, 355
 structure of, 355–356, 358f
 transporter. *See* Membrane transport; Transporters
- Membrane transport
ABC transporters in, 378–380, 378f, 379f
across endoplasmic reticulum, 911–914
active, 371
ATP hydrolysis in, 374–381
concentration gradient in, 373–374
free energy in, 373–374, 373f
gap junctions in, 393–394, 393f, 394f
ion channels in, 372, 382–393. *See also* Ion channels
ion pumps in, 371, 374–381. *See also* Ion pumps
membrane potentials in, 373, 382, 382f, 392. *See also* Membrane potential
passive, 371–373
rate of, 382, 387
signaling in, 911–913
transport vesicles in, 913–914, 914f
transporters in, 371–372, 380–381. *See also* Transporters
water channels in, 394
- Membrane-spanning proteins, 911
- Memory B and T cells, 1002
- Menten, Maud, 230
- β -Mercaptoethanol, in ribonuclease denaturation, 49, **49**, 49–50, 50f
- 6-Mercaptopurine, 1047–1048, **1048**
- Mercury poisoning, 517
- Meromysin, 1009, 1009f
- Merrifield, R. Bruce, 98
- Meselson, Matthew, 119
- Messenger RNA. *See* mRNA (messenger RNA)
- Metabolons, 512
- Metabolic pathways, 428–430, 428f. *See also* *specific pathways*
amphibolic, 429
branched, regulation of, 723
committed step in, 474, 723
coordinated action of, 662
 in fatty acid synthesis, 654f, 662, 666f
 in purine synthesis, 744
degradative vs. synthetic, 429
evolution of, 447
salvage, 740
 definition of, 740
 in nucleotide synthesis, 736, 736f, 744–745
- Metabolic syndrome, 800
- Metabolism, 427–447
activated carriers in, 438–442
allosteric interactions in, 291, 446
anabolic reactions in, 428–429
bioenergetics of, 429–435
of carbohydrates, 454
catabolic reactions in, 428, 435–438
 electron carriers in, 438–439
common motifs in, 438–447
definition of, 427
drug, 1034–1036
electron carriers in, 438–439, 440t
energy charge in, 446–447, 446f
evolution of, 447
first-pass, 1035
free energy in, 429–430
functional group addition in, 445
group-transfer reactions in, 436–437, 443t, 444
hydrolysis in, 444–445
interconnected reactions in, 428–430, 428f
isomerization in, 443t, 444
ligation reactions in, 443–444
lyase-catalyzed reactions in, 445
overview of, 427–428
oxidation-reduction reactions in, 443, 443t
regulation of, 445–447
 via catalytic activity, 446–447
 via enzyme amounts, 446
 via substrate availability, 447
substrate cycles in, 489, 489f
thermodynamics of, 429–430. *See also* Energy; Thermodynamics
- Metabolites, 2
- Metal ion catalysis, 221, 221t, 253–254, 254–255
 in ATP hydrolysis, 280
 in carbon dioxide hydrolysis, 221, 221t, 267–269, 267f–269f
 in DNA cleavage, 274, 277
 in DNA replication, 821–822, 821f
- Metalloproteases, in peptide bond cleavage, **263**, 264, 264f
- Metals, coenzyme, 221, 221t
- Metamorphic proteins, 55, 55f
- Metarhodopsin II (R*), 968, 968f
- Methionine, **693**
 in activated methyl cycle, 717–718, 717f
 conversion to succinyl CoA, 693, 693f
 in emphysema, 307
 structure of, 28, 29f
 synthesis of, 650, 716–718, 724
- Methionine sulfoxide, 307, 307f
- Methionine synthase, 717
- Methionyl-tRNA, 901–902, 902f
- Methotrexate, 750
- Methyl cycle, 717–718, 717f
- Methylase, in DNA cleavage, 277–278
- Methylation
 in amino acid synthesis, 716–718, 717f, 718f
 of DNA, 718, 718f, 945–946
 in amino acid synthesis, 716–718, 718f
 in cleavage, 277–278, 278f
 in gene regulation, 945–946, 951
 hypomethylation and, 945
 of tRNA, 889–890
- 3-Methylbutane-1-thiol, 958, **958**
- Methylcobalamin, 717
- Methylcrotonyl CoA, 694, **694**
- 5-Methylcytidine (mC), **890**
- 5-Methylcytosine, **945**, 945–946
- N⁵,N¹⁰-Methylenetetrahydrofolate, 715, **716**
- Methylglutaconyl CoA, 694, **694**
- Methylmalonyl CoA, **649**, 650, 693
- Methylmalonyl CoA mutase, 650–652, **652**, 693
- N⁵,N¹⁰-Methyltetrahydrofolate, 749f, **750**
- N⁵-Methyltetrahydrofolate, 715, **716**, 717
 in thymidylate synthesis, 748
- Metmyoglobin, 198
- Metoprolol, 1047, **1047**
- Mevalonate, in cholesterol synthesis, 767–768
- Meyerhof, Otto, 454
- MHC. *See* Major histocompatibility complex (MHC)
- Mice, transgenic, 164, 164f
- Micelle, 352, 352f
- Michaelis constant (K_M), 231–235
 calculation of, 233
 definitions of, 232, 234
 for selected enzymes, 233t
- Michaelis, Leonor, 230
- Michaelis-Menten equation, 229–237, 231f

- Michaelis-Menten kinetics, 229–237, 231f
- Microarrays, DNA, 162–163, 162f
- Microbodies, 593
 - fatty acid metabolism in, 653f
- Microinjection, of recombinant DNA, 163, 163f
- MicroRNA (miRNA), 124, 872, 872f, 953–954
- Microscopy
 - fluorescence, 90–91, 90f
 - immunoelectron, 91, 91f
- Microsomal ethanol-oxidizing system (MEOS), 811
- Microtubules, 1018–1020
 - in cilia, 1019
 - dynamic instability of, 1019
 - in flagella, 1019
 - functions of, 1019
 - kinesin movement along, 1020–1022, 1020f, 1021f
 - structure of, 1018–1019, 1019f
- Microvilli
 - intestinal, 328f
 - in taste buds, 963, 963f
- Milstein, César, 87
- Mineralocorticoids. *See also* Steroid hormones
 - synthesis of, 780, 780f
- Minor groove, 822, 822f
- Minoxidil sulfate, 1034, **1034**
- miRNA (microRNA), 124, 842, 872f, 953–954
- Mismatch repair, 840, 840f
- Mitchell, Peter, 544–545
- Mitchison, Tim, 1019
- Mitochondria
 - in apoptosis, 559
 - ATP synthase in, 526, 544–550, 558
 - brown fat, 556–557
 - citric acid cycle in, 498, 498f
 - endosymbiotic origin of, 527–528
 - fatty acid metabolism in, 652
 - genome of, 527–528, 527f, 528f
 - oxidative phosphorylation in, 525–528
 - properties of, 526–527
 - structure of, 526, 527f
- Mitochondrial ATPase. *See* ATP synthase
- Mitochondrial diseases, 558–559
- Mitochondrial DNA, 527–528
 - genetic code of, 131, 131t
 - sequencing of, 158
- Mitochondrial outer membrane
 - permeabilization (MOMP), 559
- Mitochondrial porins, 526–527
- Mitochondrial transporters, in oxidative phosphorylation, 551–553, 551f–553f
- Mixed-function oxygenases, 695, 781
- Mobile genetic elements, 159–160
- Molecular models, 60–62, 61f, 62f
 - ball-and-stick, 22, 23f, 61, 61f
 - space-filling, 21, 23f
- Molecular motors, 1007–1026. *See also* Motor proteins
- Molecules
 - homologous, 174–181, 175f
 - three-dimensional structure of, 21–22
- Moloney murine leukemia virus vectors, 163
- Molybdenum–iron protein, **708**, 708–709
- Monoacylglycerol, **642**
- Monoamine oxidase, suicide inhibition of, 242, 242f
- Monoclonal antibodies
 - for cancer, 421
 - preparation of, 86–88, 87f
- Monod, Jacques, 202, 924
- Monoxygenases, 695, 781
- Monosaccharides, 320–327. *See also* Carbohydrates
 - abbreviations for, 330b
 - with alcohols, 326
 - aldoses, 320, 321
 - with amines, 326
 - boat form of, 324, 325f
 - chair form of, 324, 325f
 - definition of, 320
 - D-isomers of, 320, 322f
 - envelope form of, 325, 325f
 - envelope forms of, 325f
 - furanose, 323–325, 323f
 - isomers of, 321
 - ketoses, 320, 322
 - linkage of, 327–329. *See also* Disaccharides
 - modified, 326, 326f
 - nomenclature for, 323
 - nonreducing sugars, 325
 - phosphorylated, 327
 - pyranose, 322–325, 323f
 - reducing sugars, 325
 - ring forms of, 322–325, 323f, 325f
 - stereoisomers of, 321, 321f
 - structure of, **320**, 320–321
- Montagnier, Luc, 999
- Morphine glucuronidate, 1034, **1034**
- Morphine, oral bioavailability of, 1032–1033, 1032f
- MotA–MotB pairs, 1023, 1023f, 1024f
- Motifs, 47, 47f
 - repeating, 79
 - sequence homology of, 184, 185f
- Motor proteins, 1007–1026
 - ATP binding to, 1010–1012, 1011f, 1012f
 - dynein, 1008, 1010, 1011f
 - kinesin, 1008, 1010–1012, 1018–1022, 1020–1022
 - myosin, 1007–1018. *See also* Myosin
 - overview of, 1007–1008
 - P-loop NTPase superfamily, 1008–1012
 - structure of, 1009–1012, 1009f–1012f
- Mouse, transgenic, 164
- mRNA (messenger RNA), 109, 123–124, 123t. *See also* RNA
 - in attenuation, 931–932
 - complementarity with DNA, 126, 126f
 - 5' cap of, 870–871, 871f
 - functions of, 123–124
 - hairpin turns in, 42, 43f, 127, 127f
 - in transcription termination, 859–860, 859f
- iron-response elements in, 952–953
- polycistronic, 901
- precursor of, processing of, 870–872
- in protein synthesis, 123–124, 130, 130f
- reductase, in cholesterol regulation, 771
- splicing of, 869
- structure of, in eukaryotes, 908
- 3' poly(A) tail of, 871–872, 871f
- transferrin-receptor, 951, 952f
- in translation, 123–124, 130, 130f. *See also* Translation
 - translocation of, 904–906
 - translation of, 130, 130f
- MS ring, 1023, 1023f, 1024f
- μ chains, 938f, 982
- Mucins, 330, 333, 333f
- Mucopolysaccharidoses, 332
- Mucoproteins, 330, 333, 333f
- Muller, Hermann, 839
- Mullis, Kary, 145
- Multidrug resistance, 378
- Multidrug-resistance (MDR) protein, 378, 378f
- Multienzyme complexes, 660–661
 - substrate channeling by, 722–723, 722f
- Multiple myeloma, 87–88
- Muscle
 - amino acid degradation in, 684
 - cardiac, H and M isozymes in, 297, 297f
 - drug-related injury of, 1040
 - energy storage in, 641, 805t, 806
 - glycolysis in, 473–474, 475f, 489–490
 - metabolism in, 804–806, 804f
 - interchanges with liver, 490, 490f, 684–685
 - in starvation, 809–810
 - triacylglycerols in, 641
- Muscle contraction. *See also* Exercise
 - actin in, 1012–1018. *See also* Actin/actin filaments
 - ATP formation during, 434–435, 435f, 489–490, 805–806, 805t
 - ATP hydrolysis in, 1009–1012, 1011f, 1012f, 1015, 1016f
 - creatine phosphate and, 434–435, 435f
 - gluconeogenesis in, 489–490, 490f
 - lactate formation during, 435f
 - myosin in, 1012–1018. *See also* Myosin
 - pyruvate in, 489–490, 490f
 - sliding filament model of, 1016–1017, 1017f
- Mushroom poisoning, α -amanitin in, **865**, 865–866
- Mutagenesis
 - in recombinant DNA technology, 156–157, 156f, 157f
 - site-directed, in catalysis investigation, 262–263
- Mutagens, 838
- Mutases, 464

- Mutations
 base-pair substitution, tests for, 843–844
 deletion, production of, 156
 disease-causing, 157. *See also* Diseases and disorders
 functional effects of, 157
 identification of, 147–148
 frameshift, tests for, 843–844
 insertion, production of, 157
 point, production of, 157
 production of, 156–157, 156f, 157f
 in recombinant DNA technology, 156–157
 somatic, antibody diversity and, 989
 substitution, production of, 156, 156f
- MWC (concerted) model
 of allosteric enzyme kinetics, 296, 296f
 of hemoglobin oxygen binding, 202–203, 203f, 214–216, 216f
- myc* gene, in cancer, 869
- Mycobacterium tuberculosis*, 679
- Myelin, protein content of, 355
- Myeloma, 87–88
- Myofibrils, 1016
 sarcomere of, 1016–1017, 1017f
- Myogenin, 165, 165f
- Myoglobin
 electron-density map of, 100f
 evolution of, 187–188, 187f
 forms of, 196
 Hill plot for, 213–214, 214f
 overview of, 195–196
 oxygen binding by, 196–198, 198f–200f, 200
 oxygen-binding curve for, 200–201, 200f, 201f
 sequence homology with hemoglobin, 175–181, 176f–182f, 199
 structure of, 46, 46–48, 46f, 196, 196–197
 tertiary, 183, 183f
 vs. hemoglobin, 195–196
- Myopathy, drug-related, 1040
- Myosin, 279–284, 1007–1018
 ATP binding to, 1010–1012, 1011f, 1012f
 ATP hydrolysis and, 279–283, 281f–283f
 ATPase domains of, 279–280, 280f
 functions of, 279
 kinesin and, 1008. *See also* Kinesin
 lever arm of, 1011–1012, 1011f, 1018, 1018f
 movement along actin, 1012–1018. *See also* Actin/actin filaments
 direct observation of, 1014–1015
 power stroke in, 1015
 rate of, 1018, 1018f
 P-loop of, 283–284
 relay helix of, 1012, 1012f
 S1, 1009, 1009f, 1011f
 S2, 1009, 1009f
 structure of, 279, 279f, 1008–1010, 1009f, 1010f, 1011f
 conformational changes in, 280–283, 282f
 in thick filaments, 1016, 1017f
 in thin filaments, 1016, 1017f
- Myosin-actin complex, 1014, 1014f
- Myristoylation, 298t
- Na⁺. *See under* Sodium
- NAD⁺ (nicotinamide adenine dinucleotide)
 in catabolism, 438, 438f
 in citric acid cycle, 501–502, 512
 dehydrogenase binding sites for, 469, 469f
 in fatty acid metabolism, 646, 647, 647f
 in glycolysis, 469
- NADH (nicotinamide adenine dinucleotide reduced)
 ADP units in, 447, 447f
 in ATP synthesis, 439, 589
 in citric acid cycle, 498, 498f, 502, 503, 512, 514f
 ethanol and, 811
 in fatty acid metabolism, 646–647, 647f, 664
 in gluconeogenesis, 483–484
 in glycolysis, 466–468
 in oxidative phosphorylation, 525
 electron-transfer potential of, 530–531
 reduction potential of, 528–530
 transport of, 551–552, 551f, 552f
 vs. NADPH, 589–590
- NADH dehydrogenase, in respiratory chain, 531–535, 532f
- NADH-cytochrome *b*₅ reductase, 664, 664f
- NADH-Q oxidoreductase (Complex I), in respiratory chain, 531–535, 532f
- NADP⁺ (nicotinamide adenine dinucleotide phosphate), 438, 439
 as electron carrier, 439
 in pentose phosphate pathway, 601, 602f, 606–607
 in photosynthesis, 576–577
 in reductive biosynthesis, 439
- NADPH (nicotinamide adenine dinucleotide phosphate reduced), 438, 439
 in Calvin cycle, 589–590, 590f, 596f, 599
 as electron carrier, 439
 pathways requiring, 601t
 in pentose phosphate pathway, 589–590, 601–603, 604t, 607–609
 in photosynthesis, 566–567, 576–577, 579–581, 589–590, 599
 in reductive biosynthesis, 439, 589–590
 in steroid hydroxylation, 781–782
- Nalidixic acid, 831, 831
- Nasal anatomy, in olfaction, 958, 959f. *See also* Olfaction
- Nathans, Daniel, 141
- Neanderthals, DNA sequencing for, 188–189, 189f
- Neck linker, 1012, 1012f
- Neher, Erwin, 383
- Nernst equation, 391
- Nerve gases, 241
- Nerve impulse, propagation of, 382, 382f
- Neuberg, Carl, 454
- Neural-tube defects, 755
- Neuraminidase, 339, 340f
- Neuroglobin, 212
- Neurological diseases. *See* Diseases and disorders
- Neuropeptide Y, 796
- Neurotransmitters
 definition of, 389
 ion channels and, 389–390
 release of, 366f
- Neutral fat. *See* Triacylglycerol(s)
- Niacin, 441, 441t
- Nicolson, Garth, 362
- Nicotinamide adenine dinucleotide. *See* NAD⁺
- Nicotinamide adenine dinucleotide phosphate. *See* NADP⁺; NADPH
- Nicotinamide, synthesis of, 726f, 727
- Nicotinic acid, 441t
 9 + 2 array, 1019
- 19S regulatory unit, 667f, 677
- Ninhydrin, in Edman degradation, 81, 81
- Nirenberg, Marshall, 128
- Nitric oxide
 in signaling, 728
 synthesis of, 727–728, 728f
- Nitric oxide synthase, 728
- Nitrogen excretion
 ammoniotelic organisms in, 690
 glucose-alanine cycle in, 684–685, 685f
 transamination in, 680–685
 transport to liver in, 684–685
 urea cycle in, 673, 685–690
 ureotelic organisms in, 685, 690
- Nitrogen fixation, 706–710, 707f
- Nitrogen, in ammonia, 706. *See also* Ammonia
- Nitrogenase, 707
 iron-molybdenum cofactor of, in nitrogen fixation, 708–709
- Nitrogenase complex, 707
- Nitrogen-starvation promoter, 858, 858f
- N-linked oligosaccharides, 330, 330f, 336
- NMP kinases. *See* Nucleoside monophosphate (NMP) kinases
- Nociceptors, 973
- NOESY (nuclear Overhauser enhancement spectroscopy), 101–104, 102f, 103f
- NompC, 972
- Noncompetitive inhibition, 238, 238f, 239–240, 239f, 240f
- Noncovalent bonds, 7–8. *See also* Bonds
 electrostatic interactions, 7–8
 in enzyme-substrate complex, 228, 228f
 hydrogen bonds, 8, 9, 9f. *See also* Hydrogen bonds
 hydrophobic effect and, 9–10, 9f
 surface complementarity and, 11
 van der Waals interactions, 8, 8f, 10, 10f, 11, 46
- Nonessential amino acids, 711, 711t, 712f
 synthesis of, 712–713

