

19	Organelle Biogenesis: The Mitochondrion, Chloroplast, Peroxisome, and Nucleus	809	22	Microfilaments: Cell Motility and Control of Cell Shape	991
20	Cell-to-Cell Signaling	853	23	Microtubules and Intermediate Filaments	1051
21	Nerve Cells	925	24	Multicellularity: Cell-Cell and Cell-Matrix Interactions	1123
25	Regulation of the Eukaryotic Cell Cycle	1201	26	Cancer	1247
27	Immunity	1295			

► **Part IV**
Integrative and Specialized Cellular Events
850



Chapter-Opening Illustrations	xiv	RNA Is the Molecule That Is the Product of the Genome	12
► Part I		<i>Cells Have Both a Fixed Identity and an Ability to Change</i>	12
Laying the Groundwork	1	<i>Molecular Cell Biology</i>	14
1 THE DYNAMIC CELL	3	2 CHEMICAL FOUNDATIONS	15
<i>Evolution: Biology as a Historical Science</i>	4	<i>Energy</i>	16
<i>The Construction of Cells</i>	5	<i>Covalent Bonds</i>	16
Cells Are Surrounded by Water-Impermeable Membranes	6	Each Atom Can Make a Defined Number of Covalent Bonds	17
The Biological World Has Two Types of Cells	7	The Making or Breaking of Covalent Bonds Involves Large Energy Changes	18
Membranes Serve Functions Other Than Segregation	8	Covalent Bonds Exhibit Precise Orientations	18
Eukaryotic Cells Contain Organelles Thought to Have Evolved as Independent Organisms	9	Polar Covalent Bonds Result from Unequal Sharing of Electrons	19
<i>The Molecules of Life</i>	9	<i>Asymmetric Carbon Atoms and the Structure of Amino Acids and Carbohydrates</i>	20
Genetics Allowed DNA Organization to Be Analyzed Before the Structure of DNA Was Discovered	10	The α Carbon in Amino Acids Is a Chiral Carbon	20
The Ultimate Triumph of Genetics Is the Human Genome Project	12	Chiral Carbons Influence the Three-Dimensional Structure of Carbohydrates	20

<i>Noncovalent Bonds and the Structures of Biological Molecules</i>	21	Many Cellular Processes Involve the Transfer of Electrons in Oxidation-Reduction Reactions	37
The Hydrogen Bond Underlies Water's Biological Properties	22	An Unfavorable Chemical Reaction Can Proceed If It Is Coupled with an Energetically Favorable Reaction	39
Ionic Interactions Are Attractions Between Oppositely Charged Ions	23	Hydrolysis of the Phosphoanhydride Bonds in ATP Releases Substantial Free Energy	40
Van der Waals Interactions Are Caused by Transient Dipoles	24	ATP Is Used to Fuel Many Cellular Processes	42
Hydrophobic Bonds Cause Nonpolar Molecules to Adhere to Each Other	25	Polymers of Glucose with Specific Glycosidic Linkages Serve as Storage Reservoirs	43
Binding Specificity Can Be Conferred by Multiple Weak Bonds	26	<i>Activation Energy and Reaction Rate</i>	44
<i>Biomembranes: Hydrophobic Sheets Separating Aqueous Compartments</i>	27	Energy Is Required to Initiate a Reaction	44
Phospholipids Are the Principal Components of Biomembranes	27	Enzymes Catalyze Biochemical Reactions	45
Phospholipids Spontaneously Form Bilayers in Aqueous Solutions	27	<i>Summary</i>	47
<i>Chemical Equilibrium</i>	28	<i>Review Questions</i>	48
<i>pH and the Concentration of Hydrogen Ions</i>	30	<i>References</i>	49
Water Dissociates into Hydronium and Hydroxyl Ions	30	3 PROTEIN STRUCTURE AND FUNCTION	51
Acids Release Hydrogen Ions, and Bases Combine with Hydrogen Ions	31	<i>General Structure of Proteins</i>	52
Biological Molecules Can Have Both Acidic and Basic Groups	31	Form and Function Are Inseparable in Protein Architecture	52
The Henderson-Hasselbalch Equation Describes the Relationships between pH and Equilibrium Constants for Acids and Bases	32	Amino Acids, the Building Blocks of Proteins, Differ Only in Their Side Chains	52
Buffers Maintain the pH of Cells and of Extracellular Fluids	32	Polypeptides Are Amino Acids Connected by Peptide Bonds	56
<i>Biochemical Energetics: Free Energy in Biochemical Reactions</i>	34	Four Levels of Structure Determine the Shape of Proteins	56
The Change in Free Energy, ΔG , Determines the Direction of a Chemical Reaction	34	Polypeptides Can Be Chemically Analyzed and Synthesized	59
The ΔG of a Reaction Depends on Changes in Heat and Entropy	34	Three-Dimensional Protein Structure Is Determined through X-Ray Crystallography and NMR Spectroscopy	59
Temperature, Concentrations of Reactants, and Other Parameters Affect the ΔG of a Reaction	35	Graphical Representations of Proteins Highlight Internal Organization or Surface Structures	61
The Standard Free-Energy Change, ΔG° , Can Be Determined from Measurement of the Equilibrium Constant, K_{eq}	36	Secondary Structures Are Crucial Elements in Protein Architecture	63
The Generation of a Concentration Gradient Requires an Expenditure of Energy	37	Motifs Are Regular Combinations of Secondary Structures	66
		Structural and Functional Domains Are Modules of Tertiary Structure	67
		Sequence Homology Suggests Functional and Evolutionary Relationships among Proteins	68
		Many Proteins Contain Tightly Bound Prosthetic Groups	70

Chemical Modifications Alter the Biological Activity of Proteins	71
Proteolytic Processing and Protein Splicing Alter Protein Activity	72
A Protein Can Be Unfolded by Heat, Extreme pH, and Certain Chemicals	73
Many Denatured Proteins Can Refold into Their Native State In Vitro	73
Folding of Proteins In Vivo Is Promoted by Chaperones	74
<i>Enzymes</i>	75
The Active Site of an Enzyme Is a Cage of Amino Acids That Binds Substrates and Catalyzes Reactions	75
Proteases Degrade Proteins by Reducing Activation Energy for Peptide-Bond Hydrolysis	76
Coenzymes Are Essential for Certain Enzyme-Catalyzed Reactions	78
Activity of Some Enzymes Depends on a Conformational Change Induced by Substrate Binding	80
The Catalytic Activity of an Enzyme Can Be Characterized Mathematically	81
Enzymatic Activity Can Be Regulated by Various Mechanisms	83
<i>Antibodies</i>	86
Antibodies Are Multidomain, Multisubunit Proteins	86
Antigen-Binding Site Complements the Surface of the Antigen	87
Antibodies Are Valuable Tools for Identifying and Purifying Proteins	87
Antibodies Can Catalyze Chemical Reactions	87
<i>Techniques for Purifying and Characterizing Proteins</i>	88
Centrifugation Can Separate Particles and Molecules That Differ in Mass or Density	88
Electrophoresis Separates Molecules According to Their Charge: Mass Ratio	92
Liquid Chromatography Resolves Proteins by Mass, Charge, and Binding Affinity	94
Highly Specific Assays Detect Individual Proteins	96

<i>Summary</i>	97
<i>Review Questions</i>	99
<i>References</i>	100
4 NUCLEIC ACIDS, THE GENETIC CODE, AND PROTEIN SYNTHESIS	101
<i>Nucleic Acids: Linear Polymers of Nucleotides</i>	102
DNA	103
The Native State of DNA Is a Double Helix of Two Antiparallel Chains with Complementary Nucleotide Sequences	103
The Two Strands Can Separate, Causing DNA to Denature	108
Many DNA Molecules Are Circular	109
Linking Number, Twist, and Writhe Describe DNA Superstructure	110
<i>RNA: The Basic Chemical Structure and Its Function in Gene Expression</i>	111
<i>Rules for the Synthesis of Proteins and Nucleic Acids and Macromolecular Carpentry</i>	113
<i>Nucleic Acid Synthesis</i>	114
Nucleic Acid Polymerization Can Be Described by Four Rules	115
Organization of Genes in DNA Differs in Prokaryotes and Eukaryotes	116
Eukaryotic Primary RNA Transcripts Are Processed to Form Functional mRNAs	119
<i>Protein Synthesis: The Three Roles of RNA in Translation</i>	119
Messenger RNA Carries Information from DNA in a Three-Letter Genetic Code	120
Experiments with Synthetic mRNAs and Trinucleotides Break the Genetic Code	122
Folded Structure of tRNA Is Integral to Its Function	124
Aminoacyl-tRNA Synthetases Activate tRNA	126
Each tRNA Molecule Is Recognized by a Specific Aminoacyl-tRNA Synthetase	128
Ribosomes Are Protein-Synthesizing Machines	128
<i>The Steps in Protein Synthesis</i>	133
AUG Is the Initiation Signal in mRNA	133

Initiation Factors, tRNA, mRNA, and the Small Ribosomal Subunit Form an Initiation Complex	133	<i>Sorting Cells and Their Parts</i>	161
Ribosomes Provide Three tRNA-Binding (A, P, and E) during Protein Elongation	136	Flow Cytometry Is Used to Sort Cells Optically	161
Polypeptide Termination Requires Protein Factors That Specifically Recognize UAA, UAG, and UGA	138	Fractionation Methods Isolate Subcellular Structures	161
<i>Summary</i>	138	<i>The Biomembranes and Organelles of the Eukaryotic Cell</i>	166
<i>Review Questions</i>	139	The Plasma Membrane Has Many Varied and Essential Roles	167
<i>References</i>	139	The Eukaryotic Nucleus Is Bounded by a Double Membrane	167
5 CELL ORGANIZATION, SUBCELLULAR STRUCTURE, AND CELL DIVISION	141	The Nucleus Contains the Nucleolus, a Fibrous Matrix, and DNA-Protein Complexes	168
<i>Prokaryotic and Eukaryotic Cells</i>	142	The Cytosol Contains Many Cytoskeletal Elements and Particles	168
Prokaryotes Have a Relatively Simple Structure	142	The Endoplasmic Reticulum Is an Interconnected Network of Internal Membranes	170
Eukaryotic Cells Have Complex Systems of Internal Membranes and Fibers	143	Golgi Vesicles Process Secretory and Membrane Proteins and Sort Them to Their Proper Destinations	172
Prokaryotes and Eukaryotes Contain Similar Macromolecules	143	Lysosomes Are Acidic Organelles That Contain a Battery of Degradative Enzymes	173
Prokaryotes and Eukaryotes Differ in the Amount of DNA per Cell	144	Vacuoles in Plant Cells Store Small Molecules and Enable the Cell to Elongate Rapidly	174
The Organization of DNA Differs in Prokaryotic and Eukaryotic Cells	147	Peroxisomes Produce and Degrade Hydrogen Peroxide	174
<i>Light Microscopy and Cell Architecture</i>	148	The Mitochondrion Is the Principal Site of ATP Production in Aerobic Cells	174
The Resolution of Standard Light (Bright-Field) Microscopy Is Limited to about 0.2 μm	148	Chloroplasts Are the Sites of Photosynthesis	175
Immunofluorescence Microscopy Reveals Specific Proteins and Organelles within a Cell	150	Cilia and Flagella Are Motile Extensions of the Eukaryotic Plasma Membrane	175
Fluorescence Microscopy Can also Measure the Local Concentration of Ca^{2+} Ions and the Intracellular pH	153	The Plasma Membrane Binds to the Cell Wall or the Extracellular Matrix	176
The Confocal Scanning Microscope Produces Vastly Improved Fluorescent Images	154	<i>Cell Division and the Cell Cycle</i>	177
Phase-Contrast and Nomarski Interference Microscopy Visualize Unstained Living Cells	156	In Prokaryotes DNA Replication Is Followed Immediately by Cell Division	177
<i>Electron Microscopy</i>	158	In Eukaryotic Cells DNA Synthesis and Cell Division Occur in Special Phases of the Cell Cycle	177
Transmission Electron Microscopy Depends on the Differential Scattering of a Beam of Electrons	158	Mitosis Is the Complex Process That Apportions the New Chromosomes Equally between Daughter Cells	178
Minute Details Can Be Visualized on Viruses and Subcellular Particles	159	Plant Cells Show Some Variations in Mitosis	180
Scanning Electron Microscopy Visualizes Details on the Surface of Cells or Particles	161		

Yeast Cells Have a Simplified Division	181	Six Animal-Virus Classes Are Recognized Based on Genome Composition and Pathway of mRNA Synthesis	208
Meiosis Is the Form of Cell Division in Which Haploid Germ Cells Are Produced from Diploid Cells	181	<i>Radioisotopes: Indispensable Tools for Following Biological Activity</i>	212
<i>Summary</i>	185	Several Factors Determine the Choice of a Radiolabel	213
<i>Review Questions</i>	186	Radiolabeled Molecules Can Be Detected by Visual and Quantitative Methods	214
<i>References</i>	187	Intracellular Precursor Pools Affect the Outcome of Pulse-Chase Experiments	215
6 MANIPULATING CELLS AND VIRUSES IN CULTURE	189	Synthesis Time of Macromolecules Can Be Estimated from Labeling Experiments	216
<i>Growth of Microorganisms in Culture</i>	190	The Dintzis Experiment Demonstrated That Proteins Are Synthesized from the Amino End to the Carboxyl End	216
Many Microorganisms Can Be Grown in Minimal Medium	190	<i>Summary</i>	218
Mutant Strains of Bacteria and Yeast Can Be Isolated by Replica Plating	190	<i>Review Questions</i>	219
<i>Growth of Animal Cells in Culture</i>	193	<i>References</i>	220
Rich Media Are Required for Culture of Animal Cells	193	7 RECOMBINANT DNA TECHNOLOGY	221
Most Cultured Animal Cells Only Grow on Special Solid Surfaces	193	<i>DNA Cloning with Plasmid Vectors</i>	222
Primary Cell Cultures Have a Finite Life Span	194	Plasmids Are Extrachromosomal Self-Replicating DNA Molecules	222
Transformed Cells Can Grow Indefinitely in Culture	196	<i>E. coli</i> Plasmids Can Be Engineered for Use as Cloning Vectors	222
<i>The Use of Hybrid Cells in Genetic Analysis of Animal Cells and Production of Monoclonal Antibody</i>	198	Plasmid Cloning Permits Isolation of DNA Fragments from Complex Mixtures	224
Genes Can Be Mapped to Specific Chromosomes with Interspecific Hybrid Cells	199	<i>Production of Recombinant Plasmids</i>	225
Mutants in Purine- and Pyrimidine-Salvage Pathways Are Good Selective Markers	200	Restriction Enzymes Cut DNA Molecules at Specific Sequences	225
Hybridomas Are Fused Lymphoid Cells That Make Monoclonal Antibodies	201	Many Restriction Enzymes Generate DNA Fragments with "Sticky" Ends	226
<i>Viruses: Structure and Function</i>	202	DNA Ligase Covalently Links Restriction Fragments	227
Viral Capsids Are Regular Arrays of One or a Few Types of Proteins	202	Restriction Fragments Are Readily Inserted into Plasmid Vectors	228
Most Viral Host Ranges Are Narrow	204	<i>Formation and Uses of Synthetic DNA</i>	228
Viruses Can Be Cloned and Counted in Plaque Assays	205	<i>λ-Phage Cloning Vectors and Construction of a Genomic Library</i>	229
Viral Growth Cycles Are Classified as Lytic or Lysogenic	205	Bacteriophage λ Can Be Modified for Use as a Cloning Vector and Assembled In Vitro	230
Four Types of Bacterial Viruses Are Widely Used in Biochemical and Genetic Research	206	Nearly Complete Genomic Libraries of Higher Organisms Can Be Prepared by λ Cloning	231
Experiments with Plant Viruses Proved That RNA Can Act as a Genetic Material	208	Larger DNA Fragments Can Be Cloned in Cosmids and Other Vectors	233

<i>Construction of a cDNA Library</i>	234	From Protein to Gene and from Gene to Protein with Recombinant DNA Technology	256
cDNAs Are Produced by Copying Isolated mRNAs with Reverse Transcriptase	235	Summary	257
cDNAs Can Be Enzymatically Converted to Double-Stranded DNA and Cloned	235	Review Questions	258
<i>Identification of Specific Clones in a Genomic or cDNA Library</i>	236	References	260
Membrane Hybridization Can Be Used to Screen a Library	237	8 GENETIC ANALYSIS IN CELL BIOLOGY	263
Certain cDNAs and Synthetic Oligonucleotides Are Used as Probes	238	<i>The Isolation and Characterization of Mutants</i>	264
Expression Cloning Identifies Specific Clones Based on Properties of the Encoded Proteins	240	Mutations Are Recessive or Dominant	264
<i>Analyzing and Sequencing Cloned DNA</i>	240	Mutations Involve Large or Small DNA Alterations	266
Cleavage with an Appropriate Restriction Enzyme Separates a Cloned DNA from Its Vector	240	Mutations Occur Spontaneously and Can Be Induced	267
Gel Electrophoresis Resolves DNA Fragments of Different Size	242	Some Human Diseases Are Caused by Spontaneous Mutations	268
Multiple Restriction Sites Can Be Mapped on a Cloned DNA Fragment	243	Various Genetic Screens Are Used to Identify Mutants	269
Pulsed-Field Gel Electrophoresis Separates Large DNA Molecules	244	Complementation Analysis Determines If Different Mutations Are in the Same Gene	274
Nucleotide Sequencing of Cloned DNA Fragments Paves the Way for Sequencing Entire Genomes	245	Metabolic and Other Pathways Can Be Genetically Dissected	274
<i>Analysis of Specific Nucleic Acids in Complex Mixtures</i>	248	Suppressor Mutations Can Identify Genes Encoding Interacting Proteins	274
Southern Blotting Detects Specific DNA Fragments	248	<i>Genetic Mapping of Mutations</i>	277
Northern Blotting Detects Specific RNAs	249	Segregation Patterns Indicate Whether Mutations Are on the Same or Different Chromosomes	277
Nuclease Protection Is Used to Quantitate Specific RNAs and Map the DNA Regions Encoding Them	249	Chromosomal Mapping Locates Mutations on Particular Chromosomes	277
Transcription Start Sites Can Be Mapped by S1 Protection and Primer Extension	251	Recombinational Analysis Can Map Genes Relative to Each Other on a Chromosome	279
<i>Designing Expression Systems That Produce Abundant Amounts of Specific Proteins</i>	252	DNA Polymorphisms Are Used to Map Human Mutations	279
Full-Length Proteins Encoded by Cloned Genes Can Be Produced in <i>E. coli</i> Expression Systems	252	Some Chromosomal Abnormalities Can Be Mapped by Banding Analysis	281
Proteins with Post-Translational Modifications Can Be Produced in Eukaryotic Expression Systems	253	<i>Molecular Cloning of Genes Defined by Mutations</i>	284
Proteins Encoded by Cloned Genes and cDNAs Can Be Expressed In Vitro	253	Physical Maps of Human Chromosomes Y and 21 Have Been Constructed by Screening YAC Clones for Sequence-Tagged Sites	284
The Polymerase Chain Reaction: An Alternative to Cloning	254	Physical and Genetic Maps Can Be Correlated	284
		Physical Mapping of Selected Genomic Regions is the First Step in Cloning Many Genes	285