- Nonheme iron proteins. *See* Iron-sulfur proteins
- Nonhomologous end joining, 841
- Nonpolar molecules, 9
- Nonreducing sugars, 325
- Nonshivering thermogenesis, 556–557
- Northern blotting, 142
- Nose. *See also* Olfaction
anatomy of, 958, 959f
electronic, 961–962, 962f
- Novobiocin, 831
- N-terminal rule, 676
- NTP. *See* Nucleoside triphosphates (NTPs)
- NTPase domains, P-loop, 284, 284f
- NTPases, P-loop. *See* P-loop NTPases
- Nuclear envelope, 365
- Nuclear hormone receptors, 946–948, 947f–949f, 948f, 949f, 950
DNA-binding domains of, 946, 947f
drug binding to, 948–949, 949f
ligand-binding domains of, 946–947, 947f
- Nuclear localization signal, 79
- Nuclear magnetic resonance (NMR)
spectroscopy, 101–104, 101f–103f
- Nuclear Overhauser enhancement
spectroscopy (NOESY), 101–104, 102f, 103f
- Nuclear pores, 365
- Nucleation-condensation model, 53
- Nucleic acids, 109. *See also* DNA; RNA
abbreviations for, 112, 112f
evolution of, molecular studies of, 188–191, 190f
sequence of, notation for, 112, 112f
- Nucleoside(s), 111, **111**
nomenclature of, 736t
- Nucleoside diphosphate (NDP), 739
phosphorylation of, 431
- Nucleoside diphosphate kinases, 431, 739
- Nucleoside diphosphokinase, 629
in citric acid cycle, 508
- Nucleoside monophosphate, 739
phosphorylation of, 431
- Nucleoside monophosphate kinases, 248–249, 431, 739
P-loop of. *See* P-loop(s)
structure of, **284**
- Nucleoside phosphorylases, 752
- Nucleoside triphosphate-magnesium complex, 280
- Nucleoside triphosphates (NTPs), 739.
See also P-loop NTPases
hydrolysis of, energy from, 431
- Nucleosome core particle, 939
- Nucleosomes, 939–941, 940f
- Nucleotidases, 752
- Nucleotide(s), 110, **110**, 111–112.
See also Bases/base pairs;
Deoxyribonucleotide synthesis; Purine nucleotides; Pyrimidine nucleotides
definition of, 735
disorders of, 752–755
functions of, 735
nomenclature of, 736t
synthesis of, 735–755
de novo pathways in, 736–740, 736f
deoxyribonucleotide, 745–750, 752, 752f
disorders of, 753–755
inosinate in, 743–744, 743f
purine, 740–745, 751, 751f
pyrimidine, 736–740, 736f, 751
regulation of, 750–752
salvage pathways in, 736, 736f, 744–745
substrate channeling in, 738
transformation to amino acids. *See* Translation
- Nucleotide-excision repair, 840–841, 841f
- Nucleotides, nomenclature for, 112
- NusA, in transcription termination, 861
- Nutrition, 20, 20f. *See also* Diet; Food;
Starvation
starved-fed cycle and, 807–808
- Obesity, 792–803
causes of, 792–794
definition of, 792
diabetes and, 798–803
dieting and, 797–798
evolution and, 792–793
fatty acids in muscle and, 800–801
health consequences of, 793t
insulin resistance and, 798–800, 800
metabolic syndrome and, 800
pancreatic function in, 801–802
prevalence of, 792–794
- Obligate anaerobes, 468–469
pathogenic, 468–469, 469t
- Odorant receptors, 958–960, 960f, 961f
- Okazaki fragments, 823–824, 823f, 833
- Okazaki, Reiji, 823
- Oleate, 347, **347**, 664, **664**
- Olfaction, 958–962, 964, 964f
anatomic structures in, 958, 959f
combinatorial mechanisms in, 960–962
by electronic nose, 961–962, 962f
evolution of, 959–960, 959f
impaired, 958
odorant receptors in, 958–960, 960f, 961f
7TM receptors in, 959
signal transduction in, 959–960, 960f
- Oligomerization, in B-cell activation, 989–990
- Oligonucleotide-directed mutagenesis, 156, 156f
- Oligopeptides, 34. *See also* Peptide(s)
- Oligosaccharides, 327. *See also*
Disaccharides; Polysaccharides
abbreviations for, 330b
in gangliosides, 764, 765f
in glycoproteins, 329–337
N-linked, 330, 330f, 336
O-linked, 330, 330f, 336
sequencing of, 336–337
O-linked oligosaccharides, 330, 330f, 336
Ω loops, 42, 43f
- Omeprazole, 1046, **1046**
- Oncogenes, 420
- One-carbon units
in amino acid degradation, 716
in amino acid synthesis, 715–716, 715t, 716f
- Operator DNA, 922f
- Operon(s), 924–928
histidine, 932–933, 932f
lac, 925–928, 925f, 926f, 927. *See also* under *lac*
phenylalanine, 932–933, 932f
structure of, 924–925, 925f
threonine, 932–933, 932f
trp, 931
- Opsin, 967
- Optical trap, 1015, 1015f
- Oral bioavailability, 1032–1033, 1032f
- oriC* locus, 834, 834f
- Origin of replication
in bacteria, 834, 834f
in eukaryotes, 835–836
- Origin of replication complexes, 835
- Ornithine, 686, **686**
- Ornithine transcarbamoylase, 686
deficiency of, 689
- Orotate, **738**, 738–739
- Orotidylate, 739, **739**
- Orotidylate decarboxylase, 739
- Orthologs, 174–175, 175f
- Orthophosphate
in gluconeogenesis, 483
resonance structures of, 433, 433f
- Osteoarthritis, 332
- Osteogenesis imperfecta, 45
- Osteomalacia, 786
- Oster, George, 548
- Overlap peptides, 82, 83f
- Overweight, 792, 793f
- Oxaloacetate, **237**, **443**
in amino acid degradation, 692
in amino acid synthesis, 712
in Calvin cycle, 599, 600f
in citric acid cycle, 498, 498f, 504, 505f, 509–510, 515, 516f, 653
in gluconeogenesis, 482, 483–484, 484f
in glyoxylate cycle, 518–519, 519f
synthesis of, 443–444
transfer from mitochondria to cytoplasm, 662–663
in urea cycle, 687, 687f
- Oxidation, of xenobiotic compounds, 1035
- Oxidation–reduction potential, 528–530, 529t
measurement of, 528f, 529–530
in oxidative phosphorylation, 528–531
- Oxidation–reduction reactions
free energy change in, 530
in metabolism, 443, 443t
reduction potential of, 529–530, 529t
- Oxidative damage
defenses against, 540–542
in DNA, 838

- Oxidative phosphorylation, 437, 525–561.
See also ATP, formation of
 ATP in, 525–526
 ATP yield in, 554–555, 555t
 ATP-ADP translocase in, 552–553, 553f, 554f
 cellular respiration in, 526
 chemiosmotic model of, 544–545, 544f, 545f
 in citric acid cycle, 498
 electron transfer in, 528–531. *See also* Respiratory chain
 rate of, 542–543, 542f
 during exercise, 806
 glycerol 3-phosphate shuttle in, 551, 551f
 heat from, 556–557
 inhibition of, 558, 558f
 malate–aspartate shuttle in, 552, 552f
 NADH in, 525
 electron-transfer potential of, 530–531
 reduction potential of, 528–530
 transport of, 551–552, 551f, 552f
 overview of, 525–526, 526f, 551f
 oxidative damage and, 540–542, 541t, 542f
 proton gradients in, 530–531, 543–550, 559–560, 560f
 proton pumps in, 525
 proton-motive force in, 525, 544–545, 544f, 545f
 rate of, 555–556, 556f
 reduction potential in, 528–531
 respiratory chain in, 525, 531–543. *See also* Respiratory Chain
 in thermogenesis, 556–557
 transporters in, 551–553, 551f–553f
 uncoupling of, 556–557, 558
 vs. photosynthesis, 578, 579f
- Oxidoreductases, 249t
- Oxidosqualene cyclase, 769
- 8-Oxoguanine, mutagenicity of, 838, 838f
- Oxyanion hole, 259, 259f
 of chymotrypsin, 261, 261f
- Oxygen
 fractional saturation of, 199
 hemoglobin affinity for, 204–205, 204f
 hemoglobin binding of, 196–199. *See also* Hemoglobin, oxygen binding by
 hemoglobin release of, 200, 201f, 206–208, 208f
 carbon dioxide in, 207–208, 208f
 myoglobin binding of, 196–198, 198f–200f, 200
 partial pressure of, 200
 photosynthetic production of, 572–574, 574f
 reactive. *See* Reactive oxygen species (ROS)
 in steroid hydroxylation, 781–782
- Oxygen therapy, hyperbaric, 206
- Oxygen transport, 200–201, 207–208, 208f
- Oxygenases
 in amino acid degradation, 695–696
 mixed-function, 695, 781
- Oxygenation, in amino acid degradation, 695–696
- Oxygen-binding curve, 199–200, 200f, 201f
 with concerted model, 214–216, 216f
 for Hill coefficients, 214, 214f
- Oxymyoglobin, 196, **198**. *See also* Myoglobin
- P clusters, 708, 708f
- P site, ribosomal, 900, 900f, 903
- p53, 843
- p160 family, 948
- P680, 573–574, 573f
- P700, 576
- P960, 571
- Pain management, capsaicin in, 974
- Pain sensation, 973–974
- PALA (*N*-phosphonacetyl-L-aspartate), **293**, 293–294
- Palade, George, 526
- Palindrome, 141b
- Palindromic sequences, 141
- Palmitate, 347, **347**
 oxidation of, 647–648, 648f
 synthesis of, 661–662
- Palmitoleate, 664, **664**
 oxidation of, 648, 648f
- Palmitoleoyl CoA, 648, **648**
- Palmitoyl CoA, 647–648, 666
 in sphingolipid synthesis, 764, **764**
- Palmitoylcysteine, 359, **359**
- Pamaquine, hemolytic anemia and, 610
- PAMP (pathogen-associated molecular pattern), 978–979, 979f
- Pancreas
 in diabetes, 801–802. *See also* Diabetes mellitus
 disorders of. *See* Diabetes mellitus
 gene expression in, 939t
- Pancreatic β cells, 802
- Pancreatic enzymes, 255–260, 303–307, 303t, 304f, 674
- Pancreatic lipases, 641–642, 642f, 643–644
- Pancreatic trypsin inhibitor, 306
- Pancreatic zymogens, 303–307, 303t, 304f
- Panthothenic acid (coenzyme A), **440**, 441t
 as acyl group carrier, 440
 ADP units in, 447, 447f
 in fatty acid metabolism, 644–645
- Papain, 220–221
- Paralogs, 174, 175f
- Paraquat, 584
- Pardee, Arthur, 291
- Park, James, 1038
- Parkinson disease, 55–56, 242, 676
- Parnas, Jacob, 454
- Partition coefficient, in drug absorption, 1032
- Passive transport, 371, 373. *See also* Membrane transport
- Pasteur, Louis, 454, 1002
- Patch-clamp technique, 372f, 383, 383f
- Pathogen-associated molecular pattern (PAMP), 978–979, 979f
- Pathological conditions. *See* Diseases and disorders
- Pauling, Linus, 38, 197, 209, 226b, 243
- pBR322 plasmid, 149, 149f
- PCR. *See* Polymerase chain reaction (PCR)
- Pectin, 329, 329f
- Penicillin
 discovery and development of, 1037–1038
 mechanism of action of, 244–245, 244f, 245f, 1038
 resistance to, 1050
 structure of, 1037, **1037**
- Pentose phosphate pathway, 589–590, 601–611
 Calvin cycle and, 609
 functions of, 608t
 glycolysis and, 601–609
 modes of, 607–609, 607f
 nonoxidative phase of, 601–606, 603f, 604t
 oxidative phase of, 601–603, 603f, 604t
 rate of, 607–609
 reactions of, 602f, 604t
 regulation of, 607–609
 in selected tissues, 608t
 stoichiometry of, 607–609, 607f
 transaldolase in, 601–604, 605, 606f
 transketolase in, 601–605, 605f
- Pentoses, 320
- Pepsin, 674
- Peptide(s). *See also* Protein(s)
 definition of, 34
 synthetic, 95–98, 96f, 97f
- Peptide bonds, 33, 33f, 36–37, 36f, 37f.
See also Bonds
 angles of rotation for, 37, 37f, 38f
 cis configuration of, 36–37, 36f, 37f
 cleavage of, 58, 220–221, 255, 258–260, 259f
 acyl-enzyme intermediate in, 257, 257f, 259f
 chromogenic substrate for, 256–257, 257f
 deacylation in, 259–260, 259f, 260f
 proteases in, 255–266
 aspartyl, **263**, 264, 264f
 cysteine, **263**, 263–264, 264f
 metal ion, **263**, 264, 264f
 serine, 255–266
 tetrahedral intermediate in, 258–259, 259f
 double-bond character of, 36
 formation of, 903–904, 904f
 hydrolysis of, 220–221, 255–260
 length of, 36, 36f
 planarity of, 36, 36f
 torsion angles for, 37, 37f, 38f
 trans configuration of, 36–37, 36f, 37f