Mutation-Defined Genes Are Identified in Candidate Regions by Comparing Mutant and Wild-Type DNA Structure and mRNA Expression	287	Pseudogenes Are Duplicated Genes That Have Become Nonfunctional	314
Protein Structure Is Deduced from cDNA Sequences	289	rRNAs, tRNAs, and Histones Are Encoded by Tandemly Repeated Genes	315
<i>Gene Replacement and Transgenic Animals</i>	291	<i>Discovery of Repetitious DNA Fractions</i>	316
Specific Sites in Cloned Genes Can Be Altered In Vitro	291	Repeated DNA Reassociates More Rapidly Than Nonrepeated DNA	316
DNA Can Be Transferred into Eukaryotic Cells in Various Ways	292	Reassociation Experiments Reveal Three Major Classes of Eukaryotic DNA	317
Normal Genes Can Be Replaced with Mutant Alleles in Yeast and Mice	292	<i>Simple-Sequence DNA</i>	318
Foreign Genes Can Be Introduced into Plants and Animals	296	Higher Eukaryotes Contain Several Types of Simple-Sequence DNA	318
Gene Therapy Involves Use of Transgenes to Treat Genetic Diseases	299	Most Simple-Sequence DNA Is Located in Specific Chromosomal Regions	319
Summary	300	Differences in Lengths of Simple-Sequence Tandem Arrays Permit DNA Fingerprinting	319
Review Questions	301	<i>Immediate-Repeat DNA and Mobile DNA Elements</i>	320
References	302	Movement of Bacterial Mobile Elements Is Mediated by DNA	323
► Part II		Movement of Some Eukaryotic Mobile Elements Is Mediated by DNA	326
Control of Cellular Activity by the Nucleus	304	Two Major Categories of Retrotransposons Are Found in Eukaryotic Cells	328
9 THE MOLECULAR ANATOMY OF GENES AND CHROMOSOMES	307	Most Mobile Elements in Yeast Are Viral Retrotransposons	328
<i>Molecular Definition of a Gene</i>	308	<i>Copia</i> Retrotransposons Are the Most Common <i>Drosophila</i> Mobile Elements	333
Most Prokaryotic Genes Lack Introns and Those Encoding Related Proteins Form Operons, Which Produce Polycistronic mRNA	308	LINES and SINES, the Most Abundant Mobile Elements in Mammals, Are Nonviral Retrotransposons	334
Most Eukaryotic Transcription Units Produce Monocistronic mRNAs	308	Retrotransposed Copies of Cellular RNAs Are Present in Eukaryotic Chromosomes	336
Simple Eukaryotic Transcription Units Give Rise to One mRNA	309	<i>Functional Rearrangements in Chromosomal DNA</i>	338
Complex Eukaryotic Transcription Units Give Rise to Alternative mRNAs	309	Salmonella Flagellar Antigens Can Switch through Inversion of a Transcription-Control Region	338
Some Genes Do Not Encode Protein	310	Yeast Mating Types Can Switch by Gene Conversion	339
<i>Organization of Genes on Chromosomes</i>	311	Trypanosome Surface Antigens Undergo Frequent Changes via Gene Conversion	341
Genomes of Higher Eukaryotes Contain Much "Nonfunctional" DNA	311	Generalized DNA Amplification Produces Polytene Chromosomes	343
Cellular DNA Content Does Not Correlate with Phylogeny	312	Localized DNA Amplification of rRNA and Other Genes Occurs in Some Eukaryotic Cells	343
About a Quarter to Half of All Eukaryotic Protein-Coding Genes Are Solitary	313		
Gene Families Are Formed by Gene Duplication and Encode Homologous Proteins	313		

Vertebrate Genes Encoding Antibodies Are Assembled from Gene Segments by Controlled Deletion of Intervening DNA	344	DnaA Protein Initiates Replication in <i>E. coli</i>	372
<i>Organizing Cellular DNA into Chromosomes</i>	344	DnaB Is a Helicase That Unwinds Duplex DNA	372
Prokaryotic Chromosomes Contain Highly Compacted Circular DNA Molecules with a Single Replication Origin	344	Primase Catalyzes Formation of RNA Primers for DNA Synthesis	374
Eukaryotic Nuclear DNA Associates with Highly Conserved Histone Proteins to Form Chromatin	346	At a Growing Fork One Strand Is Synthesized Discontinuously from Multiple Primers	374
Chromatin Exists in Extended and Condensed Forms	347	DNA Polymerase III Synthesizes Both the Leading and Lagging Strands	375
<i>Morphology and Functional Characteristics of Eukaryotic Chromosomes</i>	349	The Leading and Lagging Strands Are Synthesized Concurrently	376
Chromosome Number and Shape Are Species Specific	349	Interaction of Tus Protein with Termination Sites Stops DNA Replication	378
Nonhistone Proteins Provide a Structural Scaffold for Long DNA Loops in Chromosomes	349	<i>Eukaryotic DNA Replication</i>	378
Chromatin Contains Small Amounts of DNA-Binding Proteins in Addition to Histones and Scaffold Proteins	354	Eukaryotic Proteins That Replicate SV40 DNA In Vitro Exhibit Similarities and Differences with <i>E. coli</i> Replication Proteins	378
Each Chromosome Contains One Linear DNA Molecule	354	Telomerase Prevents Progressive Shortening of Lagging Strands during DNA Replication	380
Stained Chromosomes Have Characteristic Banding Patterns	354	<i>Role of Topoisomerases in DNA Replication</i>	381
Heterochromatin Consists of Chromosome Regions That Do Not Uncoil	355	Type I Topoisomerases Relax DNA by Nicking and Closing One Strand of Duplex DNA	381
Three Functional Elements Are Required for Replication and Stable Inheritance of Chromosomes	355	Type II Topoisomerases Change DNA Topology by Breaking and Rejoining Double-Stranded DNA	382
Yeast Artificial Chromosomes Can Be Used to Clone Megabase DNA Fragments	359	Replicated Circular DNA Molecules Are Decatenated by Type II Topoisomerases	383
<i>Summary</i>	359	Linear Daughter Chromatids Also Are Separated by Type II Topoisomerases	383
<i>Review Questions</i>	360	<i>Repair of DNA</i>	385
<i>References</i>	361	Proofreading by DNA Polymerase Corrects Copying Errors	385
10 DNA REPLICATION, REPAIR, AND RECOMBINATION	365	Environmental DNA Damage Can Be Repaired by Several Mechanisms	386
<i>General Features of Chromosomal Replication</i>	366	Excision Repair in <i>E. coli</i> Removes Bulky Chemical Adducts Caused by UV Light and Carcinogens	387
DNA Replication Is Semiconservative	366	Genetic Studies in Eukaryotes Have Identified DNA-Repair Genes	388
Most DNA Replication Is Bidirectional	366	<i>Recombination between Homologous DNA Sites</i>	389
DNA Replication Begins at Specific Chromosomal Sites	370		
<i>DNA Replication in E. coli</i>	372		

Holliday Recombination Model Is Supported by Observation of Predicted Intermediate Structures	389	Binding of <i>lac</i> Repressor to the <i>lac</i> Operator Blocks Transcription Initiation by RNA Polymerase	416
Recombination in <i>E. coli</i> Occurs by Three Similar Pathways That All Require RecA Protein	391	Most Bacterial Repressors Are Homodimers Containing α Helices That Insert into Adjacent Major Grooves of Operator DNA	418
Site-Specific Integration of λ Phage Mimics a Homologous Recombination Event	395	Positive Control of the <i>lac</i> Operon Is Exerted by cAMP-CAP	421
Studies in Yeast Are Providing Insights into Meiotic Recombination	396	Cooperative Binding of cAMP-CAP and RNA Polymerase to <i>lac</i> Control Region Activates Transcription	423
Gene Conversion Can Occur near the Crossover Point during Reciprocal Recombination	396	Control of Transcription from All Bacterial Promoters Involves Similar But Distinct Mechanisms	423
<i>Summary</i>	400	Transcription from Some Promoters Is Initiated by Alternative Sigma (σ) Factors	424
<i>Review Questions</i>	401	RNA Polymerase Containing σ^{54} Is Regulated by Proteins That Bind at Enhancer Sites Distant from the Transcription Initiation Site	425
<i>References</i>	402	<i>Eukaryotic Gene Control: Purposes and General Principles</i>	426
11 REGULATION OF TRANSCRIPTION INITIATION	405	Most Genes in Higher Eukaryotes Are Regulated by Controlling Their Transcription	427
<i>Early Genetic Analysis of lac-Operon Control in E. coli</i>	406	DNA Regulatory Sites Often Are Located Many Kilobases from Eukaryotic Transcription Start Sites	428
Enzymes Encoded at <i>lac</i> Operon Can Be Induced and Repressed	407	<i>Structure and Function of Eukaryotic Nuclear RNA Polymerases</i>	430
Mutations in <i>lacI</i> Cause Constitutive Expression of the <i>lac</i> Operon	407	Three Eukaryotic Polymerases Catalyze Formation of Different RNAs	430
Operator Constitutive Mutations Identify Binding Site for <i>lac</i> Repressor	408	Eukaryotic RNA Polymerases Have Complex Subunit Structure	430
Mutations in Promoter Prevent Expression of <i>lac</i> Operon	409	The Largest Subunit in RNA Polymerase II Has an Essential Carboxyl-Terminal Repeat	432
Regulation of <i>lac</i> Operon Depends on Cis-Acting DNA Sequences and Trans-Acting Proteins	409	RNA Polymerase II Initiates Transcription at DNA Sequences Corresponding to the 5' Cap of mRNAs	433
<i>Molecular Mechanisms of Transcription Initiation in Bacteria</i>	411	<i>Cis-Acting Regulatory Sequences in Eukaryotic DNA</i>	435
Induction of the <i>lac</i> Operon Leads to Increased Synthesis of <i>lac</i> mRNA	411	The TATA Box Positions RNA Polymerase II for Transcription Initiation in Many Genes	435
<i>E. coli</i> RNA Polymerase Generally Initiates Transcription at a Unique Position on DNA Template	411	Promoter-Proximal Elements Help Regulate Many Eukaryotic Genes	436
Protein-Binding Sites in <i>lac</i> Control Region Have Been Identified by Sequence Comparison and Footprinting Experiments	412		
RNA Polymerase Interacts with Specific Promoter Sequences	413		
σ^{70} Subunit of RNA Polymerase Functions as an Initiation Factor	414		
α -Subunit Dimer Bends to rRNA Promoters in -40 to -60 Region	416		

Transcription by RNA Polymerase II Often Is Stimulated by Distant Enhancer Sites	439
Most Eukaryotic Genes Are Regulated by Multiple Transcription-Control Elements	441
<i>Eukaryotic Transcription Factors</i>	442
Biochemical and Genetic Techniques Have Been Used to Identify Transcription Factors	442
Many Transcription Factors Are Modular Proteins Composed of Distinct Functional Domains	445
A Variety of Protein Structures Form the DNA-Binding Domains of Eukaryotic Transcription Factors	447
Heterodimeric Transcription Factors Increase Regulatory Diversity	452
A Diverse Group of Amino Acid Sequences Are Found in Activation Domains	452
<i>RNA Polymerase II Transcription-Initiation Complex</i>	453
Transcription-Initiation Complex Contains Many Proteins Assembled in a Specific Order	453
Transcription Activators Influence Assembly of Initiation Complex	456
Some Eukaryotic Regulatory Proteins Function as Repressors	456
<i>Regulating the Activity of Eukaryotic Transcription Factors</i>	456
Expression of Many Transcription Factors Is Restricted to Specific Cell Types	457
Some Transcription Factors Are Controlled by Lipid-Soluble Hormones	458
Polypeptide Hormones Signal Phosphorylation of Some Transcription Factors	462
<i>Influence of Chromatin Structure on Eukaryotic Transcription Initiation</i>	464
Association of Genes with Heterochromatin Can Lead to Their Repression	464
Transcriptionally Inactive DNA Regions Are Resistant to DNase I	466
Cytosine Methylation Is Associated with Inactive Genes in Vertebrates	468
<i>Transcription by RNA Polymerase I</i>	468
Pre-rRNA DNA from All Eukaryotes Is Similar	468