- Peptide ligation, 96
- Peptidoglycans, 244, 244f
- Peptidyl transferase center, 903–904
- Perforin, 996
- Perilipin A, 643
- Peripheral membrane proteins, 355–356, 355f
- Periplasm, 365
- Peroxide bridge, in cytochrome *c* oxidase, 539f, 540, 540f
- Peroxide detoxification, 727
- Peroxisomes, 593
 - fatty acid metabolism in, 652, 653f
- Perutz, Max, 199
- PFK. *See* Phosphofructokinase (PFK)
- P-glycoprotein, 378
- pH
 - buffers and, 15–17
 - definition of, 13
 - oxygen affinity of hemoglobin and, 206–207, 206f
 - physiological, 16
- Phagocytes, 978
- Pharmacology. *See also* Drug development
 - definition of, 1030b
- Phase I transformations, in oxidation, 1035
- Phase II transformations, in conjugation, 1035
- Phenyl isothiocyanate, in Edman degradation, 81, 81
- Phenylacetate, 689
- Phenylalanine
 - degradation of, 695–696
 - in phenylketonuria, 697–698
 - structure of, 28, 29f, 696
 - synthesis of, 719–720, 720f, 721f
- Phenylalanine hydroxylase, 695
 - deficiency of, in phenylketonuria, 697–698
- Phenylalanine operon, 932–933, 932f
- Phenylketonuria (PKU), 674, 697–698
- Phenylpyruvate, 720, 721
- Pheromones, 974
- Phi (ϕ) angle of rotation, 37–38, 37f, 38f
- Phosphatase(s)
 - deficiency of, 514
 - in signal transduction, 415
- Phosphatase and tensin homolog, 799
- Phosphate carrier, 554, 554f
- Phosphate, in myosin movement, 1015
- Phosphate solutions, as buffers, 16
- Phosphatidate, 348, 348, 762
 - in membrane lipid synthesis, 760, 761, 761f
 - synthesis of, 760
- Phosphatidic acid phosphatase (PAP), 761, 766–767, 766f
- Phosphatidylcholine, 349, 349
 - melting temperature of, 362t
 - synthesis of, 763, 763f
- Phosphatidylethanolamine, 349, 349
 - synthesis of, 763, 763
- Phosphatidylethanolamine methyltransferase, 763
- Phosphatidylglycerol, 349, 349
 - Phosphatidylinositol, 349, 349, 762, 762, 763
 - Phosphatidylinositol 3,4,5-trisphosphate (PIP₃), in signal transduction, 414, 799, 799f
 - Phosphatidylinositol 4,5-bisphosphate (PIP₂), 762
 - in signal transduction, 408, 409f, 414, 799, 799f
 - Phosphatidylserine, 349, 349
 - synthesis of, 763
 - 3'-Phosphoadenosine-5'-phosphosulfate (PAPS), 1035
 - Phosphocreatine, synthesis of, 236–237
 - Phosphodiester bridges, 110, 110, 111
 - hydrolysis of, 272–274
 - Phosphoenolpyruvate, 434, 445
 - in amino acid synthesis, 719, 720f
 - formation of, 445, 465
 - in gluconeogenesis, 480f, 481, 482, 483–484
 - in glycolysis, 464f, 465
 - NAD⁺ regeneration in, 466–468
 - phosphoryl-transfer potential of, 434, 434t, 465
 - Phosphoenolpyruvate carboxykinase, 488, 488f
 - Phosphofructokinase (PFK), 473
 - in gluconeogenesis, 487
 - in glycolysis, 455f, 458
 - in liver, 475–476, 475f, 476f, 487, 488
 - in muscle, 473–474, 473f
 - Phosphofructokinase 2, 487
 - Phosphoglucomutase, 471, 620, 621f
 - 6-Phosphogluconate, in pentose phosphate pathway, 601, 603
 - 6-Phosphoglucono- δ -lactone, in pentose phosphate pathway, 601–603, 603
 - Phosphoglucose isomerase, 457
 - 2-Phosphoglycerate, 445
 - in glycolysis, 445, 464, 466t
 - 3-Phosphoglycerate, 464
 - in Calvin cycle, 591–592
 - in cysteine synthesis, 714–715
 - in glycine synthesis, 714–715
 - in glycolysis, 463–464, 464f, 466t
 - in serine synthesis, 714–715, 714f, 723
 - 3-Phosphoglycerate dehydrogenase, 723, 723, 724, 724f
 - Phosphoglycerate kinase, in glycolysis, 463–464
 - Phosphoglycerate mutase
 - in glycogen metabolism, 464, 620
 - in glycolysis, 464, 464f
 - Phosphoglycerides, 348, 349, 351, 351f
 - Phosphoglycolate, in Calvin cycle, 593, 593–594
 - 3-Phosphohydroxypyruvate, 714
 - in proline synthesis, 714, 714f
 - Phosphoinositide cascade, 408–409, 409f
 - in glycogen metabolism, 626
 - Phospholipase C, in signal transduction, 408, 409f
 - Phospholipid(s). *See also* Lipid(s) membrane, 352–355. *See also* Membrane(s); Membrane lipids
 - phosphoglycerides, 348, 349
 - structure of, 348, 348–349
 - synthesis of, 760–767, 760f
 - 5-Phosphomevalonate, 768
 - N-Phosphonacetyl-L-aspartate (PALA), 293, 293–294
 - Phosphopentose epimerase, 596, 596f
 - in Calvin cycle, 596, 596f
 - in pentose phosphate pathway, 603, 604t
 - Phosphopentose isomerase, in Calvin cycle, 596, 596f
 - Phosphoribomutase, 752
 - 5-Phosphoribosyl-1-pyrophosphate (PRPP), 720–721, 721, 755
 - in purine synthesis, 741, 751
 - in pyrimidine synthesis, 738–739
 - Phosphoribosylamine, 741, 742
 - 5-Phosphoribosylanthranilate, 721, 722
 - Phosphoribulose kinase, 596, 596f
 - Phosphorolysis, in glycogen metabolism, 617–621
 - Phosphorothioates, in DNA cleavage, 273–274, 274f
 - Phosphoryl group transfer, 432–434, 444
 - active carriers in, 438–442, 438f, 439f
 - ATP and, 434–435, 434f, 434t, 436–437, 437f
 - in glycolysis, 444, 444f
 - Phosphorylase. *See* Glycogen phosphorylase
 - Phosphorylase *a*, 622–623
 - Phosphorylase *b*, 622–623
 - Phosphorylase kinase, in glycogen metabolism, 623–624, 624f, 629
 - Phosphorylaspartate, 374, 374
 - Phosphorylation, 298–301
 - in amino acid synthesis, 724
 - ATP in, 298–301, 432–434, 436–437, 437f, 444
 - in chemotaxis, 1024, 1025f
 - in cholesterol regulation, 772
 - in citric acid cycle, 513–514
 - in enzyme regulation, 298–301
 - in fatty acid metabolism, 666–667, 666f
 - in gluconeogenesis, 483–484, 485
 - in glycogen metabolism, 617–618
 - in glycogen synthesis, 629–630
 - in glycolysis, 455–457, 456f, 457, 458
 - in immune response, 989–990, 989f
 - kinases in, 457
 - in metabolism, 432–434, 444
 - oxidative, 436–437, 525–561. *See also* Oxidative phosphorylation
 - of phosphorylase kinase, 623–624, 624f
 - phosphoryl-transfer potential and, 434–435, 434f, 434t
 - protein kinases in, 298–301
 - in purine synthesis, 741–743, 742, 742f
 - regulatory functions of, 300–301

- in signal transduction, 299t, 406–407, 407f, 408–409, 409f, 411–415, 413f, 417, 418
 substrate-level, 463–464, 507–508
 of sugars, 326–327
- Phosphorylation potential, 447
- Phosphorylcholine, antibody binding of, 985–986, 985f
- Phosphorylethanolamine, synthesis of, 763, **763**
- Phosphoryl-group-transfer potential, 434f, 434t
- Phosphoryl-transfer potential, 434–435
- Phosphoserine, **57**, 58, 714, **714**
- Phosphothreonine, 58
- Phosphotriesters, in DNA synthesis, 144
- Phosphotyrosine, 58
- Photoinduced charge separation, 569–572, 569f
- Photophosphorylation, cyclic, 580–581, 580f
- Photoreceptors, 966
 cones, 966, 969–970
 evolution of, 970, 970f
 rods, 966–967, 966f
- Photorespiration
 in C₄ pathway, 599–600
 in Calvin cycle, 593f, 594
- Photosynthesis, 565–586
 accessory pigments in, 581–584, 582f, 583f
 ATP synthase in, 578–579, 583, 583f
 in autotrophs, 590
 basic equation of, 565
 C₄ pathway in, 599–600, 600f
 carotenoids in, 582–583
 chlorophyll *a* in, 568–572, 568f, 569f, 582f, 583, **592**
 chlorophyll *b* in, **582**, 582f, 583
 in chloroplasts, 567–568, 567f
 components of, location of, 583–584, 583f
 cyclic photophosphorylation in, 580–581, 580f
 dark reactions of, 566, 580, 589, 590–601.
See also Calvin cycle
 coordination with light reactions, 599
 definition of, 565
 electron transfer in, 568–572, 569f, 571f
 energy conversion in, 566–567
 evolution of, 568, 584, 600
 herbicide inhibition of, 584, **584**
 light reactions of, 566–567, 566f, 572–584, 589
 coordination with dark reactions, 599
 in photosystem I, 567, 572, 572f, 574f, 575–577, 575f, 583, 583f
 in photosystem II, 567, 572–577, 572f–575f, 583, 583f
 stoichiometry of, 580–581
 yield of, 580–581
 light-harvesting complexes in, 583, 583f
 photoinduced charge separation in, 569–572, 569f
 proton-motive force in, 566, 566f, 578–579
- Q cycle in, 575, 575f
 reaction centers in, 569–572, 570f
 energy transfer to, 581–582, 582f
 resonance energy transfer in, 581–582, 582f
 in thylakoid membranes, 567–568, 567f, 574–575, 577–581, 583, 583f
 in tropical plants, 599–600
 vs. oxidative phosphorylation, 578, 579f
 yield in, 566b
 Z scheme of, 577, 577f
- Photosynthetic bacteria, 584, 584t
 reaction center of, 569–572, 570f
- Photosynthetic catastrophe, 567b
- Photosynthetic yield, 566b
- Photosystem I, 567, 572, 572f, 574f, 575–577, 575f
 location of, 583, 583f
- Photosystem II, 567, 572–577, 572f–575f
 location of, 583, 583f
- Phototrophs, 428
- Pigments
 accessory, in photosynthesis, 581–584, 582f, 583f
 visual, 969–970, 970f. *See also* Color vision
 in cones, 969–970
 in rods, 966–967
- Ping-pong reactions, 237
- Pinopsin, 970, 970f
- PIP₂ (phosphatidylinositol 4,5-trisphosphate), in signal transduction, 414, **414**
- PIP₃ (phosphatidylinositol 3,4,5-bisphosphate), in signal transduction, 414, **414**
- pK_a values, 15, A2
- PKU (phenylketonuria), 674, 697–698
- Planar bilayer membrane, 354, 354f
- Plants
 C₃, 599
 C₄, 600
 crassulacean acid metabolism in, 600–601, 600f
 genetically engineered, 166–167, 167f
 glyoxylate cycle in, 518–519, 519f
 lectins in, 339
 nitrogen fixation in, 706–710
 photosynthesis in. *See* Photosynthesis
 starch in, 597
 sucrose synthesis in, 597, 598f
 tropical, photosynthesis in, 599–600
- Plaque, atherosclerotic, 776, 777f
- Plaques, in genomic library screening, 153, 153f
- Plasma cells, 979
- Plasmid(s), 148
 in drug resistance, 1050
 pBR322, 149, 149f
 pUC18, 149f
 tumor-inducing, 166–167, 167f
- Plasmid vectors, 149–151, 149f, 150f
- Plasmin, 312
- Plasmodium falciparum*
 glycan-binding proteins of, 340
 mitochondrial genome of, 527
- Plastocyanin, 575, 584
- Plastoquinol, 573, **573**, 575
- Plastoquinone, 572–573, 573, **573**, 584
- Pleckstrin homology domain, 414, 419
- P-loop, 283–284, 284f
- P-loop(s), in G proteins, 405
- P-loop NTPases
 ABC proteins as, 378–380
 in G proteins, 405
 in microtubules, 1019, 1019f
 in motor proteins, 1008–1012, 1009f
- PLP. *See* Pyridoxal phosphate (PLP)
- Pluripotent stem cells, 944
- Point mutations, production of, 157
- Poisons
 mushroom, **865**, 865–866
 protein inhibition by, 910–911
- Polar head group, 351, 352
- Polarization, membrane, action potential and, 382
- Polyacrylamide gel electrophoresis, 71–73, 72f, 73f
- Polyampholytes, in isoelectric focusing, 73
- Polycistronic mRNA, 901
- Polyclonal antibodies, 86, 86f
- Polygalacturonase, 167
- Polylinkers, 150, 150f
- Polymerase chain reaction (PCR), 145–147, 145f–147f
 in ancient DNA amplification, 147, 188, 189f
 procedure for, 145–146, 145f
 quantitative, 161–162, 162f
 real-time, 161–162, 162f
 uses of, 146–148
- Polymerase switching, 835
- Polymorphisms, 147
- Polypeptide chains, 34–35, 34f, 35f, 36–38.
See also Protein(s)
 cleavage of, 82–83, 82f
 cross-linked, 35, 35f
 disulfide bonds of, 35, 35f
 formation of, 903–904, 904f. *See also* Translation
 side chains of, 34, 34f
 subunits of, 48, 48f
- Polypyrimidine tract, 873, 873f
- Polyribosomes, 906, 906f
- Polysaccharides, 328, 328f, 329f
 abbreviations for, 330b
 cellulose, 328–329
 glycogen, 328, 329f
 starch, 328, 329f
- Polysomes, 906, 906f
- Poly(A) tail, 871, 872
- Polyunsaturated fatty acids. *See also* Fatty acid(s)
 eicosanoids from, 664–665, **665**, 665f

- Pompe disease, 634t, 635, 635f
- Pores, nuclear, 365
- Porins, 47, 47f, 357, 357f
mitochondrial, 526–527
- Porphobilinogen, 728, **729**
- Porphobilinogen deaminase, 728–729
- Porphyrias, 730–731
- Porphyrins
disorders of, 730–731
synthesis of, 728–730, 729f
- Potassium ion channels, 364–393, 382.
See also Ion channels
inactivation of, 388–389, 389f
rate of transport in, 387
selectivity filter in, 385–386, 386f, 387f
sequence homologies of, 384, 384f, 386
specificity of, 385–387
structure of, 384–385, 388f
voltage-gated, 387–388, 388f
- Potassium ions, in Na⁺–K⁺ pump, 374, 377. *See also* Ion pumps
- Potential energy, 11. *See also* Energy
- Power stroke, in myosin, 1015
- pppA, 854, **854**
- pppG, 854, **854**
- Predisposition, to disease, 19–20
- Pregnenolone
corticosteroids from, 783
progesterone from, 783
structure of, **784**
synthesis of, 783
- Pre-mRNA, processing of, 870–872, 871f, 878–879
splicing in, 873–879, 875f–878f. *See also* Splicing
- Prephenate, 720, **721**
- Prepriming complex, 834, 834f
- Pre-rRNA, processing of
in bacteria, 863
in eukaryotes, 869–870, 870f
- Pressure, sensation of, 973
- Pre-tRNA, processing of
in bacteria, 871f
in eukaryotes, 870–872, 871f
in prokaryotes, 870
- Prevacid (lansoprazole), 1046, **1046**
- Pribnow box, 126f, 127
- Prilosec (omeprazole), 1046, **1046**
- Primary active transport, 371
- Primary messengers, 402
- Primary protein structure, 33–38. *See also* Amino acid sequences
- Primase, 823, 823f
- Primers
in DNA replication, 122, 145, 821
in polymerase chain reaction, 145
- Prions, 56–57, 56f
- Probes, DNA, 80, 142, 144–145, 151–153
generation of, 144–145, 151–153
solid-phase approach in, 144–145, 144f
for genomic library, 151–153, 152f
- Procaspases, 303
- Processivity
definition of, 832b
in DNA replication, 831–832
- Procollagen, 303
- Procollagenase, 303
- Proenzymes. *See* Zymogens
- Progestagens. *See also* Steroid hormones
synthesis of, 780, 780f
- Progesterone
aldosterone from, 783
cortisol from, 783, **784**
synthesis of, 783, **784**
- Programmed cell death
mitochondria in, 559
T cell, 1000, 1000f
zymogens in, 303
- Proinsulin, 303, 802
bacterial synthesis of, 155, 155f
- Prokaryotes, 3. *See also* Bacteria
- Proliferating cell nuclear antigen, 836
- Proline
hydroxyl groups of, 44, **57**, 57–58
structure of, 28, 29f
synthesis of, 714, 714f
- Proline racemase, inhibition of, 243, 243f
- Prolyl hydroxylase, 812–813
- Prolyl hydroxylase 2, in cancer, 515
- Promoters, 126–127, 126f, 852
bacterial, 852, 856–858, 857f
eukaryotic, 866–869, 866f
for RNA polymerase I, 866, 866f
for RNA polymerase II, 866–867, 866f, 867–868
for RNA polymerase III, 866, 866f
heat-shock, 858, 858f
nitrogen-starvation, 858, 858f
- Proofreading
evolution of, 895
in replication, 839–840, 839f
in transcription, 856
in translation, 895
- Proopiomelanocortin (POMC), 796
- PROP (6-*n*-propyl-2-thiouracil), **963**
- Propionyl CoA, **649**, 649–650, 693, **693**, 694
conversion to succinyl CoA, 649–650, 650f
- 6-*n*-Propyl-2-thiouracil (PROP), **963**
- Prostacyclins, 664–665, **665**, 665f
- Prostaglandin E₂, 665, **665**
- Prostaglandin H₂, 357–358, **358**, 358f, 665, 665f
- Prostaglandin H₂ synthase-1, 357–358, 358, 358f
- Prostaglandin inhibitors, 358, 665, 1040
aspirin as, 358, 665, 1040
- Prostaglandins, 664–665, **665**, 665f
- Prosthetic groups, 221
- Protease(s)
active sites of, 185–186, 185f, 257–258
convergent evolution of, **185**, 185–186
aspartyl, in peptide bond cleavage, **263**, 264, 264f
cysteine, in peptide bond cleavage, **263**, 263–264, 264f
metal ion, in peptide bond cleavage, **263**, 264, 264f
in peptide bond cleavage, 255–266. *See also* Peptide bonds, cleavage of
in carbohydrates, 337
serine, in peptide bond cleavage, 255–266
site-directed mutagenesis of, 262–263, 262f
specificity of, 260, 260f
- Protease inhibitors, 306–307
α₁-antitrypsin, 307
pancreatic trypsin inhibitor, 306
pharmaceutical, 264–266, **265**, 358, 665
development of, 1043, 1043f
resistance to, 1050
- Proteasomes, 677–678, 677f, 678f, 992. *See also* Amino acid degradation
eukaryotic, 677–678, 678f
evolution of, 677–678, 678f, 679
of *M. tuberculosis*, 679
prokaryotic, 678, 678f
- Protein(s), 2. *See also* Peptide(s)
acetylation of, 57
adaptor, 414
in signal transduction, 414, 417
aggregated, in neurological diseases, 56–57, 56f
allosteric, 289, 290–296. *See also* Allosteric enzymes
α helix of, 38–40, **39**, 39f, **40**, 40f
amino acids of. *See* Amino acid(s)
antibody-tagged, 88
β sheet of, 40–42, 40f–42f
carbohydrate units of, 57, 329–337. *See also* Glycoproteins
cleavage of, 49, 58, 82–83, 82f, 83f
coiled-coil, 43, 44f
covalent modification of, 57–58, 57f, 297–302, 298t. *See also* Phosphorylation
definition of, 34
degradation of, 673–700. *See also* Amino acid degradation
denatured, 49–50, 49f, 50f, 52, 52f
dietary, digestion and absorption of, 255–260, 303–307, 303t, 304f, 674, 674f. *See also* Amino acid degradation
evolution of, 133
experimental studies of. *See* Protein studies
fibrous, 43–45
flexibility of, 26–27, 26f
folding of, 18, 19f, 38, 48–49, 52–57
cooperative transition in, 52
cumulative selection in, 53
denaturation and, 49f, 50, 50f, 52, 52f
heat shock protein 70 in, **183**, 183–184
hydrophobicity and, 45–46, 46f, 47, 47f
intermediates in, 52–54, 53f
Levinthal's paradox in, 53
mistakes in, in neurological diseases, 56–57
nucleation-condensation model of, 53

- prediction of, 54
 into regular structures, 38–45
 steps in, 53–54, 53f
 function of, structural correlates of,
 25–26, 26f, 57–59
 functional groups of, 26
 genes encoding, 19
 genetically engineered, 157
 glycan-binding, 337–338
 glycosylation of, 329–337
 congenital disorders of, 336
 sites of, 333–334, 337
 half-life of, 675, 676t
 hemoglobin as model of, 195–216. *See also* Hemoglobin
 hydroxylation of, 30, 30f, 57–58
 identification of, 65–66
 immunological methods for, 86
 intrinsically unstructured, 54–55
 as linear polymers, 33–35
 lysosomal, 911
 mass of, 34
 measurement of
 electrophoresis in, 74, 74f
 mass spectrometry in, 91–95, 92f,
 93f, 95f
 membrane. *See* Membrane proteins
 membrane-spanning, 911
 metabolism of, 437f
 metamorphic, 55, 55f
 molecular models of, 21–22, 23f, 60–62,
 61f, 62f
 molecular weight of, 34
 multiple conformations of, 54–55, 55f
 Ω loops in, 42, 43f
 peptide bonds of, 33, 33f, 36–37, 36f, 37f
 polypeptide chains of, 33–35, 34f, 35f,
 36–38
 post-translational modification of,
 57–59, 58f
 properties of, 25–26
 random-coil conformation of, 49, 49f
 refolding of, 50, 50f
 regulation of
 covalent modification in, 298t
 phosphorylation in, 298–301. *See also*
 Phosphorylation
 reverse turns in, 42, 43f
 ribosomal. *See also* Ribosome(s)
 in translation, 900
 rigidity of, 26, 26f
 secretory, 911
 signal sequences in, 79
 similarity among, 2, 2f
 sorting of, in Golgi complex, 334, 334f
 structure of, 2f, 3
 amino acid sequences and, 18–19, 19f,
 25, 35–36, 49–59
 functional correlates of, 25–26, 26f,
 57–59
 models of, 21–22, 23f, 60–62, 61f, 62f
 primary, 25, 33–38. *See also* Amino acid
 sequences
 quaternary, 26, 48, 48f
 secondary, 25, 38–45, 47
 supersecondary, 47, 47f
 tertiary, 45–47, 46f, 47f, 183–184.
See also Protein(s), folding of
 subunits of, 48, 48f
 synthesis of. *See also* Translation
 initiation of, 130
 mRNA in, 123–124, 130, 130f
 synthetic, 96–98, 96f, 97f, 157
 translocation of, 911–914
 unfolding of, 52, 52f
 Protein blots, 89, 142
 Protein Data Bank, 60, 104
 Protein domains, 47, 47f
 exon encoding of, 133, 133f
 Protein kinase(s), 298
 calmodulin-dependent, 410–411
 cyclin-dependent, 836
 dedicated, 299
 in enzyme regulation, 298–301
 multifunctional, 299
 in phosphorylation, 298–301
 regulation of, cAMP in, 301, 301f
 serine, 298–299, 299f, 299t
 in signal transduction, 299t, 406–407,
 408, 409, 409f, 419
 specificity of, 299
 threonine, 298–299, 299f, 299t
 tyrosine, 298–299, 299f
 in cancer, 420
 Protein kinase A
 pseudosubstrate binding to, 302, 302f
 regulation of, 301, 301f
 in signal transduction, 406–407, 419
 in glycogen metabolism, 624, 625f, 626
 structure of, 302, 302f
 Protein kinase B (Akt), in signal
 transduction, 414, 799, 799f
 Protein kinase C, in signal transduction,
 409, 409f
 Protein kinase inhibitors, for cancer, 421
 Protein phosphatase 1 (PP1), in glycogen
 metabolism, 626–627, 631–634, 631f
 Protein phosphatases, 300
 Protein purification, 65, 66–79
 affinity chromatography in, 70–71, 70f
 assays in, 67
 autoradiography in, 73
 dialysis in, 69, 69f
 differential centrifugation in, 67–68, 68f
 fractionation in, 67–68, 68f
 gel electrophoresis in, 71–73, 72f, 73f
 gel-filtration chromatography in, 69, 69f
 gradient centrifugation in, 77–78, 77f
 high-pressure liquid chromatography in,
 71, 71f
 homogenization in, 67, 75t
 ion-exchange chromatography in, 69–70,
 70f, 80–82, 80f
 isoelectric focusing in, 73, 73f
 with SDS-PAGE, 74, 74f
 monoclonal antibodies in, 87–88
 protein concentration in, 67
 quantitative analysis of, 75–76, 75f, 75t
 recombinant DNA technology in, 78–79
 salting out in, 68, 75t
 SDS-PAGE in, 74, 74f, 75, 75f
 with isoelectric focusing, 74, 74f
 sedimentation-equilibrium technique
 in, 78
 two-dimensional electrophoresis in,
 74, 74f
 Protein regulation
 covalent modification in, 298t
 phosphorylation in, 298–301. *See also*
 Phosphorylation
 Protein sequencing. *See* Amino acid
 sequences, determination of
 Protein sorting, 911–914
 Protein studies
 amino acid sequencing in, 79–84.
See also Amino acid sequences,
 determination of
 electron-density maps in, 99–100, 100f
 electrospray ionization in, 91–92
 enzyme-linked immunosorbent assay in,
 88–89, 89f
 fluorescence microscopy in, 90–91, 90f
 genomic analysis in, 84
 immunoelectron microscopy in, 91, 91f
 immunologic techniques in, 84–91. *See also*
 Monoclonal antibodies
 mass spectrometry in, 91–95, 92f, 93f, 95f
 nuclear magnetic resonance spectroscopy
 in, 101–104, 101f–103f
 nuclear Overhauser enhancement
 spectroscopy in, 101–104, 102f, 103f
 proteomic analysis in, 84, 94–95, 95f
 purification methods for, 65, 66–79. *See also*
 Protein purification
 recombinant DNA technology in. *See*
 Recombinant DNA technology
 synthetic peptides in, 96–98, 96f, 97f
 time of flight analysis in, 92, 92f
 western blotting in, 89, 89f, 142
 X-ray crystallography in, 98–100, 98f–100f
 Protein targeting, 334, 334f, 911–914
 Protein transport, 911–914. *See also*
 Membrane transport
 Protein turnover, 255, 673. *See also* Amino
 acid degradation; Amino acid synthesis
 Protein tyrosine kinases, 298–299, 299f, 412
 in cancer, 420
 receptor, 412
 Proteins, synthesis of, DNA technology in,
 78–79
 Proteoglycans, 329–330, 331f
 Proteolytic enzymes, 220–221, 302–313
 activation of, 302–313
 in blood clotting, 307–312
 chymotrypsinogen as, 303–305
 in digestion, 303–307
 functions of, 303
 inhibitors of, 306–307
 in starvation, 809, 810

- Proteomes, definition of, 66
- Prothrombin, 309f, 310, 310f
calcium binding by, 310–311
- Proton gradients, 437
free energy from, 559–560, 560f
in oxidative phosphorylation, 530–531, 543–550, 559–560, 560f
in photosynthesis, 571–572, 578–581
- Proton pumps
in oxidative phosphorylation, 525
in respiratory chain, 525
- Proton shuttle, in carbon dioxide hydration, 269–270, 270f
- Proton transport, by flagella, 1023, 1024f
- Proton-motive force, 525
in oxidative phosphorylation, 525, 544–545, 544f, 569
in photosynthesis, 566, 566f, 578–579
- Protons, chemical, 540f
- Proto-oncogenes, 420
- Protoplasts, 167
- Protoporphyrin, **196**, 196–197
- Protoporphyrin IX, **729**, 730
- Provitamin D₃, 785, **785**
- Proximal histidine, 197
- PRPP. *See* 5-Phosphoribosyl-1-pyrophosphate (PRPP)
- Pseudo-first-order reactions, 230
- Pseudogenes, 159
- Pseudosubstrate sequence, 302
- Pseudouridylate, 863, **863**
- Psi (Ψ) angle of rotation, 37–38, 37f, 38f
- Psoralen, 876
- PTEN, 799
- P-type ATPases, 374
evolution of, 378–379
functions of, 378
in membrane transport, 374–381.
See also Ion pumps
types of, 378
- pUC18 plasmid, 150f
- Puffer fish
genome of, 161, 161f
tetrodotoxin of, 384, **384**
- Pumps. *See* Ion pumps; Proton pumps
- pur* repressor, 927, 927f
- Purine nucleotides, **111**, 111–112
degradation of, 752–755, 753f
derivatives of, 111, **111**
synthesis of, 726, 740–745, 740f, 751. *See also* Nucleotide(s), synthesis of
phosphorylation in, 741–743, 742f
steps in, 740–743, 741t, 742f
- Purinosomes, 744, 744f
- Puromycin, 909t, 910, **910**
- Pyranose, 322–325, 323f
- Pyridoxal phosphate (PLP), 674
in amino acid degradation, **657**, **681**, 681–684
in amino acid synthesis, 712f, 713
in glycogen metabolism, 618–619, 618f
- Pyridoxal phosphate enzymes
in amino acid degradation, 681–684, 683f
in amino acid synthesis, 712f, 713
catalytic activity of, 683–684, 683f
- Pyridoxal phosphate-dependent transaminases, 712–713
- Pyridoxamine phosphate, 682, **682**, 712
- Pyridoxine (vitamin B₆), **441**, 441t, 681
- Pyrimidine(s), 111, **111**
derivatives of, 111, **111**
synthesis of, 726
aspartate transcarbamoylase in, 290–296, 738
- Pyrimidine nucleotides, 111, **111**
recycling of, 740
synthesis of, 736–740, 736f, 751. *See also* Nucleotide(s), synthesis of
- Pyrimidine phosphoribosyltransferase, 739
- Pyrophosphate, hydrolysis of, 627–628, 645
in fatty acid metabolism, 645
- 5-Pyrophosphomevalonate, **768**
- Pyrrrole-2-carboxylic acid, 243, **243**
- Δ^1 -Pyrroline 5-carboxylate, in proline synthesis, 714
- Pyruvate, **236**
in amino acid degradation, 684–685, 685f, 691
in amino acid synthesis, 712
in citric acid cycle, 500–501
conversion to acetyl coenzyme A, 500–501, 500f, 501f
in Cori cycle, 490, 490f, 685
in ethanol formation, 466–467, 467f
formation of, 691, 691f
in gluconeogenesis, 453, 479–485
in glucose–alanine cycle, 685, 685f
in glycolysis, 453, 464–466, 464f–466f
metabolic fates of, 466–468, 466f
in nitrogen transport, 684–685, 685f
oxaloacetate synthesis from, 443–444, 443f
- Pyruvate carboxylase
in citric acid cycle, 516
in gluconeogenesis, 481
- Pyruvate carrier, 554, 554f
- Pyruvate decarboxylase, 466
- Pyruvate dehydrogenase complex
in citric acid cycle, 499–503, 499f, 499t, 502f, 503f
components of, 499, 499t
phosphorylation of, 513–514
reactions of, 502–503, 503f
regulation of, 513–514
structure of, 502, 502f
- Pyruvate dehydrogenase kinase, in cancer, 515
- Pyruvate kinase, in glycolysis, 465
in liver, 476–477, 476f
in muscle, 474
- Pyruvate-P_i dikinase, in C₄ pathway, 599
- Q (coenzyme Q), 531, 532–533, 533f
in fatty acid metabolism, 646
- Q cycle, 575, 575f
in oxidative phosphorylation, 536–537
in photosynthesis, 575
- Q pool
in oxidative phosphorylation, 533
in photosynthesis, 571f, 572
- Q_A, 571–572, 571f, 573
- Q_B, 571, 571f, 573
- Q-cytochrome *c* oxidoreductase (Complex III), 531, 532f, 532t, 535–536, 536f
- QH₂, 571–572
- Quantitative polymerase chain reaction, 161–162, 162f
- Quaternary protein structure, 26, 48, 48f
- Quinine, **962**
taste of, 962
- Quinones
in oxidative phosphorylation, 531, 533, 533f
in photosynthesis, 570, 571
- Quinonoid dihydrobiopterin, 695, **695**
- Quorum sensing, 930–931, 930f
biofilms and, 930–931
- R* (metarhodopsin II), 968, 968f
- R groups. *See* Amino acid side chains
- R state, of hemoglobin, 202–204, 203f
- Radiation, mutagenicity of, 839
- Raloxifene, 948, **948**
- Ramachandran diagrams
for angles of rotation, 37, 38f
for helices, 39–40, 40f
- Ramachandran, Gopalasamudram, 37
- Random-coil conformation, 49, 50f
- Ranitidine (Zantac), 1045, **1045**
- Ras
farnesylation of, 298t
in signal transduction, 417–418, 418f
- Rate constant (k), 230
- Rate, reaction. *See* Reaction rates
- RBP4, 796
- Reaction(s)
activation energy for, 222, 226
anabolic, 428–429
anaplerotic, 516–517
biomolecular, 230
bisubstrate, 236
catabolic, 428, 435–438
electron carriers for, 438–439
catalysis of. *See* Catalysis; Enzyme(s)
chemical modification, 256
Cleland notation for, 236, 237
coupled, thermodynamics of, 429–430, 431–433
double-displacement (ping-pong), 237
electrocyclic, 720
endergonic, 222
enzyme-catalyzed. *See* Catalysis; Enzyme(s)
exergonic, 222
first-order, 229
free energy change of, 12, 222–225
group-transfer, 436–437, 443t, 444