Only Essential Function of Polymerase I Is to Produce pre-rRNA	468
Species-Specific Initiation Factors Are Utilized by RNA Polymerase I	469
<i>Transcription by RNA Polymerase III</i>	470
tRNA Genes Bind Two Multisubunit Initiation Factors	471
5S-rRNA Gene Binds Three Initiation Factors	471
TBP Is Required for Transcription Initiation by All Three Eukaryotic RNA Polymerases	472
<i>Other Transcription Systems</i>	473
T7 and Related Bacteriophages Express Monomeric, Largely Unregulated RNA Polymerases	473
Mitochondrial DNA Transcription Exhibits Features Typical of Bacteriophage, Bacteria, and the Eukaryotic Nucleus	473
Chloroplasts Contain an RNA Polymerase Homologous to the <i>E. coli</i> Enzyme	474
Archaeobacteria Have an RNA Polymerase and Putative General Transcription Factors Similar to Those of the Eukaryotic Nucleus	475
<i>Summary</i>	475
<i>Review Questions</i>	478
<i>References</i>	480
12 TRANSCRIPTION TERMINATION, RNA PROCESSING, AND POSTTRANSCRIPTIONAL CONTROL	485
<i>Transcription Termination in Prokaryotes</i>	486
Rho-Independent Termination Sites Have Characteristic Sequences	486
Attenuation Can Cause Premature Chain Termination	486
Transcription Termination at Some Sites Requires Rho Factor	488
Antitermination Can Prevent Premature Chain Termination	490
<i>Eukaryotic Transcription-Termination Control</i>	491
HIV Tat Protein Is an RNA-Binding Antitermination Protein	492
Premature Termination of c-myc Transcription Occurs in Nondividing Cells	492

RNA Polymerase II Pauses during Transcription of <i>Drosophila</i> Heat-Shock Genes under Normal Conditions	492
<i>mRNA Processing in Higher Eukaryotes</i>	494
mRNA Precursors Are Associated with Abundant Nuclear Proteins Containing Conserved RNA-Binding Domains	494
HnRNP Proteins May Have Multiple Functions	496
Pre-mRNAs Are Cleaved at Specific 3' Sites and Rapidly Polyadenylated in Animal Cells	498
RNA-DNA Hybridization Reveals Spliced Out Introns	498
Splice Sites in Pre-mRNAs Exhibit Short, Conserved Sequences	500
Excision of Introns and Splicing of Exons in Pre-mRNA Occur via Two Transesterification Reactions	501
Small Nuclear Ribonucleoprotein Particles Assist in Splicing	501
Portions of Two Different RNAs Are Trans-Spliced in Some Organisms	508
Self-Splicing Group II Introns Provide Clues to Evolution of snRNPs	508
Regulation of RNA Processing Controls Expression of Some Proteins	509
<i>Subnuclear Organization and Transport of Nuclear mRNA to the Cytoplasm</i>	513
Most Transcription and RNA Processing Occurs in a Limited Number of Domains in Mammalian Cell Nuclei	513
Messenger Ribonucleoproteins (mRNPs) Exit the Nucleus through Nuclear Pore Complexes	515
5'-Cap Structures Are Recognized by the Nuclear Transport Mechanism	516
Pre-mRNAs Associated with Spliceosomes Are Not Transported to the Cytoplasm	518
mRNA Remains Associated with Protein in the Nucleus and Cytoplasm	518
Transport of mRNPs to the Cytoplasm Is Regulated by Some Viral Proteins	518
<i>Regulation of mRNA Cytoplasmic Localization, Stability, and Translation</i>	520
Some mRNAs Are Directed to Specific Cytoplasmic Sites by Sequences in Their 3' Untranslated Regions	521

Stability of Cytoplasmic mRNAs Varies Widely	522
Degradation Rate of Some Eukaryotic mRNAs Is Regulated	524
Translation of a Few mRNAs Is Regulated by Specific RNA-Binding Proteins	525
Antisense RNA Regulates Translation of Transposase mRNA in Bacteria	527
<i>Processing of rRNAs and tRNAs</i>	528
Pre-rRNA Binds Proteins, Then Is Cleaved and Methylated in the Nucleolus	528
Pre-rRNA Genes Act as Nucleolar Organizers	530
Self-Splicing Group I Introns in Some Pre-rRNAs Were the First Examples of Catalytic RNA	530
Processing of Pre-tRNA Involves Cleavage, Modification of Bases, and Sometimes a Unique Type of Splicing	532
<i>RNA Editing</i>	535
RNA Editing Regulates Protein Function in Mammals	535
RNA Editing in Trypanosome Mitochondria Drastically Alters mRNA Sequences	536
<i>Summary</i>	537
<i>Review Questions</i>	539
<i>References</i>	540
13 GENE CONTROL IN DEVELOPMENT	543
<i>Lysogeny or Lysis in λ-Phage Infection of E. coli</i>	544
Phage Mutants Unable to Undergo Lysogeny Fall into Three Main Complementation Groups	544
cI Protein Maintains Lysogeny by Repressing and Activating Transcription from Different Promoters	545
cII and cIII Proteins Are Critical to Establishment of Lysogeny	547
Induction of Lytic Cycle Requires Derepression of <i>cro</i> Gene	548
Cro and cI Have Similar DNA-Binding Domains But Interact Differently with λ Operators	549
Choice between Lysis and Lysogeny Involves Regulatory Mechanisms Found in More Complex Developmental Systems	550

<i>Cell-Type Specification and Mating-Type Conversion in Yeast</i>	550	Specification of the Anterior Region Depends on the Maternal <i>bicoid</i> Gene	568
Cell Type-Specific Gene Expression in Yeast Is Regulated by Numerous DNA-Binding Proteins	551	Protein Encoded by Maternal <i>nanos</i> Gene Represses Translation of <i>hunchback</i> mRNA in Posterior Region	572
Mating-Type Conversion Is Determined by Transcriptional Regulation of the <i>HO</i> Locus	554	Hunchback Protein Regulates Expression of Several Gap Genes along the Anteroposterior Axis	573
Silencer Elements Repress Expression at <i>HML</i> and <i>HMR</i>	556	Initial Patterning along Dorsoventral Axis Depends on Dorsal Protein	573
<i>Myogenesis in Mammals</i>	556	Maternal Terminal Genes Regulate Early Patterning of the Extreme Anterior and Posterior Ends of the Embryo	575
Embryonic Somites Give Rise to Myoblasts, the Precursors of Skeletal Muscle Cells	557	Subsequent Anteroposterior Patterning Is Regulated by a Cascade of Transcription Factors Expressed from Three Groups of Zygotic Genes	576
Certain Fibroblasts Can Be Converted into Muscle (Myotubes)	558	Selector Genes Control Regional Identity and Development of Adult Structures	581
The <i>myoD</i> Gene Can Trigger Muscle Development	558	<i>Mammalian Homologs of Drosophila ANT-C and BX-C</i>	584
Myogenic Proteins Are HLH Transcription Factors	560	Mammalian Hox Genes Are Colinear Homologs of <i>Drosophila</i> HOM-C Genes	584
Myogenic Gene Activation Depends on Specific Amino Acids in MyoD	560	Mutations in Hox Genes Result in Homeotic Transformations in the Developing Mouse	585
Id Protein Inhibits Activity of MyoD	560	<i>Summary</i>	587
Knockout Experiments Have Demonstrated Role of Myogenic Proteins In Vivo	560	<i>Review Questions</i>	588
<i>Neurogenesis in Drosophila and Mice</i>	561	<i>References</i>	590
<i>Drosophila</i> Sensory Hairs Arise from Proneural Clusters, Which Express Achaete and Scute Proteins	562	► Part III	
A Single Sensory Organ Precursor Develops from a Proneural Cluster in <i>Drosophila</i>	562	Building and Fueling the Cell	592
<i>Drosophila</i> Neurogenesis and Mammalian Myogenesis May Occur via Analogous Pathways Involving HLH Proteins	562	14 MEMBRANE STRUCTURE: THE PLASMA MEMBRANE	595
MASH1, a Homolog of Achaete and Scute Proteins, Regulates Neurogenesis in the Mouse	562	<i>General Architecture of Lipid Membranes</i>	596
Specification of Other Cell Types Is Controlled by Different Classes of Transcription Factors	565	All Membranes Contain Phospholipids and Proteins	596
<i>Regional Specification during Drosophila Embryogenesis</i>	565	The Phospholipid Bilayer Is the Basic Structural Unit of Biological Membranes	599
<i>Drosophila</i> Has Two Life Forms	565	Phospholipid Bilayers Exhibit Two-Dimensional Fluidity That Depends on Temperature and Composition	599
Patterning Information Is Generated during Oogenesis and Early Embryogenesis	565	Several Types of Evidence Point to the Universality of the Phospholipid Bilayer	602
Morphogens Regulate Development as a Function of Their Concentration	568	Phospholipid Bilayers and Biological Membranes Form Closed Compartments	603
Four Maternal Gene Systems Regulate Regionalization in the Early Embryo	568		