- interconnected, 428–430, 428f
 ligation, 443–444
 lyase-catalyzed, 445
 metabolic, 428–430. *See also* Metabolism
 multiple-substrate, 235–237
 oxidation-reduction, 443, 443t
 free energy change in, 530
 in metabolism, 433t, 443
 reduction potential of, 528–530, 529t
 second-order, 230
 sequential, 236–237
 thermodynamics of, 222–225
 transition state in, enzymes and, 225–226, 225f, 227–228
- Reaction centers, in photosynthesis, 569–572, 570f, 582, 582f
 energy transfer to, 581–582, 582f
- Reaction equilibrium, enzymes and, 224–225
- Reaction rates, 229–237. *See also* Kinetics
 catalytic acceleration of, 220, 220t, 225–229, 226f
 definition of, 229
 in enzyme-catalyzed reactions, 229–237.
 See also Enzyme kinetics
 in first-order reactions, 229–230
 maximal, calculation of, 233
 Michaelis constant (K_M) for, 231–235
 in pseudo-first-order reactions, 230
 in second-order reactions, 230
- Reactive oxygen species (ROS),
 541–542, 541t
 cytochrome P450 and, 782–783, 782f
 glucose 6-phosphate and, 610
 mutagenicity of, 838
- Reactive substrate analogs, 241–242
- Reading frame, 130
- Reagents, group-specific, 241
- Real-time polymerase chain reaction,
 161–162, 162f
- RecA*, 845
- Receptor(s). *See also specific types*
 ligand binding to, 926, 947
 in signal transduction, 402
 G-protein-coupled, 404–406
 insulin, 412–415
 serpentine, 404
 7TM, 404–406, 404t
- Receptor tyrosine kinases, in signal
 transduction, 412
 in cancer, 421
- Reclinomonas americana*, genome of, 528
- Recognition helix, 923
- Recognition sites (sequences), 141, 141f,
 272, 275–277
 in cognate vs. noncognate DNA,
 275–277, 276f
 distortion of, 276–277, 276f
 inverted repeats as, 275
 structure of, 275, 275f
- Recombinant DNA
 production of, 154–155, 154f
 transfer of, by microinjection, 163, 163f
 vectors for, 163–164. *See also* Vectors
- Recombinant DNA technology, 139–169
 in amino acid sequencing, 84
 autoradiography in, 73, 143
 bacterial artificial chromosomes in, 151
 bombardment-mediated transformation
 in, 167
 cloning in, 149–151, 149f–151f
 cohesive-end method in, 148–149, 149f
 complementary DNA in, 154–155,
 154f, 162f
 designer genes in, 157
 for disease-causing mutations, 157
 DNA microarrays in, 162–163, 162f
 DNA microinjection in, 163, 163f
 DNA probes in, 80, 142, 144–145,
 151–153
 DNA sequencing in, 143–144, 143f
 DNA synthesis in, 144–145, 148–149
 electroporation in, 167, 167f
 expression vectors in, 154–155
 fluorescence detection in, 143–144, 143f
 gel electrophoresis in, 141–142, 142f
 gene guns in, 167
 gene manipulation in, 161–168
 gene-expression analysis in, 161–162,
 162f, 163–164
 genomic libraries in, 151–153,
 152f, 153f
 lambda phage in, 150–151, 150f, 151f
 medical applications of, 167–168
 mutations in, 156–157
 overview of, 139–141
 in plants, 166–167, 167f
 plasmid vectors in, 149–151, 149f, 150f
 polymerase chain reaction in, 145–147,
 145f–147f, 188
 in protein purification, 78–79
 restriction-enzyme analysis in, 141–142
 solid-phase approach in, 144–145, 144f
 transgenic animals in, 164, 164f
 vectors in, 149–151, 149f–151f, 154–155
 yeast artificial chromosomes in,
 151, 151f
- Recombinases, 845–846
- Recombination
 in antibodies, 987–991, 988f
 DNA. *See* DNA recombination
 homologous, 970b
 in color blindness, 970
 in gene knockout, 164–165
- Recombination signal sequences
 (RSSs), 988
- Recombination synapse, 846
- Red blood cells. *See also* Hemoglobin
 2,3-bisphosphoglycerate in, oxygen
 affinity of hemoglobin and,
 204–205
 carbohydrates in, 335
 disorders of, 209–211
 Heinz bodies in, 610, 610f
 life span of, 730
 sickled, 209–210, 209f
- Red photoreceptors, 969–970, 969f, 970f
- Redox couples, 529
 redox potential of, 529–530, 529t
- Redox potential. *See* Reduction potential
- Redox reactions. *See* Oxidation–reduction
 reactions
- Reducing sugars, 325
- Reductase, in nitrogenase complex,
 708–709
- Reductase mRNA, in cholesterol regulation,
 770, 771
- Reduction potential
 measurement of, 528f, 529–530
 in oxidative phosphorylation, 528–531
- Reed, Randall, 959
- Regulatory domains. *See* Domains
- Regulatory sites, 291
- Rejection, in transplantation, 998
- Relaxed DNA, 117, 117f
- Relay helix, 1012, 1012f
- Release factors (Rfs), 130, 906, 907f
- Renal function. *See* Kidney
- Renal gluconeogenesis, 481
- Repeating motifs, 79
 sequence homology of, 184, 185f
- Replication. *See* DNA replication
- Replication factor C, 836
- Replication fork, 823, 823f, 832–833, 833f
- Replication protein A, 835
- Replicon, 835
- Repressors, 924–925
 corepressors, 927
 lac, 922f, 923, 925–928, 926f, 927
 λ , 928–929, 928f, 929f
 pur, 927, 927f
- Resistin, 796
- Resonance structures, 7
 of ATP, 433
 improbable, 433f
 of orthophosphate, 433
- Respiration, cellular, 498, 499f,
 593f, 594
 definition of, 526b
 in photosynthesis, 593f, 594
 regulation of, 554–560
- Respiratory chain, 525, 531–543
 coenzyme Q in, 531
 components of, 531–532, 532f, 533f
 cytochrome *c* oxidase (Complex IV) in,
 531, 532f, 532t, 535–536
 electron carriers in, 438–439,
 438f, 439f
 linkage to ATP synthase, 544–545,
 544f, 545f
 NADH-Q oxidoreductase (Complex I)
 in, 531–535, 532f, 532t
 Q cycle in, 536–537, 537f
 Q-cytochrome *c* oxidoreductase
 (Complex III) in, 531, 532f, 532t,
 535–536, 536f
 succinate-Q reductase (Complex II) in,
 531, 532f, 532t, 535
- Respiratory control, 556
- Respiratory distress syndrome, 765–766

- Restriction enzymes (endonucleases),
141–142, 271–279
binding affinity of, 275–277
in DNA cleavage, 141–142, 271–279. *See also* Restriction fragment(s)
in *E. coli*, 272–279, 274f–277f
evolution of, 278–279
recognition sites for, 141, 141f, 271–272, 275–277. *See also* Recognition sites (sequences)
in restriction-modification systems, 272
specificity of, 141, 141f, 272, 275–277, 275f
type II, 278–279, 278f
- Restriction fragment(s)
separation of, gel electrophoresis in, 141–142
in Southern blotting, 142
- Restriction fragment length polymorphisms, 147
- Restriction-modification systems, 277
- 11-*cis*-Retinal, 967, **967**, 968f
all-*trans*-Retinal, 967, **968**
- Retinitis pigmentosa, 877–878
- Retinol (vitamin A), 442, **442**, 442t
deficiency of, alcohol-related, 812
- Retroviruses, 122–123, 123f, 999–1000
as vectors, 163
- Reverse cholesterol transport, 778–779
- Reverse transcriptase, 123, 123f
in complementary DNA production, 154–155
- Reverse turns, 42, 43f
amino acid residues in, 50–51, 51t
- Reversible covalent modification, 446, 725–726, 725f
- RFs (release factors), 130, 906, 907f
- Rhizobium*, in nitrogen fixation, 706–707
- Rho, 127
in transcription termination, 860–861
- Rhodospseudomonas viridis*, photosynthetic reaction center in, 569–570, 570f, 584
- Rhodopsin, 404, 966–968
absorption spectrum of, 967f
cone photoreceptors and, 969–970, 970f
structure of, 404, 404f
- Rhodopsin kinase, 968
- Ribbon diagrams, 62, 62f
- Riboflavin (vitamin B₂), **441**, 441t
- Ribonuclease
amino acid sequences in, 49–50, 49f
reduction and denaturation of, 49–50, 49f, 50f
scrambled, 50, 50f
sequence comparison for, 173, **174**
structure of, 49–50, 49f, 50f
in transcription, 863
- Ribonuclease P, 863
- Ribonuclease III, 863
- Ribonucleic acid. *See* RNA
- Ribonucleoproteins
small nuclear, 852, 875–876, 876t
small nucleolar, 870, 875–877
- Ribonucleotide reductase, **718**, 745–750, 745f, **746**, 752, 752f
- Ribose, 110, **110**, 111, 321, 322, 322f
ring form of, 323, 323f
- Ribose 1-phosphate, 752
- Ribose 5-phosphate, **596**
in Calvin cycle, 595f, 596, 596f
in pentose phosphate pathway, 601, 602, 602f, 603f, 607–609
- Ribosomal RNA. *See* rRNA (ribosomal RNA)
- Ribosome(s), 130, 897–907
in codon–anticodon interactions, 902
definition of, 887
endoplasmic reticulum-bound, 911–914
in eukaryotes vs. bacteria, 907
evolution of, 900
functions of, 900
initiation sites in, 902, 903f
polyribosomal, 906, 906f
as ribozymes, 887
structure of, 887f, 897–898, 898f
subunits of, 897–898, 898f
formation of, 902
tRNA binding by
mechanism of, 900f, 903–904
sites of, 900, 900f, 902–904
- Ribosome release factor, 906, 907f
- Riboswitches, 860, 860f
- Ribosylation, 298t
- Ribothymidylate, 863, **863**
- Ribozymes, 879, 887
- Ribulose 1,5-bisphosphate carboxylase/oxygenase. *See* Rubisco
- Ribulose 1,5-bisphosphate, in Calvin cycle, 591–597, **592**, 595f, 596, **596**, 596f
- Ribulose 5-phosphate
in Calvin cycle, 596, **596**
in pentose phosphate pathway, 602, 602f
- Ricin, 911
- Ricketts, 786
- Rickettsia prowazekii*, genome of, 527–528
- Rieske center, 536
- Rifampicin, 861–862, **862**
- Rise, in α helix, 39
- RNA, 111
ATP-binding region of, 190–191, 191f
backbone of, 110, 110f
catalytic activity of, 879–881, 900
evolution of, molecular studies of, 188–191, 190f
in gene expression, 123–128
messenger. *See* mRNA
micro, 124
nucleosides in, 111
post-transcriptional processing of
in bacteria, 863
in eukaryotes, 869–879
pre-mRNA, 870–872, 871f, 878–879
splicing in, 873–879, 875f–878f
pre-rRNA, 869–870, 870f
in bacteria, 863
in eukaryotes, 869–870, 870f
- pre-tRNA
in bacteria, 870, 871f
in eukaryotes, 870–872, 871f
- ribosomal. *See* rRNA
- self-splicing in, 879–881, 880f–882f
sequence homologies of, 186–187, 187f
small interfering, 124
small nuclear, 124, 875–876
in splicing, 875–876, 876t
splicing of, 132–133, 132f, 851–852. *See also* Splicing
stem-loop motif in, 117f
structure of, **110**, 111–112, 117–118, 117f, 186–187, 187f
sugars in, 110f, 111
synthesis of, 124–127, 125f, 126f, 851–882. *See also* Transcription
transcriptional modification of, 127, 127f
transfer. *See* tRNA
types of, 123–124
- RNA blots, 142, 142f
- RNA editing, 852, 872–873, 873f
- RNA interference, 165–166, 167f
- RNA polymerase(s), 124–127, 125f, 852, **852**, 853–858
ADP ribosylation of, 298t
backtracking and, 856, 856f
bacterial, 853–858
active site of, 853, 854f
promoter recognition by, 856–857
structure of, 852, **852**, 853, 853t
subunits of, 853, 853t, 856–858
catalytic action of, 853–858
in DNA replication, 823, 823f
eukaryotic, **852**, 864
promoter elements in, 866–869, 866f
in proofreading, 856
RNA-directed, 122
structure of, **852**, 853
- RNA polymerase holoenzyme complex, **857**, 857–858, 857f
- RNA polymerase I, 865, 865t, 866
rRNA processing by, 869–870, 870f
- RNA polymerase II, 865, 865t, 866–867, 943
bromodomains and, 949–950, 950f
in transcription initiation, 950f
- RNA polymerase III, 865, 865t, 866
- RNA processing, 132–133. *See also* Transcription
in bacteria, 863
in eukaryotes, 869–879
of pre-rRNA, 869–870, 870f
RNA polymerase I in, 869–870, 870f
of tRNA, 870, 871f
in prokaryotes, of tRNA, 870
- RNA splicing. *See* Splicing
- RNA viruses, 122–123, 123f
- RNA world, 447, 881
- RNA-directed RNA polymerase, 122
- RNA-inducing silencing complex (RISC), 166
- RNase P, 881
- Roberts, Richard, 131

- Rods, 966–967, 966f
- Rofecoxib (Vioxx), **1044**, 1044–1045, 1049
- Rossmann fold, 469, 469f, 509, 509f
- Rossmann, Michael, 469
- Rotation, flagellar, 1022–1025
- Rotational catalysis, in ATP synthesis, 547–550, 547f–549f
- Rotenone, 558
- Rough endoplasmic reticulum, 911. *See also* Endoplasmic reticulum
- Roundup, 719–720
- Rous sarcoma virus, 420
- rRNA (ribosomal RNA), 123t, 124. *See also* RNA
 See also RNA
 in base-pairing, 892
 bases in, 863
 folding of, 898, 898f
 functions of, 124, 900
 16S, in translation, 892, 901
 transcription and processing of, 863, 869–870, 870f
 transcription of, 863
 in translation, 892, 898–900, 901, 903–904
- RsrI endonuclease, 278
- RSS (recombination signal sequence), 988
- Rubisco, **591**, 591–597
 evolution of, 600
 light activation of, 598
- Rubisco activase, 592
- Saccharomyces cerevisiae*, genome of, 158
- Sakmann, Bert, 383
- Salmonella* test, for mutagens, 843–844
- Salt bridges, oxygen release from hemoglobin and, 206–207, 207, 207f
- Salting out, 68, 75, 75t
- Salty taste, 962, 965
- Salvage pathways, 740
 purine, 744–745
 pyrimidine, 736, 736f
- Sandwich ELISA, 89, 89f
- Sanger dideoxy method, 143–144, 143f
- Sanger, Frederick, 35, 143, 158
- Sarcomere, 1016–1017, 1016f, 1017f
- Sarcoplasmic reticulum Ca^{2+} ATPase (SERCA), 374
- SARS, drug therapy for, 1046–1047, 1047f
- Satiation signals, 795–797, 796f
- Saturated fatty acids. *See* Fatty acid(s)
- SCAP (SREBP cleavage activating protein), 770–771, 771f
- Schiff bases, 681–682, **709**
 in amino acid degradation, 681–682, 709
 in amino acid synthesis, 709
 in aminoacrylate, 722, **722**
 in glycogen phosphorylation, 619, 619f
 in retinal, 967–968, 968f
 in transaldolase reaction, 605–606, 606f
 in transamination, 618–682
- Scrapie, 56
- Screw sense, of helix, 39, 40f
- Scurvy, 57, 812–813
- SDS (sodium dodecyl sulfate), in gel electrophoresis, 73, 78
- SDS-PAGE, 74, 74f, 75–76, 75f
 with isoelectric focusing, 74, 74f
- SDS–polyacrylamide gel electrophoresis, of membrane proteins, 355, 355f
- Second Law of Thermodynamics, 11–12, 792. *See also* Thermodynamics
- Second messengers, 402–403, 403f, 409–411, 409f, 419
- Secondary active transport, 371
- Secondary protein structures, 38–45, 50–52, 51t
 alternative conformations of, 51–52, 51f
 prediction of, 51
- Secondary transporters, 381, 381f
- Second-order reactions, 230
 rate of, 230
- Secretory proteins, 911
- Sedimentation coefficients, 76, 76t, 77f
- Sedimentation-equilibrium technique, 78
- Sedimentation-velocity technique, 78
- Sedoheptulose 1,7-bisphosphate, in Calvin cycle, **595**
- Sedoheptulose 7-phosphate, **595**
 in Calvin cycle, 595f, 596f
 in pentose phosphate pathway, 602, 602f, 603, 603f
- Segmental flexibility, 982, 982f
- Seizures, ketogenic diet for, 656
- Selectins, 339
- Selective estrogen receptor modulators (SERMs), 948
- Selectivity filters, 385–386, 386f, 387f
- Selenolate, 727, 727f
- Self-antigens, immune response to, 1001
- Self-splicing, 879–881, 880f–882f. *See also* Splicing
- Self-tolerance, 1001
- Semiconservative replication, 118–120, 120f
- Sense strand, 845, 854
- Sensory systems, 957–975
 hearing, 971–973
 overview of, 957–958
 smell, 958–962
 taste, 962–966
 touch, 973–974
 vision, 966–971
 yet-to-be-studied, 974
- Sequence alignment, 175–181, 176f–182f
- Sequence homologies. *See also* Evolution
 analysis of, 175–181, 176f–182f
 of cytochrome *c*, 543, 543f
 evolutionary trees and, 187–188, 187f
 of hemoglobin and myoglobin, 175–181, 176f–182f, 199
 of histones, 940–941, 940f
 identification of
 databases for, 181, 182f
 sequence alignment in, 175–181, 176f–182f
 shuffling in, 177–178, 177f
 statistical analysis in, 175–177
 substitution matrices in, 178–181
 of ion channels, 384, 384f, 386
 repeated motifs and, 184, **184**
 RNA secondary structures and, 186–187, 187f
 three-dimensional structure and, 183–184
 of tubulin, 1019
 of urea cycle enzymes, 688
- Sequence specifies conformation, 50
- Sequence template, 184
- Sequential model
 of hemoglobin oxygen binding, 202–203, 203f, 216
 of substrate binding, 294
- Sequential reactions, 236–237
- SERCA, 375–377
- SERCA (sarcoplasmic reticulum Ca^{2+} ATPase), 374
- Serine
 in catalytic triads, 258–260. *See also* Catalytic triads
 in chymotrypsin, 255–256, 256f
 in cysteine synthesis, 714–715, 719
 from glycine, 692
 in glycine synthesis, 714–715
 in glycoproteins, 330
 pyruvate formation from, 691, 691f
 in sphingolipid synthesis, 764, **764**
 sphingosine from, 726, 726f
 structure of, 30, 30f
 synthesis of, 714–715, 714f, 716, 723
- Serine dehydratase, in amino acid degradation, 684, 691
- Serine hydroxymethyltransferase, 715
- Serine kinases, 298–299, 299f, 299t
- Serine proteases
 active sites on, convergent evolution of, **185**, 185–186
 catalytic strategies of, 253, 255–256
- SERMs (selective estrogen receptor modulators), 948
- Serotonin, synthesis of, 726f, 727
- Serpentine receptors, 404
- Serum albumin, in drug distribution, 1003f, 1033
- 7TM (seven-transmembrane-helix receptors), 404–406, 404f, 404t, **408**, 408–409
 for drugs, 404, 1045
 in olfaction, 959
 in phosphoinositide cascade, 408–409
 in taste, 963–965
 of bitterness, 962, 963–964
 of sweetness, 964–965
 in vision, 967–969, 968f, 969
- 70S initiation complex, 902, 903f
- 70S subunit, of ribosome, 897–898, 898f
 formation of, 902, 903f
- Severe acute respiratory syndrome (SARS), drug therapy for, 1046–1047, 1047f

- Severe combined immunodeficiency (SCID), 753
 gene therapy for, 167–168
- Sex hormones. *See also* Hormone(s)
 regulation of, 946
 synthesis of, 780, 780f, 784–785, 784f
- SH2 domain, in signal transduction, 414, 417, 419, **420**
- SH3 domain, in signal transduction, 417, **420**
- Shaker channel, 388, 389f
shaker gene, 384
- Sharp, Philip, 131
- Shemin, David, 728, 728b
- Shikimate 3-phosphate, **720**
- Shikimate, in amino acid synthesis, 719, 720f
- Shine–Dalgarno sequences, 130, 901
- Short interspersed elements (SINES), 160
- Sialic acid, influenza virus and, 339, 340f
- Sialidase, 339, 340f
- Sickle-cell anemia, 209–210, 209f, 210f
- Side chains
 amino acid. *See* Amino acid side chains
 polypeptide, 34, 34f
- Side effects, 1031
 genetic variations in, 1047–1048
- σ subunit, of RNA polymerase, 853t, 857–858, 868
- Sigmoid binding curve, 200, 294–295, 295f
- Sigmoidal kinetics, enzymatic, 200, 291, 291f, 294, 295f
- Signal peptidase, 912
- Signal sequences, 79
 nuclear localization signal, 79
 in protein targeting, 912, 912f
- Signal transduction, 401–423
 abnormalities in
 in cancer, 420–421
 in cholera, 421–422
 in whooping cough, 422
 adaptor proteins in, 414, 417
 β -adrenergic receptor in, 404–405, 404f
 calcium in, 409–411, 409f–411f
 calmodulin in, 410–411, 411f
 in caloric homeostasis, 794–797, 795f–797f, 795t
 cAMP in, 406–407
 in chemotaxis, 1024, 1025f
 cross talk in, 403
 cytokines in, 998
 definition of, 401
 epidermal growth factor in, 402f, 415–418, 416f–418f
 epinephrine in, 402–410, 402f, 406f
 evolution of, 419
 G proteins in, 417–418, 418t. *See also* G protein(s)
 gap junctions in, 393
 in gene expression/regulation, 929–930
 GTPases in, 298, 298t, 407–408
 in hearing, 927f, 972
 hormone–receptor complexes in, 405–406
 in immune response, 989–990, 998
 insulin in, 402f, 411–415, 798–800, 799f
 ligands in, 402
 molecular circuits in, 402–403
 nitric oxide in, 728
 in olfaction, 959–960, 960f
 overview of, 401–402, 419
 phosphoinositide cascade in, 408–409, 409f
 phosphorylation in, 298–299, 299t, 406–407, 408–409, 409f, 411–415, 417, 419
 primary messengers in, 402
 principles of, 402f
 protein kinase A in, 406–407, 419
 protein kinase C in, 408, 409
 protein kinases in, 298–299, 299t, 419
 in protein sorting, 911–914
 Ras in, 417–418, 418f
 reactive oxygen species in, 542
 receptor protein kinases in, 411
 receptor tyrosine kinases in, 412, 415
 receptors in, 402, 405–406
 second messengers in, 402–403, 403f, 409–411, 409f, 419
 7TM receptors in, 404–406, 404t
 specialized domains in, 419
 Src homology domains in, 414, 414f, 417, 419, 420, **420**
 steps in, 402–403
 in taste, 963–966
 termination of, 407f
 in touch, 973–974
 in vision, 968–969, 968f
- Signal-recognition particle (SRP), 124, 911, 912f
 receptor for, 911
- Sildenafil, **1039**
 discovery of, 1039
- Simple diffusion, 372
- SINES, 160
- Singer, S. Jonathan, 362
- Single-strand-binding protein, 832
- siRNA (small interfering RNA), 124. *See also* RNA
- Site-directed mutagenesis, in catalysis
 investigation, 262–263
- 16S rRNA, in translation, 892, 901
- Sjöstrand, Fritjof, 526
- Slack, C. Roger, 599
- Sliding DNA clamp, 831–832, 831f, 834
- Sliding filament model, 1016–1017, 1017f
- Small G proteins. *See also* G protein(s)
 in signal transduction, 418, 418t
- Small interfering RNA (siRNA), 124. *See also* RNA
- Small nucleolar ribonucleoproteins (snRNPs), 852, 875–876, 876t
- Small nuclear RNA (snRNA), 124, 875–876. *See also* RNA
 in splicing, 875–876, 876t
- Small nucleolar ribonucleoproteins (snoRNPs), 870
- Smallpox, 1003
- Smell, 958–962. *See also* Olfaction
- Smith, Emil, 543
- Smith, Hamilton, 141
- Smooth endoplasmic reticulum, 911. *See also* Endoplasmic reticulum
- SNARE proteins, 366, 914
- snoRNPs (small nucleolar ribonucleoproteins), 870
- snRNA (small nuclear RNA), 124, 875–876
 in splicing, 875–876, 876t
- snRNPs (small nuclear ribonucleoproteins), 852, 862t, 875–876
- Snurps, 875
- SOD1 gene, 152, 157
- Sodium dodecyl sulfate (SDS). *See also* under SDS
 in gel electrophoresis, 73, 78
- Sodium ion channels, 382, 384, 384f, 387–392. *See also* Ion channels
 amiloride-sensitive, 965, 965f
 inactivation of, 388–389, 389f
 sequence homologies of, 384, 384f, 386
 in taste, 962, 965
- Sodium ion, salty taste of, 962, 965
- Sodium–potassium pump, 364, 364f, 374, 377, 392
 digitalis inhibition of, 377
 evolution of, 378
- Solid-phase method, 144f
- Solid-phase methods, 97f, 98, 144–145, 144f
- Solid-phase peptide synthesis, 97f, 98
- Somatic mutations, antibody diversity and, 989
- Sonication, 353
- Sos, in signal transduction, 417
- Sound, perception of, 971–973
- Sour taste, 962, 962f, 965–966
- Southern blotting, 142, 142f
- Southern, Edwin, 142
- Space-filling molecular models, 21, 23f, 61, 61f
- Special pairs, 571, 573, 573f
- Specific activity, 67
- Sphingolipids
 functions of, 765
 gangliosides, 764–765, 765f
 synthesis of, 764–765
- Sphingomyelin, 349, **349**, 351, 351f
 synthesis of, 764, **764**
- Sphingosine, 348, 349, **349**, 764, **764**
 synthesis of, 726, 726f
- Spicy foods, capsaicin in, 973–974, 973f
- Spin, 101, 101t
- Spina bifida, 755
- Spleen tyrosine kinase (Syk), 989–990
- Spliceosomes, 132, 874, 875–877, 875f
- Splicing, 132–133, 132f, 851–852, 869, 873–879
 alternative, 133, 133f, 878–879, 878f
 branch points in, 874, 875, 875f

- consensus sequences in, 132f, 133, 873–874, 873f
 definition of, 873
 errors in, 877–878
 internal guide sequence in, 881, 881f
 mutations affecting, 877–878
 self-splicing and, 879–881, 880f–882f
 sites of, 873–874, 873f, 875–876, 877, 881, 881f
 spliceosomes in, 132, 874, 875–877, 875f
 transesterification in, 874–875, 880
- Splicing factors, 875
- Split genes, 131–132, 132f, 133f
 evolutionary advantages of, 133
- Split-pool synthesis, 1041, 1042f
- Squalene, 768–770
- Squalene epoxide, 769, **770**
- Squalene synthase, 769
- SR Ca^{2+} ATPase, 375–377
- Src
 in cancer, 420
 myristoylation of, 298t
- Src homology domains, 414, 414f, 417, 419, 420, **420**
- SREBP (sterol regulatory element binding protein), 770–771, 771f
- SREBP cleavage activating protein (SCAP), 770–771, 771f
- SRP (signal-recognition particle), 124, 911, 912f, 913f
- SRP receptor, 912, 913f
- SRP54, 911, 913
- Stadtman, Earl, 725
- Stahl, Franklin, 119
- Staining, in gel electrophoresis, 73, 73f
- Staphylococcus aureus*, peptidoglycan of, 244, 244f
- Starch, 328, 329f. *See also* Carbohydrates in plants, 597
- Starvation, metabolic adaptations in, 809–810
- Starved–fed cycle, 807–808
- Statins, 779, **779**, **1040**, 1040–1041, **1041**
- Steady-state assumption, 231
- Steatorrhea, 642
- Steitz, Tom, 821
- Stem cells, pluripotent, 944
- Stem-loop motif, 117, 117f
- Stereochemistry, 21
 notation in, 27
- Stereocilia, 971–973, 971f
- Stereoisomers, 27
 carbohydrate, 321, 321f
- Steric exclusion, 37
- Steroid hormones. *See also* Hormone(s)
 anabolic, 785, 948
 cardiogenic, 377, 377f
 functions of, 780
 hydroxylation of, 781–782
 structure of, 781, **781**
 synthesis of, 780f, 783–785
- Steroid receptors, nuclear localization of, 90–91, 90f. *See also* Nuclear hormone receptors
- Sterol regulatory element, 770
- Sterol regulatory element binding protein (SREBP), 770–771, 771f
- Sticky ends, 148, 149f
- Stoma, in *Crassulaceae*, 600f, 601
- Stomach. *See also under* Gastric protein digestion in, 674, 674f
- Strand invasion, 845, 845f
- Streptomycin, **909**, 909–910, 909t
- Stroma, 567
- Strominger, Jack, 1038
- Structural formulas, 21–22, 23f
- Structure-based drug development, 1042–1045, 1043f, 1044f
- Substitution(s)
 in amino acid sequences, 178–181, 179f–181f
 conservative, 178
 production of, 156, 156f
- Substitution matrices, 178–181, 179f–181f
- Substrate(s), 220. *See also* Enzyme-substrate complex
 binding of, enzyme specificity and, 275–277
 chromogenic, 256
- Substrate binding. *See also* Enzyme-substrate complex
 concerted mechanism in, 294–296
 cooperative, 200–201, 201f, 294
 energy for, 229, 254, 275–277. *See also* Binding energy
 sequential model of, 294
 specificity of, 220–221, 221f, 275–277
- Substrate channeling
 in amino acid synthesis, 722, 722f
 in citric acid cycle, 512
 in nucleotide synthesis, 737–738
- Substrate cycle, 489
- Substrate-level phosphorylation, 463–464, 507–508
- Subtilisin, **186**, 261, 261f
 active sites on, 186, 186f
 site-directed mutagenesis of, 262, 262f
- Subunit vaccines, 1002
- Subunits, protein, 48, 48f
- Succinate dehydrogenase, in citric acid cycle, 509–510
- Succinate, in 4-hydroxyproline synthesis, 812f, 813
- Succinate thiokinase, in citric acid cycle, 507–508
- Succinate-Q reductase (Complex II), 531, 532f, 532t, 535–536
- Succinyl CoA, **649**
 in amino acid degradation, 693
 in citric acid cycle, 507–508, 508f, 514, 514f
 formation of, 649–652, 650f, 651f, 693
 porphyrins from, 728–730, 729f
- Succinyl CoA synthetase, in citric acid cycle, 507–508
- Sucrase, 327, 454
- Sucrose, 327
 plant synthesis of, 597, 598f
- Sugar(s). *See also* Carbohydrates
 amino, 330
 disaccharide, 327–329. *See also* Disaccharides
 monosaccharide, 320–327. *See also* Monosaccharides
 in DNA, 110–111, 110f
 in RNA, 110f, 111
 nonreducing, 325
 reducing, 325
- Sugars, phosphorylated, 326–327
- Suicide inhibition, 242, 750, 754
- Sulfate, conjugation of, 1034, **1035**
- Sulfation, 298t
- Sulfolipids, in thylakoid membrane, 567
- Supercoiled DNA, 117, 117f, 826, 827f, 828f
 DNA condensation from, 828
 linking number and, 826, 827f
 negative supercoiling in, 826, 829–831, 941
 positive supercoiling in, 826
 relaxation of, 828–829, 829f
 topoisomerases and, 828–831
 twist in, 826–827, 827f
 writhe in, 826–828, 827f
- Supercompensation, 806
- Supernatant, in centrifugation, 67, 68f
- Superoxide anion, 198, 198f
- Superoxide dismutase, 541–542, 542f
- Superoxide ion, 540, 542f
- Supersecondary structures, 47, 47f, 82–83, 83f, 174, 175f. *See also* Motifs
- Suppressors of cytokine signaling (SOCS), 797, 797f, 800
- Surface complementarity, noncovalent bonds and, 11
- Svedberg units (S), 76, 76t
- Syk (spleen tyrosine kinase), 989–990
- Symmetry matching, 922
- Symporter, 380–381, 380f, 381f
- Synapses, 389, 390f
- Synaptic cleft, 389, 390f
- Synonyms, 129, 129t
- Synthetic analog system, 269
- T cell(s), 980–981
 activation of, 995–996
 cytotoxic (killer), 980, 994–995, 997–998
 helper, 980, 996–998
 in HIV infection, 999–1000
 major histocompatibility complex and, 980–981
 memory, 1002
 negative selection of, 1000–1001, 1000f
 positive selection of, 1000, 1000f
- T state, of hemoglobin, 202–204, 203f, 207–208, 207f
- T1R proteins, as sweet receptors, 964–965
- T2R proteins, as bitter receptors, 963–965
- Tactile sensation, 973–974
- Takepron (lansoprazole), 1046, **1046**
- Tamoxifen, 948, **948**