<i>Membrane Proteins</i>	604	<i>Summary</i>	628
Proteins Interact with Membranes in Different Ways	604	<i>Review Questions</i>	629
Transmembrane Proteins Contain Long Segments of Hydrophobic Amino Acids Embedded in the Phospholipid Bilayer	604	<i>References</i>	631
Proteins Can Be Removed from Membranes by Detergents or High-Salt Solutions	604	15 TRANSPORT ACROSS CELL MEMBRANES	633
Many Integral Proteins Contain Multiple Transmembrane α Helices	606	<i>Major Types of Membrane Transport Proteins</i>	634
Porins Are Transmembrane Proteins Composed of Multiple β Strands	609	<i>Diffusion of Small Molecules across Pure Phospholipid Bilayers</i>	635
Some Integral Proteins Are Bound to the Membrane by Covalently Attached Hydrocarbon Chains	610	<i>Uniporter-Catalyzed Transport of Specific Molecules</i>	636
Interfacial Catalysis Involves Soluble Enzymes Acting at Membrane Surfaces	612	Three Main Features Distinguish Uniport Transport from Passive Diffusion	637
The Orientation of Proteins in Membranes Can Be Experimentally Determined	612	Two General Models Have Been Proposed for Transporters	638
<i>Glycoproteins and Glycolipids</i>	612	Glucose Entry into Erythrocytes Is Mediated by a Uniporter	638
Many Integral Proteins Contain Sugars Covalently Linked to Their Exoplasmic Domains	613	<i>Ion Channels, Intracellular Ion Environment, and Membrane Electric Potential</i>	640
Many Glycolipids Are Located in the Cell-Surface Membrane	614	Ionic Gradients and Electric Potential Are Maintained across the Plasma Membrane	640
<i>Principles of Membrane Organization</i>	615	Certain K^+ Channels Generate the Membrane Electric Potential	641
All Integral Proteins Bind Asymmetrically to the Lipid Bilayer	615	Ion Concentration Gradients and Electric Potential Drive the Movement of Ions across Biological Membranes	643
The Two Membrane Leaflets Have Different Lipid Compositions	616	<i>Active Ion Transport and ATP Hydrolysis</i>	644
Freeze-Fracture and Deep-Etching Techniques Reveal the Two Membrane Faces in Electron Microscopy	616	Ion Pumps Can Be Grouped into Three Classes (P, V, and F)	644
Most Integral Proteins and Lipids Are Laterally Mobile in Biomembranes	616	Ca^{2+} ATPase Maintains Low Cytosolic Ca^{2+} Concentration	645
Some Membrane Proteins Interact with Cytoskeletal Components	616	Coupling of ATP Hydrolysis and Ion Pumping by P-Class ATPases Involves an Ordered Kinetic Mechanism	647
Erythrocytes Have an Unusual Plasma Membrane That Is Tightly Anchored to the Cytoskeleton	620	Na^+/K^+ ATPase Maintains the Intracellular Concentrations of Na^+ and K^+ in Animal Cells	648
<i>Specializations of the Plasma Membrane</i>	623	V-Class H^+ ATPases Pump Protons across Lysosomal and Vacuolar Membranes	650
Plasma Membranes of Polarized Cells Are Divided into Two Regions with Different Compositions and Functions	623	The Multidrug-Transport Protein is an ATP-Powered Pump and ATP-Dependent Cl^- Channel	651
Tight Junctions Seal Off Body Cavities and Restrict Diffusion of Membrane Components	625	<i>Cotransport Catalyzed by Symporters and Antiporters</i>	652
Desmosomes and Gap Junctions Interconnect Cells and Control Passage of Molecules between Them	628	Na^+ -Linked Symporters Import Amino Acids and Glucose into Many Animal Cells	652

Na ⁺ -Linked Antiporter Exports Ca ²⁺ from Cells	654	Phospholipids Move from the ER to Other Cellular Membranes	673
Band 3 Is an Anion Antiporter That Exchanges Cl ⁻ and HCO ₃ ⁻ across the Erythrocyte Membrane	655	<i>Sites of Synthesis of Organelle and Membrane Proteins</i>	674
H ⁺ /K ⁺ ATPase and Anion Antiporter Combine to Acidify the Stomach Contents While Maintaining Cytosolic pH Near Neutrality	657	All Nuclear-Encoded Proteins Are Made by the Same Cytosolic Ribosomes	675
Several Symporters and Antiporters Regulate Cytosolic pH	658	Membrane-Attached and Membrane-Unattached Ribosomes Synthesize Different Proteins	676
<i>Plant and Prokaryotic Membrane Transport Proteins</i>	659	<i>Overall Pathway for Synthesis of Secretory, Lysosomal, and Membrane Proteins</i>	676
H ⁺ Pumps and Anion Channels Establish Electric Potential and a Steep H ⁺ Concentration Gradient across the Plant-Vacuole Membrane	659	Newly Made Secretory Proteins Are Localized to the Lumen of the Rough ER	676
Proton Antiporters Enable Plant Vacuoles to Accumulate Metabolites and Ions	659	Many Organelles Participate in Protein Secretion	677
The Potential across the Plasma Membrane of Plant, Bacterial, and Fungal Cells Is Generated by Proton Pumping	660	All Secretory Proteins Move from the Rough ER to Golgi Vesicles to Secretory Vesicles	677
Proton Symporters Import Many Nutrients into Bacteria	660	The Steps in Protein Secretion Can Be Studied Genetically	678
<i>Osmosis, Water Channels, and the Regulation of Cell Volume</i>	661	Plasma Membrane Glycoproteins Follow the Same Maturation Pathway as Continuously Secreted Proteins	680
Osmotic Pressure Causes Water Movement across Membranes	662	<i>The Transport of Secretory and Membrane Proteins into or across the ER Membrane</i>	681
Water Channels Are Necessary for Bulk Osmotic Flow of Water across Membranes	663	A Signal Sequence on Nascent Secretory Proteins Targets Them to the ER and Is then Cleaved Off	682
Some Animal Cells Regulate Their Volume by Modulating Their Internal Osmotic Strength	663	Several Receptor Proteins Mediate the Interaction of Signal Sequences with the ER Membrane	683
Changes in Intracellular Osmotic Pressure Cause Leaf Stomata to Open	664	Polypeptides Cross the ER Membrane in Protein-Lined Channels	686
<i>Summary</i>	665	ATP-Hydrolyzing Chaperone Proteins Prevent Protein Misfolding and Are Essential for Translocation of Secretory Proteins into the ER	687
<i>Review Questions</i>	666	Topogenic Sequences in Integral Membrane Proteins Allow Them to Achieve Their Proper Orientation in the ER Membrane	688
<i>References</i>	667	<i>Post-Translational Modifications of Secretory and Membrane Proteins in the Rough ER</i>	694
16 SYNTHESIS AND SORTING OF PLASMA MEMBRANE, SECRETORY, AND LYSOSOMAL PROTEINS	669	Disulfide Bonds Are Formed in the ER Lumen Soon after Synthesis	694
<i>The Synthesis of Membrane Lipids</i>	671	Chaperone Proteins Facilitate the Folding of Newly Made Proteins	695
Phospholipids Are Synthesized in Association with Membranes	671		
Special Membrane Proteins Allow Phospholipids to Equilibrate in Both Membrane Leaflets	671		

The Formation of Oligomeric Proteins Occurs in the ER	696	A Type of Coated Vesicle without Clathrin Mediates ER-to-Golgi Transport and Transport within the Golgi	713
<i>Quality Control in the ER</i>	697	The Steps in Vesicular Transport Can Be Studied Biochemically and Genetically	714
Only Properly Folded Proteins Are Transported from the Rough ER to the Golgi Complex	697	A Family of Small GTP-Binding Proteins May Target Transport Vesicles to Their Correct Destinations	716
Unassembled or Misfolded Proteins Are Often Degraded within the ER	698	<i>Golgi and Post-Golgi Sorting and Processing of Membrane and Secretory Proteins</i>	718
ER-Specific Proteins Are Retained in the Rough ER or Are Returned There from the Cis-Golgi	698	Sequences in the Membrane-Spanning Domain Cause the Retention of Proteins in the Golgi	719
<i>Protein Glycosylation: Discrete Steps in the ER and Golgi Complex</i>	699	Different Vesicles Are Used for Continuous and Regulated Protein Secretion	719
Different Structures Characterize N- and O-Linked Oligosaccharides	699	Secretory and Membrane Proteins Undergo Several Proteolytic Cleavages During the Late Maturation Stages	720
Nucleotide Sugars Are the Precursors of Oligosaccharides	700	The Proteolytic Maturation of Insulin Occurs in Acidic, Clathrin-Coated Secretory Vesicles	722
O-Linked Oligosaccharides Are Formed by the Sequential Addition of Sugars	703	<i>Sorting of Membrane Proteins Internalized from the Cell Surface</i>	722
The ER and Golgi Membranes Contain Transporters for Nucleotide Sugars	703	In Receptor-Mediated Endocytosis, Cell Surface Receptors Are Internalized in Clathrin-Coated Vesicles	722
The Diverse N-Linked Oligosaccharides Share Certain Structural Features That Reflect a Common Precursor	704	The Low-Density Lipoprotein (LDL) Receptor Binds and Internalizes Cholesterol-Containing Particles	724
The Processing N-Linked Oligosaccharides Involves the Sequential Removal and Addition of Sugar Residues	704	Mutant LDL Receptors Reveal a Signal for Internalizing Receptors into Clathrin-Coated Pits	724
Modifications to N-Linked Oligosaccharides Are Completed in the Golgi Vesicles	706	Receptors and Ligands Dissociate in an Acidic Late Endosome/CURL Organelle	726
The Movement of Proteins through the Secretory Pathway Can Be Monitored by Following the Processing of N-Linked Oligosaccharides	707	Transferrin Delivers Iron to Cells by Receptor-Mediated Endocytosis	727
N-Linked and O-Linked Oligosaccharides May Stabilize Maturing Secretory and Membrane Proteins	708	Some Proteins Internalized by Endocytosis Remain within the Cell, or Are Transported across the Cell and Secreted	728
Phosphorylated Mannose Residues Target Proteins to Lysosomes	709	Proteins Are Sorted in Several Different Ways to Different Domains of the Plasma Membrane	729
Genetic Defects Have Elucidated the Role of Mannose Phosphorylation	711	Viruses and Toxins Enter Cells by Receptor-Mediated Endocytosis	731
<i>The Mechanism and Regulation of Vesicular Transport to and from the ER and the Golgi Complex</i>	711	<i>Summary</i>	734
Two Types of Coated Vesicles Transport Proteins from Organelle to Organelle	711	<i>Review Questions</i>	735
Clathrin Forms a Lattice Shell around Coated Pits and Vesicles	711	<i>References</i>	737
A Chaperone Protein Catalyzes the Depolymerization of Clathrin-Coated Vesicles	713		

17 CELLULAR ENERGETICS: FORMATION OF ATP BY GLYCOLYSIS AND OXIDATIVE PHOSPHORYLATION	739	Most Electron Carriers Are Oriented in the Transport Chain in the Order of Their Reduction Potentials	765
Energy Metabolism in the Cytosol	740	Three Electron Transport Complexes Are Sites of Proton Translocation	766
In Glycolysis, ATP Is Generated by Substrate-Level Phosphorylation	742	The Q Cycle Increases the Number of Protons Transported by the CoQH ₂ -Cytochrome C Reductase Complex	767
Some Eukaryotic and Prokaryotic Cells Metabolize Glucose Anaerobically	744	The Cytochrome C Oxidase Complex Couples the Reduction of Oxygen to the Translocation of Protons	768
Mitochondria and the Metabolism of Carbohydrates and Lipids	745	Metabolic Regulation	770
The Outer and Inner Membranes of the Mitochondrion Are Structurally and Functionally Distinct	745	Respiration Is Controlled by the Production of ATP through the Proton-Motive Force	770
Acetyl CoA Is a Key Intermediate in the Mitochondrial Metabolism of Pyruvate and Fatty Acids	748	An Endogenous Uncoupler in Brown-Fat Mitochondria Converts H ⁺ Gradients to Heat	770
The Citric Acid Cycle Oxidizes the Acetyl Group of Acetyl CoA to CO ₂ and Reduces NAD and FAD to NADH and FADH ₂	749	The Rate of Glycolysis Depends on the Cell's Need for ATP and Is Controlled by Multiple Allosteric Effectors	771
Electrons Are Transferred from NADH and FADH ₂ to Molecular O ₂ by Electron-Carrier Proteins	750	The Oxidation of Fatty Acids Occurs in Peroxisomes without Production of ATP	772
A Similar Electrochemical Protein Gradient Is Used to Generate ATP from ADP and P _i in Mitochondria, Bacteria, and Chloroplasts	751	Summary	773
The Proton-Motive Force, ATP Generation, and Transport of Metabolites	752	Review Questions	774
Closed Vesicles Are Required for the Generation of ATP	752	References	776
The Proton-Motive Force Is Composed of a Proton Concentration Gradient and a Membrane Electric Potential	753	18 PHOTOSYNTHESIS	779
The F ₀ F ₁ Complex Couples ATP Synthesis to Proton Movement Down the Electrochemical Gradient	753	An Overview of Photosynthesis	780
Reconstitution of Close Membrane Vesicles Supports the Role of the Proton-Motive Force in ATP Synthesis	756	Photosynthesis Occurs on Thylakoid Membranes	780
Many Transporters in the Inner Mitochondrial Membrane Are Powered by the Proton-Motive Force	758	Photosynthesis Consists of Both "Light" and "Dark" Reactions	782
Inner-Membrane Proteins Allow the Uptake of Electrons from Cytosolic NADH	759	The Light-Absorbing Step of Photosynthesis	783
NADH, Electron Transport, and Proton Translocation	759	Each Photon of Light Has a Defined Amount of Energy	783
Electron Transport in Mitochondria Is Coupled to Proton Translocation	759	Chlorophyll <i>a</i> Is the Primary Light-Absorbing Pigment	783
The Mitochondrial Electron Transport Chain Transfers Electrons from NADH to O ₂	761	The Absorption of Light by Reaction-Center Chlorophylls Causes a Charge Separation across the Thylakoid Membrane	784
		Molecular Analysis of Bacterial Photosynthesis	786
		Purple Photosynthetic Bacteria Utilize Only One Photosystem and Do Not Evolve O ₂	786

Photoelectron Transport in the Photosynthetic Reaction Center of Purple Bacteria Results in a Charge Separation	788	Proteins Encoded by Mitochondria DNA Are Synthesized on Mitochondrial Ribosomes	816
Photosynthetic Bacteria also Carry Out Noncyclic Electron Transport	790	Mitochondrial Genetic Codes Are Different from the Standard Nuclear Code, and They Differ among Organisms	816
Molecular Analysis of Photosynthesis in Plants	790	In Animals, Mitochondrial RNAs Undergo Extensive Processing	817
Plants Utilize Two Photosystems, PSI and PSII, with Different Functions in Photosynthesis	790	Mutations in Mitochondrial DNA Cause Several Genetic Diseases in Man	817
Both PSI and PSII Are Essential for Photosynthesis in Chloroplasts	792	Synthesis and Localization of Mitochondrial Proteins	819
PSII Splits H ₂ O	793	Most Mitochondrial Proteins Are Synthesized in the Cytosol as Precursors	819
Electrons Are Transported from PSII to PSI	794	Matrix-Targeting Sequences Direct Imported Proteins to the Mitochondrial Matrix	820
PSI Forms NADPH	796	Mitochondrial Receptors Bind Matrix-Targeting Sequences	824
PSI Can Also Function in Cyclic Electron Flow	796	Intermediates in Translocation of Proteins into the Mitochondrion Can Be Accumulated and Studied	824
PSI and PSII Are Functionally Coupled	796	The Uptake of Mitochondrial Proteins Requires Energy	824
CO ₂ Metabolism during Photosynthesis	797	Matrix Chaperones Are Essential for the Import and Folding of Mitochondrial Proteins	826
CO ₂ Fixation Is Catalyzed by Ribulose 1,5-Bisphosphate Carboxylase	797	Proteins Are Targeted to the Correct Submitochondrial Compartment by Multiple Signals and Several Pathways	827
CO ₂ Fixation Is Activated in the Light	800	Certain Mitochondrial Proteins Are Essential for Life	829
Photorespiration Liberates CO ₂ and Consumes O ₂	800	The Synthesis of Mitochondrial Proteins Is Coordinated	829
Peroxisomes Play a Role in Photorespiration	800	Chloroplast DNA and the Biogenesis of Chloroplasts and Other Plastids	830
The C ₄ Pathway for CO ₂ Fixation Is Used by Several Tropical Plants	802	Chloroplast DNA Contains over 120 Different Genes	830
Sucrose Is Transported from Leaves through the Phloem to All Plant Tissues	803	Several Uptake-Targeting Sequences Direct Proteins Synthesized in the Cytosol to the Appropriate Chloroplast Compartment	832
Summary	805	Proplastids Can Differentiate into Chloroplasts or Other Plastids	835
Review Questions	806	Peroxisome Biosynthesis	837
References	807	All Peroxisomal Proteins Are Imported from the Cytosol	837
19 ORGANELLE BIOGENESIS: THE MITOCHONDRION, CHLOROPLAST, PEROXISOME, AND NUCLEUS	809	Genetic Diseases Have Helped to Elucidate the Process of Peroxisome Biogenesis	838
An Overview of Organelle Biogenesis Outside the Secretory Pathway	810		
Mitochondrial DNA: Structure, Expression, and Variability	812		
Cytoplasmic Inheritance and DNA Sequencing Have Established the Existence of Mitochondrial Genes	812		
The Size and Coding Capacity of mtDNA Varies in Different Organisms, Reflecting Evolutionary Movement of DNA between Mitochondrion and Nucleus	813		

<i>Protein Traffic into and out of the Nucleus</i>	840
Nuclear Proteins Are Selectively Imported into Nuclei	840
Nuclear Pores Are the Portals for Protein Transport	841
Multiple Types of Nuclear Localization Sequences Direct Proteins and Ribonucleoproteins to the Nucleus	842
Receptor Proteins in Nuclear Pores Bind Nuclear Proteins for Import	844
<i>Summary</i>	844
<i>Review Questions</i>	845
<i>References</i>	847

► Part IV

Integrative and Specialized Cellular Events 850

20 CELL-TO-CELL SIGNALING: HORMONES AND RECEPTORS	853
<i>Overview of Extracellular Signaling</i>	854
Signaling Molecules Operate over Various Distances in Animals	855
Receptor Proteins Exhibit Ligand-Binding Specificity and Effector Specificity	856
Hormones Can Be Classified Based on Their Solubility and Receptor Location	856
Effects of Many Hormones Are Mediated by Second Messengers	857
Cell-Surface Receptors Can Be Categorized into Four Major Classes	859
The Synthesis, Release, and Degradation of Hormones Are Regulated	860
<i>Identification and Purification of Cell-Surface Receptors</i>	865
Hormone Receptors Are Detected by Binding Assays	865
K_D Values for Cell-Surface Hormone Receptors Approximate the Concentrations of Circulating Hormones	866
Affinity Techniques Permit Purification of Receptor Proteins	866
Many Receptors Can Be Cloned without Prior Purification	867
<i>Seven-spanning G Protein-Linked Receptors</i>	869
Binding of Epinephrine to β - and α -Adrenergic Receptors Induces Tissue-Specific Responses Mediated by cAMP	870

Analogues Provide Information about Essential Features of Hormone Structure and Are Useful as Drugs	871
Studies with Mutant β -Adrenergic Receptors Identify Residues That Interact with Catecholamines	872
Trimeric Signal-Transducing G_s Protein Links β -Adrenergic Receptors and Adenylate Cyclase	873
G_{sa} Belongs to GTPase Superfamily of Intracellular Switch Proteins	876
Some Bacterial Toxins Irreversibly Modify G Proteins	877
Adenylate Cyclase Is Stimulated and Inhibited by Different Receptor-Ligand Complexes	879
Analogous Regions in All Seven-spanning Receptors Determine G Protein and Ligand Specificity	881
Degradation of cAMP Also Is Regulated	881
<i>Role of cAMP in the Regulation of Cellular Metabolism</i>	881
cAMP and Other Second Messengers Activate Specific Protein Kinases	881
Epinephrine Stimulates Glycogenolysis in Liver and Muscle Cells	882
cAMP-Dependent Protein Kinase Regulates the Enzymes of Glycogen Metabolism	884
Kinase Cascade Permits Multienzyme Regulation and Amplifies Hormone Signal	885
Cellular Responses to cAMP Vary among Different Cell Types	885
<i>Receptor Tyrosine Kinases</i>	886
SH2-Containing Proteins Bind to Specific Phosphotyrosine Residues in Activated RTKs	886
Ras Protein Is a Key Component of RTK Signaling Pathways in Many Eukaryotes	887
Genetic Analysis of <i>Drosophila</i> Eye Development Identified Three Proteins That Link RTKs to a Kinase Cascade	891
GRB2 Is an Adapter Protein That Binds to Activated RTKs	893
Sos Protein Is Localized to the Plasma Membrane by Binding to the SH3 Domains in GRB2	893
A Highly Conserved Kinase Cascade Transmits RTK-Mediated Signals Downstream from Ras	894

Ras-Coupled RTKs Transduce Extracellular Signals by a Common Pathway	896
Yeast Mating-Factor Receptors Are Linked to G Proteins That Transmit Signals to MAP Kinase	897
<i>Other Important Second Messengers</i>	899
Cellular Effects of Ca^{2+} Depend on Its Cytosolic Level and Often Are Mediated by Calmodulin	899
Ca^{2+} Ions and cAMP Induce Hydrolysis of Muscle Glycogen	901
Inositol 1,4,5-Trisphosphate Causes the Release of Ca^{2+} Ions from the ER	901
Release of Intracellular Ca^{2+} Stores Also Is Mediated by Ryanodine Receptors in Muscle Cells and Neurons	904
1,2-Diacylglycerol Activates Protein Kinase C	904
<i>Multiplex Signaling Pathways</i>	905
Some Activated RTKs Stimulate Activity of Phospholipase C_γ	905
Multiple G Proteins Transduce Signals from Seven-Spanning Receptors to Different Effector Proteins	905
$G_{\beta\gamma}$ Acts Directly on Some Effectors in Mammalian Cells	906
<i>The Insulin Receptor and Regulation of Blood Glucose</i>	907
Insulin Has Short-Term Effects on Glucose Metabolism and Long-Term Growth-Promoting Effects	907
Insulin Signaling Pathway Involves a Soluble "Relay" Protein That Does Not Bind to the Receptor	910
Insulin and Glucagon Work Together to Maintain a Stable Blood Glucose Level	911
<i>Regulation of Cell-Surface Receptors</i>	912
Receptors for Many Peptide Hormones Are Down-Regulated by Endocytosis	912
Phosphorylation of Cell-Surface Receptors Modulates Their Activity	913
<i>From Plasma Membrane to Nucleus</i>	914
Activation of Some Transcription Factors Occurs via Several Signaling Pathways Coupled to G Protein-Linked Receptors and RTKs	914
STATs Are Transcription Factors Activated by Protein Tyrosine Kinases Associated with Cell-Surface Receptors	916