- Tandem mass spectrometry, 93–94
TAP protein, 992
Taste
 anatomic structures in, 963, 963f
 tastants in, **962**, 962–963
Taste buds, 963, 963f
Taste papillae, 963
TATA box, 126f, 127, 866–867, 867f, 868f
TATA-box-binding protein (TBP), 867–868, 867f, 868f, 950
 repeated motifs in, 184, **185**
TATA-box-binding protein associated factor, 950
Taurocholate, 642
 synthesis of, 779–780, **780**
Taxol, 1019–1020
Tay–Sachs disease, 765–766
TBP. *See* TATA-box-binding protein (TBP)
T-cell receptors, 980–981, 994–998
 CD3 and, 995, 995f
 CD4 and, 980
 CD8 and, 994–995, 995f
 cytotoxic T cells and, 980, 994–995, 997–998
 domains of, 994, 994f
 genes of, 994
 helper T cells and, 980, 996–998
 MHC complex proteins and, 994–998, 994f
 number of, 980
 structure of, 993f, 994, 994f
 in T-cell activation, 995–996, 995f
T-cell selection, 1000–1001, 1000f
T-DNA, 166
Telomerase, 124, 837
Telomerase inhibitors, 837
Telomeres, 836–837, 836f, 837f
Temperature perception, 973
Template
 in replication, 121–122, 122f, 820–821
 sequence, 184
 in transcription, 124, 125f, 126, 126t, 854, 855f
 in translation, 123–124
–10 sequence, 857, 857f
Terminal transferase, 154
Tertiary protein structure, 45–47, 46f, 47f, 183–184, 183f. *See also* Protein(s), folding of
Testosterone, **784**
 functions of, 784–785
 reduction of, 785
 synthesis of, 780, 780f, 784–785, 784f
Tetracycline, 909t
Tetrahydrobiopterin, 695, **695**
Tetrahydrofolate, **715**
 in amino acid synthesis, 715–716, 716–717, 716f
 in deoxyribonucleotide synthesis, 748–749, **749**
Tetrahymena, self-splicing in, 880f, 881
Tetrodotoxin, 384, **384**
Tetroses, 320
TFII, in transcription, 867–868
TFPI (tissue factor pathway inhibitor), 312
Thalassemia, 210–211
Therapeutic index, 1036
Thermodynamics, 11–13. *See also* Energy
 of coupled reactions, 429–430, 431–433
 enzymes and, 222–225
 in metabolism, 429–435
Thermogenesis, oxidative phosphorylation in, 556–557
Thermogenin, 557
Thiamine (vitamin B₁), 441t
 biosynthesis of, 678, 679f
 deficiency of, 517
Thiamine pyrophosphate (TPP), **500**
 in citric acid cycle, 500, 500f, 501f
 deficiency of, 517
 in pentose phosphate pathway, 605, 605f
Thiamine pyrophosphate (TPP), 594
Thick filaments, in myosin, 1016, 1017f
ThiF, 678, 679f
Thin filaments, in myosin, 1016, 1017f
Thioester intermediate, in glycolysis, 461–463, 462f
Thiogalactoside transacetylase, 924
6-Thioguanine, 1047–1048, **1048**
Thiolase, 647–648, 647t
Thioredoxin, 598–599, 598t, **599**
Thioredoxin reductase, 747
30S initiation complex, 902, 903f
30S subunit, of ribosome, 892, 897–898, 898f, 902, 903f
–35 sequence, 126f, 127, 857, 857f
ThiS, 678, 679f
Thorazine (chlorpromazine), **1038**
 discovery of, 1038
 mechanism of action of, 1038, 1039f
3' poly(A) tail, 871–872, 871f
3' splice sites, 842–843, 873f
Threonine
 in glycoproteins, 330
 pyruvate formation from, 691, 691f
 structure of, 30, 30f
 synthesis of, 724, 724f
Threonine deaminase, 723–724, 723f
Threonine kinases, 298–299, 299f, 299t
Threonine operon, 932–933, 932f
Threonyl-tRNA synthetase, active site of, **894**, 894–895
Threonyl-tRNA synthetase complex, structure of, 896, **896**
Thrombin, 221, 221f
 in blood clotting, 308–310, 308f, 312
 γ -carboxylation of, 298t
 inhibitors of, 312
Thromboxanes, 664–665, **665**, 665f
Thylakoid membrane, 567–568, 567f, 574–575
 proton gradient across, 577–581
 stacked vs. unstacked regions of, 583, 583f
Thylakoid spaces, 567, 567f
Thylakoids, 567, 567f, 574–575
Thymidine, 111
Thymidine kinase, 740
Thymidine phosphorylase, 740
Thymidine triphosphate (TTP), 752
Thymidylate, 111, **748**
 synthesis of, 748, 748f
 salvage pathway for, 740
Thymidylate inhibitors, for cancer, 749–750
Thymidylate synthase, 748
Thymine, 4, **4**, 111, **111**, 748
 in DNA repair, 841
 synthesis of, 716
Thymocytes, 1000–1001, 1000f
Thymus, T-cell selection in, 1000–1001, 1000f
Thyroxine, synthesis of, 726, 726f
Ti plasmids, 166–167, 167f
Time of flight (TOF) mass analyzer, 92, 92f
Time, sense of, 974
Tip links, 972, 972f
Tissue factor, in blood clotting, 308
Tissue factor pathway inhibitor (TFPI), 312
Tissue-type plasminogen activator (TPA), 312–313, 313f
Titin, 34
Titration, 15–16
Tobacco mosaic virus, 122
 α -Tocopherol (vitamin E), 442, **442**, 442t
 in lipid peroxidation prevention, 542
Toll receptors, 978–979
Toll-like receptors, 978–979, 978f, 979f
Tonogawa, Susumu, 987
Tongue, taste buds of, 963, 963f
Topoisomerases, 828–831
 bacterial, 831
 type I, 828–829
 structure of, **828**, 828–829
 in supercoiled DNA relaxation, 828–829, 829f
 type II, 829–831, 830f
 structure of, 829–831, **830**
Topoisomers, 826–828, 828f
Torpedo marmorata, acetylcholine receptor in, 389, 390f
Torr, 200b
Torsion angles, 37, 37f, 38f
Tosyl-L-phenylalanine chloromethyl ketone (TPCK), **241**, 241–242
Touch, 973–974
Toxoid vaccines, 1002
TPA (tissue-type plasminogen activator), 312–313, 313f
TPI. *See* Triose phosphate isomerase (TPI)
TPP. *See* Thiamine pyrophosphate (TPP)
T Ψ C loop, of tRNA, 890f, 891
Trace elements, 20
Trans configuration, of peptide bonds, 36–37, 36f, 37f
Transacetylase component, of pyruvate dehydrogenase complex, 502, 502f
Transaldolase, in pentose phosphate pathway-glycolysis linkage, 601–605, 605, 606f

- Transaminases
 in amino acid degradation, 680
 evolution of, 713
 pyridoxal phosphate-dependent, 712–713
- Transamination
 in amino acid degradation, 680–685
 in amino acid synthesis, 709–710,
 712–713, 712f
 pyridoxal phosphate enzymes in, 680–685
 reaction mechanism of, 682f, 712f
 Schiff-base intermediates in, 681–682
 stereochemistry of proton addition in,
 713, 713f
- Transcription, 124–127, 125f, 851–869
 in archaea, 869
 in bacteria, 852–863
 attenuation in, 931–932, 931f, 932f
 chain elongation in, 855–856, 855f
 DNA rewinding in, 859, 859f
 helix unwinding in, 858, 858f
 initiation of, 854–858
 promoters in, 856–858
 proofreading in, 856
 regulation of, 922–928. *See also* Gene
 expression/regulation
rho in, 860–861, 861f
 ribonucleases in, 863
 riboswitches in, 860, 860f
 RNA processing and, 133, 863. *See also*
 RNA processing
 RNA–DNA hybrid in
 backtracking of, 856, 856f
 separation of, 855, 856f, 859f
 translocation of, 855, 855f
 of rRNA, 863
 termination of, 859–860, 859f
 transcript processing in, 863
 transcription bubble in, 858–859, 859f
 transition from open to closed promoter
 complex in, 858
 translation and, 864, 864f
 of tRNA, 863
 vs. in eukaryotes, 864, 864f
 coordination with translation, 864, 864f
 definition of, 851
 direction of, 125, 854–855, 855f
 DNA template in, 124, 125f, 126, 126f,
 854, 855f
 enhancer sequences in, 127
 in eukaryotes, 864
 carboxyl-terminal domain in, 868,
 877, 877f
 chain elongation in, 867–868
 coactivators in, 947–948, 948f,
 949–951, 950f
 enhancers in, 127, 868–869,
 943–944, 943f
 histone acetylation in, 949–951, 950f
 initiation of, 866–869, 950
 nuclear membrane in, 864
 polyadenylation in, 871, 871f
 pre-mRNA processing and, 870–872,
 871f, 878–879. *See also* Splicing
 promoters in, 866–869, 866f
 regulation of, 864, 941–944. *See also*
 Gene expression/regulation
 repression of, 950–951
 RNA editing in, 872–873, 873f
 RNA polymerases in, 865–867, 866f,
 869–872. *See also* RNA
 polymerase(s)
 RNA processing and, 133, 864, 869–879.
See also RNA processing
 splicing in, 132f, 133, 851–852, 873–879.
See also Splicing
 TATA box in, 866–867, 867f, 868f
 transcript processing in, 869–879
 transcription factors in, 867–868, 867f.
See also Transcription factors
 vs. in bacteria, 864, 864f
 evolution of, 869
 fundamental reaction of, 853
 in humans, pre-mRNA processing and,
 878–879
 inhibition of, by DNA-binding proteins,
 924–927
 initiation of, 126–127, 126f
 de novo, 854
 RNA chain elongation in, 858–859, 859f
 RNA chain formation in, 858–859
 intron removal in, 132–133, 132f
 overview of, 851–852
 promoters/promoter sites in,
 126–127, 126f
 RNA modification in, 127, 127f
 RNA polymerase in, 124–127, 125f, 852,
 853–858. *See also* RNA polymerase
 splicing in, 132–133, 132f, 851–852,
 873–879. *See also* Splicing
 stages of, 852–853
 termination of, 127
- Transcription bubble, 853–854, 854f,
 858–859, 859f
- Transcription factors
 in eukaryotes, 867, 941–944, 943. *See also*
 DNA-binding proteins and *specific*
factors
 chromatin structure and, 946
 definition of, 164, 941
 DNA-binding domains of, 941,
 942–943
 in gene regulation, 942–943
 nuclear hormone receptor, 946–948, 947f
 regulatory domains of, 942–943
 in gene knockout, 164–165
 in prokaryotes, 941, 943
- Transcriptome, 162
- Transducin
 P-loop NTPase domains in, 284, 284f
 rhodopsin and, 968
- Transesterification, in splicing, 874–875
- Transfer RNA. *See* tRNA
- Transferase(s), 249t. *See also* Enzyme(s)
 in glycogen metabolism, 620, 620f
- Transferrin, 730, 951
- Transferrin receptor, 951
- Transgenic animals, 164, 164f
- Transglutaminase, 309
- Transition state
 catalytic stabilization of, 225–226, 225f,
 227, 243–244
 enzymes and, 225–226, 225f, 227
- Transition-state analogs, 243, 243f
- Transketolase, 594
 in Calvin cycle, 594, 595f
 in pentose phosphate pathway-glycolysis
 linkage, 601–605, 605f
- Translation, 130, 130f. *See also* Gene
 expression/regulation; Protein(s),
 synthesis of
 accuracy of, 888–889, 889t, 895
 activating enzymes in, 893
 adenylation in, 893–895
 in α helix, 39
 aminoacyl-tRNA synthetases in, 888,
 893–897
 activation sites of, **894**, 894–895
 amino acid activation by, 893–895
 classes of, 897, 897t
 editing sites of, 895, **895**
 proofreading by, 895
 specificity of, 893–894
 tRNA recognition by, 896
 anticodons in, 889, 891–893, 892f
 attenuation and, 931–932
 in bacteria
 transcription and, 864, 864f
 vs. in eukaryotes, 907–908
 base pairing in, 891–893, 901
 codon-anticodon interactions in,
 891–893
 wobble in, 891–893
 chain elongation in, 902–904, 903f, 904f
 codons in, 889, 891–893, 892f
 coordination with transcription,
 864, 864f
 definition of, 123, 887
 direction of, 888, 905–906
 elongation factors in, 902–903, 903f
 in eukaryotes, 908
 error rate in, 888–889, 889t, 895
 in eukaryotes
 transcription and, 864, 864f
 vs. in bacteria, 907–908
 fidelity of, 888–889, 889t, 895
 formylmethionyl-tRNA in, 901–902,
 902, 902f
 free energy of, 893–894
 in gene regulation, 951–953
 inhibition of
 by antibiotics, 909–910
 by diphtheria toxin, 910–911
 by ricin, 911
 initiation of, 130, 893–894,
 900–902, 903f
 in eukaryotes, 907–908, 907f, 908f
 sites of, 900–901, 901f
 in iron metabolism, 951–953
 mechanisms of, 905f