<i>Summary</i>	918
<i>Review Questions</i>	920
<i>References</i>	922
21 NERVE CELLS	925
<i>Neurons, Synapses, and Nerve Circuits</i>	926
Specialized Regions of Neurons Carry Out Different Functions	926
Synapses Are Specialized Sites Where Neurons Communicate with Other Cells	929
Neurons Are Organized into Circuits	931
<i>The Action Potential and Conductance of Electric Impulses</i>	932
The Resting Potential Is Generated Mainly by Open Potassium Channels	933
Opening and Closing Ion Channels Cause Specific, Predictable Changes in the Membrane Potential	935
Membrane Depolarizations Would Spread Only Short Distances without Voltage-Gated Cation Channels	935
Opening of Voltage-Gated Sodium Channels Depolarizes the Nerve Membrane during Conductance of an Action Potential	936
Voltage-Dependent Sodium Channel Proteins Propagate Action Potentials Unidirectionally without Diminution	938
Opening of Voltage-Gated Potassium Channels Causes Repolarization of the Plasma Membrane during an Action Potential	938
Movements of Only a Few Sodium and Potassium Ions Generate the Action Potential	939
Myelination Increases the Rate of Impulse Conduction	940
Action Potentials Are Generated in an All-or-Nothing Fashion by Summation of Electric Disturbances	943
<i>Molecular Properties of Voltage-Gated Ion Channel Proteins</i>	943
Patch Clamps Permit Measurement of Ion Movements through Single Sodium and Potassium Channels	944
All Voltage-Gated Ion Channels Have a Similar Molecular Structure	946

<i>Shaker</i> Mutants in <i>Drosophila melanogaster</i> Led to the Cloning of a Large Family of Voltage-Gated Potassium Channel Proteins	947	Hydrolysis of Acetylcholine Terminates the Depolarization Signal	965
Study of Toxin-Resistant Mutants Led to the Identification of Amino Acids That Line the Ion-Conducting Pore of the Potassium Channel	948	<i>Functions of Other Neurotransmitters, Their Receptors, and Their Transporters</i>	965
A Complete <i>shaker</i> K ⁺ Channel Is Assembled from Four Subunits	949	GABA and Glycine Receptors Are Ligand-Gated Anion Channels Used at Many Inhibitory Synapses	966
The S4 Segment Comprises the Voltage Sensor	949	Cardiac Muscarinic Acetylcholine Receptor Activates a G Protein and Open Potassium Channels	967
The N-terminal Segment of the <i>shaker</i> Protein Causes Channel Inactivation	949	Different Catecholamine Receptors Affect Different Intracellular Second Messengers	967
Potassium Channel Proteins Are Diverse	950	A Serotonin Receptor Modulates Potassium Channel Function via the Activation of Adenylate Cyclase	968
The Sodium Channel Protein Has Four Homologous Transmembrane Domains, Each Similar to a Potassium Channel Polypeptide	951	Neurotransmitter Transporters Are the Proteins Affected by Drugs Such as Cocaine	970
All Voltage-Gated Ion Channel Proteins Probably Evolved from a Common Ancestral Gene	951	Some Peptides Function as Both Neurotransmitters and Neurohormones	970
<i>Synapses and Impulse Transmission</i>	952	Endorphins and Enkephalins Are Neurohormones That Inhibit Transmission of Pain Impulses	971
Impulse Transmission across Electric Synapses Is Nearly Instantaneous	952	<i>Sensory Transduction: The Visual and Olfactory Systems</i>	971
Chemical Synapses Can Be Fast or Slow, Excitatory or Inhibitory, and Can Exhibit Signal Amplification and Computation	953	The Light-Triggered Closing of Sodium Channels Hyperpolarizes Rod Cells	972
Many Types of Receptors Bind the Same Neurotransmitter	955	Absorption of a Photon Triggers Isomerization of Retinal and Activation of Opsin	974
<i>Synaptic Transmission and the Nicotinic Acetylcholine Receptor</i>	956	Cyclic GMP Is a Key Transducing Molecule	975
Acetylcholine Is Synthesized in the Cytosol and Stored in Synaptic Vesicles	956	Rod Cells Adapt to Varying Levels of Ambient Light	976
Exocytosis of Synaptic Vesicles Is Triggered by Opening of Voltage-Gated Calcium Channels and a Rise in Cytosolic Calcium	958	Color Vision Utilizes Three Opsin Pigments	977
Multiple Proteins Align Synaptic Vesicles with the Plasma Membrane and Participate in Vesicle Exocytosis and Endocytosis	960	More Than a Thousand Different G-Protein-Coupled Receptors Detect Odors	978
The Nicotinic Acetylcholine Receptor Protein Is a Ligand-Gated Cation Channel	962	<i>Memory and Neurotransmitters</i>	979
Spontaneous Exocytosis of Synaptic Vesicles Produces Small Depolarizations in the Postsynaptic Membrane	962	Mutations in <i>Drosophila</i> Affect Learning and Memory	979
The Nicotinic Acetylcholine Receptor Contains Five Subunits, Each of Which Contributes to the Cation Channel	963	Gill-Withdrawal Reflex in <i>Aplysia</i> Exhibits Three Elementary Forms of Learning	979
		A Novel Glutamate Receptor Is the Coincidence Detector in Long-Term Potentiation Exhibited by Many Synapses in the Mammalian Brain	982

Retrograde Signaling by the Gas Nitric Oxide May Be a Part of Long-Term Potentiation	982	A Family of Actin-Severing Proteins Generates New Filament Ends by Breaking Actin Filaments	1007
Mice Defective in the Hippocampal Ca ²⁺ -Calmodulin-Activated Protein Kinase Are Impaired in Long-Term Potentiation and in Spatial Learning—the Beginnings of a Molecular Psychology	984	Actin Filaments Are Stabilized by Actin-Capping Proteins	1009
<i>Summary</i>	984	Many Movements Are Driven by Actin Polymerization	1010
<i>Review Questions</i>	986	<i>Myosin: A Cellular Engine That Powers Motility</i>	1012
<i>References</i>	987	Myosin Is a Diverse Family of Proteins Characterized by Distinct Head, Neck, and Tail Domains	1014
22 MICROFILAMENTS: CELL MOTILITY AND CONTROL OF CELL SHAPE	991	The Myosin Tail Domain Regulates Binding to Membranes or the Assembly of Thick Filaments	1015
<i>Actin Filaments</i>	992	The Myosin Head Domain Is an Actin-Activated ATPase	1015
All Eukaryotic Cells Contain Abundant Amounts of Actin	994	Myosin Heads Walk along Actin Filaments	1015
The Actin Sequence Has Changed Little during Evolution	994	A Myosin Head Takes an 11-nm Step Each Time an ATP Molecule Is Hydrolyzed	1017
ATP Holds Together the Two Lobes of the Actin Monomer	994	X-Ray Crystallography Reveals the Atomic Structure of the Motor Domain	1018
G-Actin Assembles into Long F-Actin Polymers	995	Conformational Changes in the Head Couple ATP Hydrolysis to Movement	1020
F-Actin Is a Helical Polymer of Identical Subunits	995	<i>Muscle, A Specialized Contractile Machine</i>	1021
F-Actin Has Structural and Functional Polarity	996	Some Muscles Contract, Others Generate Tension	1022
<i>Actin Architectures</i>	996	Striated Muscles Contain a Regular Array of Actin and Myosin	1023
The Actin Cytoskeleton Is Organized into Bundles and Networks of Filaments	997	In Smooth Muscle, Thick and Thin Filaments Are Not in Regular Arrays	1025
Actin Bundles and Networks Are Connected to the Membrane	998	Thick and Thin Filaments Slide Past Each Other during Contraction	1025
Cortical Networks of Actin Filaments Stiffen Cell Membranes and Immobilize Integral Membrane Proteins	999	A Third Filament System of Long Proteins Organizes the Sarcomere	1026
Dystrophin Anchors a Cortical Actin Network Directly to the Extracellular Matrix	1000	Calcium from the Sarcoplasmic Reticulum Triggers Contraction	1026
Actin Bundles Support Projecting Fingers of Membrane	1002	Calcium Activation of Myosin Light Chains Regulates Contraction in Smooth Muscle and Invertebrate Muscle	1030
<i>The Dynamics of Actin Assembly</i>	1003	<i>Actin and Myosin in Nonmuscle Cells</i>	1032
Actin Polymerization in Vitro Proceeds in Three Steps	1003	Actin and Myosin II Are Arranged in Sarcomere-Like Structures	1032
ATP Enhances Assembly from One End of a Filament	1003	Contractile Actin Bundles Are Attached to Specialized Sites at the Plasma Membrane	1035
Fungal Toxins Disrupt the Monomer-Polymer Equilibrium	1006	Myosin II Stiffens Cortical Membranes	1036
Actin-Binding Proteins Control the Lengths of Actin Filaments	1006		