- Translation—(Continued)
 mRNA in, 123–124, 130, 130f. *See also*
 mRNA (messenger RNA)
 in initiation, 900–901
 in termination, 901
 translocation of, 904–906, 905f
 overview of, 887–888
 peptide bond formation in, 903–904, 904f
 peptidyl tRNA in, 903–904
 proofreading in, 895
 protein sorting/transport in, 911–914
 release factors in, 906, 907f
 ribosome in, 897–906
 initiation sites in, 902, 903f
 RNA editing in, 872–873, 873f
 rRNA in, 892, 898–900, 901, 903–904
 Shine–Dalgarno sequences in, 130, 901
 signaling in, 911–914
 termination of, 130, 906, 907f
 in eukaryotes, 908
 translocation in, 904–906
 tRNA in, 127–128, 889–893, 901–906.
See also tRNA
- Translocase, 904–906, 905f
- Translocon, 911–912
- Transmissible spongiform encephalopathies,
 55–56
- Transpeptidase, penicillin inhibition of,
 245, 245f
- Transplant rejection, 998
- Transport vesicles, 913–914, 914f
- Transporters, 372
 ABC, 378–380, 378f, 379f
 antiporters, 380, 380f
 ATP–ADP translocase, 552–553,
 553f, 554f
 dicarboxylate, 554, 554f
 glucose, 372, 414, 477, 477t
 glucose 6-phosphate, 635
 inhibitors of, 558, 558f
 lactose permease, 381, 381f
 in metabolism, 438–442, 438f–440f
 in oxidative phosphorylation, 438–442,
 438f–440f, 439f, 531–543, 532t,
 551–553, 551f–553f
 phosphate, 554, 554f
 in photosynthesis, 568–572, 569f, 596f
 pyruvate, 554, 554f
 secondary, 381, 381f
 symporters, 380–381, 380f, 381f
 tricarboxylate, 554, 554f
 uniporters, 380, 380f
- Tree of life, 3f
- Triacylglycerol(s), 639, 641–642
 energy storage in, 641–642
 hydrolysis of, 643–644, 643f. *See also*
 Fatty acid metabolism
 mobilization of, 643–644, 643f
 synthesis of, 760–767, 760f, **761**
 hepatic, 773
 transport of, 642, 642f, 773–774
- Triacylglycerol synthetase complex, 761
- Tricarboxylate carrier, 554, 554f
 structure of, 28, 29f
 synthesis of, 720–722, 721f, 722f
- Tryptophan operon, 931
- Tryptophan synthase, 722–723, **723**
- Ts elongation factor, 903
- t-SNARE, 366, 914
- TTP (thymidine triphosphate), 752
- Tu elongation factor, 902–903, 903f
- Tuberculosis, proteasome inhibitors for, 679
- Tubulin
 in microtubules, 1018–1019, 1019f
 sequence homology of, 1019
- Tumor-inducing (Ti) plasmids, 166–167
- Tumor-suppressor genes, 420, 842
- Turnover number (k_{cat}), 234, 234t
- 20S proteasome, 677, 677f
 –25 region, 126f, 127
- 26S proteasome, 677, 677f
- Twist, in DNA, 826–827, 827f
- Two-dimensional electrophoresis, 74, 74f
- Typing-monkey analogy, 53, 53f
- Tyrosine
 degradation of, 695–696
 epinephrine from, 726, 726f
 melanin from, 726
 structure of, 30, 30f, **696**
 synthesis of, 719–720, 721f
 thyroxine from, 726, 726f
- Tyrosine kinases, 298–299, 299f, 412
 in cancer, 420
 receptor, 412
- Tyrosine phosphatase IB, 799
- Tyrosinemia, 698t
- Tyrosyl radical, 745–747
- U1 snRNA, 875–876, 875f, 876t
- U2 snRNA, 875f, 876, 876t
- U4 snRNA, 875f, 876, 876t
- U5 snRNA, 875f, 876, 876t
- U6 snRNA, 875f, 876, 876t
- Ubiquinol, 535
- Ubiquinone (coenzyme Q), 532, 533
 in fatty acid metabolism, 646
- Ubiquitin, 675–678
 structure of, **675**, 675–676
- Ubiquitin-activating enzyme (E1),
 675–676, 675f
- Ubiquitination, 298t, 675–678
- Ubiquitin-conjugating enzyme (E2),
 675–676, 675f
- Ubiquitin-protein ligase (E3), 675–676, 675f
- UCP-1, 557
- UCP-2, 557
- UCP-3, 557
- UDP (uridine diphosphate), hydrolysis
 of, 431
- UDP- α -glucuronic acid, **1035**
- UDP-galactose, **470**, 471
- UDP-glucose, **470**, 470–471, 627
 in glucose synthesis, 627–630
 in glycogen synthesis, 627–630
 structure of, 627, **627**
 in sucrose synthesis, 597, **598**
- Tricarboxylic acid cycle. *See* Citric
 acid cycle
- Triglycerides. *See* Triacylglycerol(s)
- Trimethoprim, 750
- Trimethoprim-sulfamethoxazole, 750
- Trinucleotide repeats, 842
- Triose kinase, 470
- Triose phosphate isomerase (TPI), 242,
242, **459**
 in glycolysis, 456f, 458–460
- Triose phosphates, in sucrose synthesis,
 597, **598**
- Trioses, 320, 320f
- Triple helix, of collagen, 44–45, 44f
- tRNA (transfer RNA), 123t, 124, 127–128,
 128f. *See also* RNA
 anticodons of, 889, 890f, 891–893,
 891f, 896
 base-pairing in, 890–893, 890f
 wobble in, 891–893
 charged, 891f, 893
 codons of, 889
 functions of, 124
 initiator, 907
 inosine in, 892
 key features of, 889–890
 post-transcriptional processing of, 863
 precursor of, processing of, 870, 871f
 ribosomal binding of
 mechanism of, 903–904, 905f
 sites for, 900, 902–904, 905
 sequencing of, 889, 890f
 structure of, 128f, 889–890, 890f–892f
 transcription and processing of, 863,
 870, 871f
 in translation, 889–893, 901–906
 as adaptor molecule, 889
 binding sites for, 900, 901f
 in chain elongation, 903–904, 904f, 905f
 function of, 889
 in initiation, 901–902
 translocation of, 904–906, 905f
- Trojan horse strategy, 245
- Trombone model, 833, 833f
- Tropical plants, photosynthesis in,
 599–600
- Tropomyosin, 1017
- Troponin complex, 1016
- TRP channels, 973
- trp* operon, 931
- Trypsin, 221, 221f, 305–306
 catalytic triad in, 260–261, 261f
 chymotrypsin and, 260–261, 261f
 in protein cleavage, 80, 82f, 306
 structure of, 260, 261f
 in zymogen activation, 306, 306f
- Trypsin inhibitor, 306, 307f
- Trypsinogen, 306
- Tryptophan, **696**
 degradation of, 696, 696f
 nicotinamide from, 726f, 727
 pyruvate formation from, 691
 serotonin from, 726f, 727

- UDP-glucose phosphorylase, 627
- Umami, 962, 962f, 965
- UMP (uridine monophosphate), synthesis of, 739
- Uncompetitive inhibition, 238, 238f, 239, 239f, 240, 240f
- Uncoupling proteins, 557, 558f
- Unfolded protein response, 802
- Uniporters, 380, 380f
- Units of measure
for distance, 7
for energy, 7
- Unsaturated fatty acids, 648–649, 664–665.
See also Fatty acid(s)
- Upstream promoter elements
in bacteria, 857
in eukaryotes, 866
- Uracil, 111, **111**
in DNA repair, 841
thymidylate from, 748
- Uracil DNA glycolase, 841, 841f
- Urate
degradation of, 752, 753f
in gout, 753–754
- Urea, **49**
- Urea cycle, 673, 685–690
carbamoyl phosphate formation in, 685–687
disorders of, 688–689
evolution of, 688
gluconeogenesis and, 687
reactions in, 685f
stoichiometry of, 687
- Ureotelic organisms, 685, 690
- Uric acid
degradation of, 752, 753f
in gout, 753–754
- Uricotelic organisms, 690
- Uridine, 111
- Uridine diphosphate. *See* UDP (uridine diphosphate)
- Uridine monophosphate (UMP), synthesis of, 739
- Uridine triphosphate. *See* UTP (uridine triphosphate)
- Uridylate, 739, **739**, 863, **863**
- Urine, as bleach, 687b
- Uroporphyrinogen III, 729, **729**
- UTP (uridine triphosphate)
in glycogen synthesis, 617
synthesis of, 739
- V genes, 987–988
in antibody switching, 990–991
- Vaccine(s), 1002–1003
HIV, 1003
synthetic, 157
- Vaccinia virus vectors, 163–164
- Valine
degradation of, 694–695
in maple syrup urine disease, 697
structure of, 28, 29f
synthesis of, 723–724
- Van der Waals interactions, 8, 8f, 11, 46.
See also Bonds
in antigen-antibody binding, 984, 985, 985f, 986
in double helix, 10, 10f
in enzyme-substrate complex, 228, 228f
in space-filling models, 61, 61f
- Vanishing white matter, 908–909, 909f
- Variable (V) genes, 987–988
in class switching, 990–991
- Variable number of tandem repeats (VNTR) region, 333, 333f
- Variable regions, 983, 984f
- Vasopressin, 96, **96**
- Vectors
cloning, 148, 149
expression, 149, 154–155
lambda phage, 150–151, 150f, 151f
plasmid, 149–151, 149f, 150f
viral, 150–151, 150f, 151f, 163–164
- Velcade (bortezomib), **678**, 679
- Very-low-density lipoproteins, 773, 773t.
See also Lipoprotein(s)
- Vesicles
formation of, 365
transport, 913–914, 914f
- Viagra (sildenafil), **1039**
discovery of, 1039
- Vibrio cholerae*
ABC transporter of, 378, 378f, 379f
infection with, 421–422
- Vibrio fischeri*, quorum sensing in, 930–931, 930f
- Vioxx (rofecoxib), **1044**, 1044–1045, 1049
- Viral infections, carbohydrates in, 339–340
- Viral vectors, 150–151, 150f, 151f, 163–164
- Viruses
cell entry by, 340f, 365–366
HIV, 999–1000, 999f
infectious mechanisms of, 339–340, 340f, 365–366
influenza, 339, 340f
protein structure of, 48, 48f
retroviruses, 999–1000
RNA, 122–123, 123f
- Vision, 966–971
color, 966, 969–971
in animals, 970, 970f
evolution of, 970, 970f
cones in, 966, 969–970
evolution of, 970, 970f
photoreceptors in, 966
rhodopsin in, 966–968
rods in, 966–967, 966f
signal transduction in, 968–969, 968f
- Visual pigments, 969–970, 970f. *See also* Color vision
in cones, 969–970
in rods, 966–967
- Vitamin(s), 20
B, **441**, 441–442, 441t
coenzyme, **441**, 441–442, 441t
deficiencies of, 441t, 442
electron carrier derived from, 441–442
electron carriers derived from, 440t
evolution of, 441–442, 441t
noncoenzyme, 442, **442**, 442t
- Vitamin A (retinol), 442, **442**, 442t
deficiency of, alcohol-related, 812
- Vitamin B₁ (thiamine), 441t
biosynthesis of, 678, 679f
deficiency of, 517
- Vitamin B₂, 441t
- Vitamin B₆ (pantothenic acid), **441**, 441t
- Vitamin B₁₂ (cobalamin), 441t, 649
in amino acid synthesis, 650–652, 650f, 651f, 717
as coenzyme, 650–652, 650f, 651f, 717
in fatty acid metabolism, 649–652
structure of, **650**, 650–651
- Vitamin C (ascorbic acid), 442, 442t, 813, **813**
deficiency of, alcohol-related, 812–813
forms of, 813, **813**
- Vitamin D (calciferol), 442, 442t
deficiency of, 786
sources of, 786
synthesis of, 785, 785f
- Vitamin E (α-tocopherol), 442, **442**, 442t
in lipid peroxidation prevention, 542
- Vitamin K, 442, 442t
in blood clotting, 310–311
deficiency of, 57, 301
structure of, **310**
- VJ recombination, 987–988, 988f
- V(D)J recombination, 988, 988f
- V_{max}, 232–234
calculation of, 233
turnover number and, 234, 234t
- VNTR region, 333, 333f
- VO₄³⁻, 1011
- Voltage-gated ion channels, 387–388, 388f.
See also Ion channels
- Von Gierke disease, 634–635, 634t
- VR1 (capsaicin receptor), 973–974, 973f
- v-SNARE, 366, 914
- v-Src, in cancer, 420
- Wang, James, 828
- Warburg effect, 478
- Warburg, Otto, 454, 478
- Warfarin, 310, **310**
- Water
dissociation of, equilibrium constant for, 14
equilibrium constant for, 14
hydrogen bonds of, 9–10, 9f
hydroxide ions in, 13–17
molecular models of, 23f
polarity of, 8–9
properties of, 8–9
- Watson, James, 5, 113
- Watson–Crick base pairs. *See* Bases/base pairs

- Watson–Crick DNA model, 5, 113–115, 114f. *See also* Bases/base pairs; DNA; Double helix
- Weight, regulation of, 791–798. *See also* Caloric homeostasis
- Wernicke–Korsakoff syndrome, 812
- Western blotting, 88f, 89, 142
- White adipose tissue, 556
- Whooping cough, 422
- Wiley, Don, 992
- Wilkins, Maurice, 113
- Withering, William, 377
- Wobble hypothesis, 891–893
- Writhe, in DNA, 826–828, 827f
- Wyman, Jeffries, 202
- Xanthine, degradation of, 752, 753f
- Xanthine oxidase inhibitors, 754
- Xanthomas, 776
- Xanthylate, **743**, 744
- Xenobiotic compounds, 1034
- Xeroderma pigmentosum, 842
- X-ray crystallography, 98–100, 98f–100f
of enzyme–substrate complexes, 227, 227f
- X-ray diffraction photographs, of DNA, 113, 113f
- Xylulose 5-phosphate, **596**
in Calvin cycle, 596, **596**
in pentose phosphate pathway, 602f, 604
- Yamanaka, Shinya, 944
- Yanofsky, Charles, 931
- Yeast artificial chromosomes, 151
- Yeast, genome of, 158, 937, 938f
- Z line, 1016, 1016f
- Z scheme of photosynthesis, 577, 577f
- Zantac (ranitidine), 1045, **1045**
- ZAP-70, 995–996
- Z-DNA, 116, 116f, 116t
- Zellweger syndrome, 652
- Zinc finger, 109f
- Zinc proteases, **263**, 264, 264f
- Zinc sites, in carbonic anhydrase, 267–269, 267f–269f
evolution of, 271
- Zinc-based domains, 946
- Zingiberene, **958**
- Zonal centrifugation, 77–78, 77f
- Zwitterions, 27–28, 27f
- Zymogens, 303–313, 674
in blood clotting, 307–312
functions of, 303
gastric, 303, 303t, 674
pancreatic, 303–307, 303t, 304f, 674

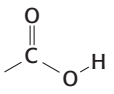
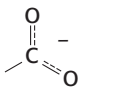


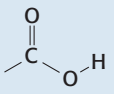
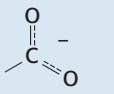
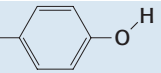
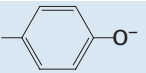
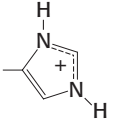
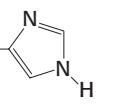


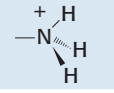
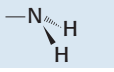
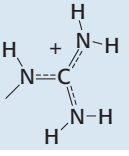
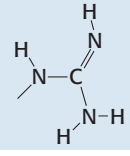
ACIDITY CONSTANTS

pK_a values of some acids

Acid	pK' (at 25°C)	Acid	pK' (at 25°C)
Acetic acid	4.76	Malic acid, pK ₁	3.40
Acetoacetic acid	3.58	pK ₂	5.11
Ammonium ion	9.25	Phenol	9.89
Ascorbic acid, pK ₁	4.10	Phosphoric acid, pK ₁	2.12
pK ₂	11.79	pK ₂	7.21
Benzoic acid	4.20	pK ₃	12.67
n-Butyric acid	4.81	Pyridinium ion	5.25
Cacodylic acid	6.19	Pyrophosphoric acid, pK ₁	0.85
Citric acid, pK ₁	3.14	pK ₂	1.49
pK ₂	4.77	pK ₃	5.77
pK ₃	6.39	pK ₄	8.22
Ethylammonium ion	10.81	Succinic acid, pK ₁	4.21
Formic acid	3.75	pK ₂	5.64
Glycine, pK ₁	2.35	Trimethylammonium ion	9.79
pK ₂	9.78	Tris (hydroxymethyl) aminomethane	8.08
Imidazolium ion	6.95	Water*	15.74
Lactic acid	3.86		
Maleic acid, pK ₁	1.83		
pK ₂	6.07		

*[H⁺][OH⁻] = 10⁻¹⁴; [H₂O] = 55.5 M.

Typical pK_a values of ionizable groups in proteins

Group	Acid	⇌	Base	Typical pK _a	Group	Acid	⇌	Base	Typical pK _a
Terminal α-carboxyl group		⇌		3.1	Cysteine		⇌		8.3
Aspartic acid Glutamic acid		⇌		4.1	Tyrosine		⇌		10.4
Histidine		⇌		6.0	Lysine		⇌		10.0
Terminal α-amino group		⇌		8.0	Arginine		⇌		12.5

Note: pK_a values depend on temperature, ionic strength, and the microenvironment of the ionizable group.

STANDARD BOND LENGTHS

Bond	Structure	Length (Å)
C—H	R ₂ CH ₂	1.07
	Aromatic	1.08
	RCH ₃	1.10
C—C	Hydrocarbon	1.54
	Aromatic	1.40
C=C	Ethylene	1.33
C≡C	Acetylene	1.20
C—N	RNH ₂	1.47
	O=C—N	1.34
C—O	Alcohol	1.43
	Ester	1.36
C=O	Aldehyde	1.22
	Amide	1.24
C—S	R ₂ S	1.82
N—H	Amide	0.99
O—H	Alcohol	0.97
O—O	O ₂	1.21
P—O	Ester	1.56
S—H	Thiol	1.33
S—S	Disulfide	2.05