Actin and Myosin II Have Essential Roles in Cytokinesis	1036	<i>Kinesin, Dynein, and Intracellular Transport</i>	1070
Myosins I and V Move Membrane-Bounded Cargoes along Actin Filaments	1038	Fast Axonal Transport Occurs along Microtubules	1070
Membrane-Bound Myosin in Vesicle Movements	1039	Microtubules Provide Tracks for the Movement of Pigment Granules	1072
Myosin I and Myosin II Are Not Essentially Required for Cell Migration	1039	Intracellular Membrane Vesicles Travel Along Microtubules	1072
<i>Cell Motility</i>	1040	Microtubule Motor Proteins Promote Vesicle Translocation along Microtubules	1075
Movements of Fibroblasts Involve Controlled Polymerization and Rearrangements of Actin Filaments	1041	Kinesin Is a (+) End-Directed Motor Protein	1075
Ameboid Movement Involves Reversible Gel-Sol Transitions of an Actin Network	1043	Dynein Is a (-) End-Directed Motor Protein	1078
Cell Movements Are Coordinated by Various Second Messengers and Signal Transduction Pathways	1044	Multiple Motor Proteins Are Associated with Membrane Vesicles	1078
<i>Summary</i>	1046	<i>Cilia and Flagella: Structure and Movement</i>	1079
<i>Review Questions</i>	1048	All Eukaryotic Cilia and Flagella Contain Bundles of Doublet Microtubules	1080
<i>References</i>	1049	Ciliary and Flagellar Beating Is Produced by Controlled Sliding of Outer Doublet Microtubules	1084
23 MICROTUBULES AND INTERMEDIATE FILAMENTS	1051	Dynein Arms Generate the Sliding Forces	1084
<i>Microtubule Structures</i>	1052	Axonemal Dyneins Are Multi-Headed Motor Proteins	1086
Tubulin Subunits Comprise the Wall of a Microtubule	1052	Flagellar Beat Requires Conversion of Sliding to Bending	1086
Microtubules Form a Diverse Array of Both Permanent and Transient Structures	1054	Genetic Studies Provide Information about the Roles of the Central Microtubules and the Radial Spokes	1087
Microtubules Grow from Microtubule-Organizing Centers	1055	Calcium Regulates the Direction of Swimming	1087
The Microtubule-Organizing Center Determines the Polarity of Cellular Microtubules	1055	Axonemes Assemble from Basal Bodies	1088
Multiple Tubulin Genes and Chemical Modification Leads to Tubulin Diversity	1059	Basal Bodies Closely Resemble Centrioles	1089
<i>Microtubule Dynamics</i>	1061	<i>Microtubule Dynamics and Motor Proteins during Mitosis</i>	1090
Microtubule Assembly and Disassembly Occur by Preferential Addition and Loss of $\alpha\beta$ Dimers at the (+) End	1061	The Mitotic Apparatus Is a Microtubule Machine for Separating Chromosomes	1091
Dynamic Instability Is an Intrinsic Property of Microtubules	1064	The Kinetochore Is a Specialized Attachment Site at the Chromosome Centromere	1091
Colchicine and Other Anti-Cancer Drugs Poison Microtubule Assembly or Disassembly	1066	Yeast Centromeres Bind a Single Microtubule	1094
<i>Microtubule-Associated Proteins</i>	1067	Centrosome Duplication and Migration During Interphase and Prophase Initiate the Assembly of the Mitotic Apparatus	
MAPs Organize Bundles of Microtubules	1067		
MAPs Stabilize Microtubules	1070		

During Prophase, Kinesin-Related Proteins and Cytoplasmic Dynein Participate in the Movements of Kinetochores and Centrosomes	1097	Collagen Is Assembled into Fibrils after Secretion	1133
Assembly of the Mitotic Apparatus Involves Dynamic Microtubules	1098	Mutations in Collagen Reveal Aspects of Its Structure and Biosynthesis	1134
At Metaphase Forces at the Kinetochore Move Chromosomes to the Equator of the Spindle	1100	Collagens Form Diverse Structures	1134
During Anaphase Chromosomes Separate and the Spindle Elongates	1100	Type IV Collagen Forms the Two-Dimensional Reticulum of the Basal Lamina	1135
Astral Microtubules Determine Where Cytokinesis Takes Place	1103	<i>Hyaluronan and Proteoglycans</i>	1136
Plant Cells Build a New Cell Wall During Cell Division	1105	Hyaluronan Is an Immensely Long, Negatively Charged Polysaccharide That Forms Hydrated Gels	1136
<i>Intermediate Filaments</i>	1106	Hyaluronan Inhibits Cell-Cell Adhesion and Facilitates Cell Migration	1137
Intermediate Filaments Are Classified into Five Types	1106	Proteoglycans Comprise a Diverse Family of Cell-surface and Extracellular-matrix Macromolecules	1139
All Subunit Proteins of Intermediate Filaments Have a Similar Structure	1109	Proteoglycans Can Bind Many Growth Factors	1142
Intermediate Filaments Are Dynamic Polymers in the Cell	1111	<i>Multiadhesive Matrix Proteins and Their Cell-Surface Receptors</i>	1143
Phosphorylation of the N-Terminal Domain Regulates Polymerization of Intermediate Filaments during Mitosis	1112	Laminin and Nidogen Are Principal Structural Proteins of All Basal Laminae	1143
Intermediate Filament-Associated Proteins Cross-Link Intermediate Filaments to Membranes and Microtubules	1113	Integrins Are Cell-Surface Receptors That Mediate Adhesion to the Extracellular Matrix and Cell-Cell Interactions	1144
<i>Summary</i>	1116	Fibronectins Bind Many Cells to Fibrous Collagens and Other Matrix Components	1146
<i>Review Questions</i>	1118	Fibronectins Promote Cell Adhesion to the Substratum	1148
<i>References</i>	1119	Fibronectins Promote Cell Migration	1149
24 MULTICELLULARITY: CELL-CELL AND CELL-MATRIX INTERACTIONS	1123	<i>Cell-Cell Adhesion: Adhesive Proteins</i>	1150
<i>The Extracellular Matrix: Primary Components and Functions</i>	1124	Adhesive Proteins Mediate Cell-Cell Interactions	1150
<i>Collagen: A Class of Multifunctional Fibrous Proteins</i>	1126	E-Cadherin Is a Key Adhesive Protein Expressed by Epithelial Cells	1150
The Basic Structural Unit of Collagen Is a Triple Helix	1127	Cadherins Influence Morphogenesis and Differentiation	1152
Most Exons in Fibrous Collagen Genes Encode Gly-X-Y Sequences	1128	N-CAMS Mediate Ca^{2+} -Independent Adhesion of Cells in Nervous Tissue and Muscle	1153
Collagen Fibrils Form by Lateral Interactions of Triple Helices	1128	Movement of Leukocytes into Tissues Requires Sequential Interaction of Specific Adhesive Proteins	1153
Denatured Collagen Polypeptides Cannot Renature to Form a Triple Helix	1131	<i>Cell-Cell Adhesion: Cell Junctions</i>	1155
Procollagen Chains Assemble into Triple Helices in the Rough ER and Are Modified in the Golgi Complex	1131	Three Types of Desmosomes Impart Rigidity to Tissues	1156
		Intermediate Filaments Stabilize Epithelia by Connecting Spot Desmosomes	1156

Hemidesmosomes Connect Epithelial Cells to the Basal Lamina	1157	Extracellular Signals Can Repel Growth Cones	1181
Gap Junctions Allow Small Molecules to Pass between Adjacent Cells	1157	Different Growth Cones Navigate along Different Axons	1182
Connexin, a Transmembrane Protein, Forms Cylindrical Channels in Gap Junctions	1159	The Basal Lamina at the Neuromuscular Junction Directs Differentiation of Regenerating Nerve and Muscle	1185
<i>Dorsoventral Patterning During Embryogenesis</i>	1159	<i>Structure and Function of the Plant Cell Wall</i>	1187
Embryologic Development Is Directed by Induction	1160	Cellulose Molecules Form Long, Rigid Microfibrils	1188
Transforming Growth Factor β (TGF β) Has Numerous Inductive Effects in Invertebrates and Vertebrates	1161	Other Polysaccharides Bind to Cellulose to Generate a Complex Wall Matrix	1188
TGF β Homolog Encoded by the <i>decapentaplegic</i> Gene Controls Dorsoventral Patterning in <i>Drosophila</i> Embryos	1162	Cell Walls Contain Lignin and an Extended Hydroxyproline-Rich Glycoprotein	1190
Sequential Inductive Events Regulate Early <i>Xenopus</i> Development	1163	Plants Grow Primarily by Auxin-Induced Cell Enlargement	1190
<i>Formation of Internal Organs and Organization of Tissues</i>	1167	The Orientation of Newly Made Cellulose Microfibrils Is Affected by the Microtubule Network	1192
The Basal Lamina Is Essential for Differentiation of Many Epithelial Cells	1167	Plasmodesmata Interconnect the Cytoplasm of Adjacent Cells in Higher Plants	1193
Direct Cell-Cell Contact Regulates Kidney Induction	1168	<i>Summary</i>	1194
Hedgehog Organizes Pattern in the Chick Limb and the <i>Drosophila</i> Wing	1169	<i>Review Questions</i>	1196
<i>Developmental Regulation by Direct Cell-Cell Contact</i>	1172	<i>References</i>	1197
Boss Is a Cell-Surface Inductive Ligand for the Sev Receptor	1172	25 REGULATION OF THE EUKARYOTIC CELL CYCLE	1201
Cell-Surface Notch and Delta Proteins Control Signaling between Many Different Types of Cells	1173	<i>Phases of the Cell Cycle</i>	1202
<i>Regulation of Neuronal Outgrowth</i>	1175	<i>Experimental Systems in Cell-Cycle Research</i>	1203
Individual Neurons Can Be Identified Reproducibly and Studied	1175	<i>Control of Entry into and Exit from Mitosis</i>	1203
Growth Cones Guide the Migration and Elongation of Developing Axons	1176	The Same Factor Promotes Oocyte Maturation and Mitosis in Somatic Cells	1203
Different Neurons Navigate along Different Outgrowth Pathways	1177	Mitotic Cycling in Early Embryos Depends on Synthesis and Degradation of Cyclin B	1207
Different Extracellular-Matrix Components Are Permissive for Neuronal Outgrowth	1178	MPF-Catalyzed Phosphorylation of Nuclear Lamins and Other Proteins Induces Early Mitotic Events	1212
Three Genes Define Dorsoventral Outgrowth in <i>C. elegans</i>	1179	Protein Degradation and Dephosphorylation Trigger Late Mitotic Stages	1216
A Chemoattractant Related to Unc6 Is Produced in the Floor Plate of the Vertebrate Neural Tube	1180	Biochemical Studies with <i>Xenopus</i> Egg Extracts Identified Central Role of MPF in Regulating Entry into Mitosis	1219
		<i>Regulation of MPF Activity</i>	1219
		MPF Catalytic Subunit Is Encoded by <i>cdc2⁺</i> Gene in <i>S. pombe</i>	1221

MPF Catalytic Subunit Contains Activating and Inhibitory Sites That Are Phosphorylated	1222	Alterations in Cell-to-Cell Interactions Are Associated with Malignancy	1249
Structure of Human Cyclin-Dependent Kinase 2 Suggests How Phosphorylation Regulates MPF Activity	1224	Tumor Cells Lack Normal Controls on Cell Growth	1251
Entry into Mitosis Is Controlled by Multiple Mechanisms That Regulate MPF Activity	1224	<i>Use of Cell Cultures in Cancer Research</i>	1251
<i>Control of Entry into the S Phase</i>	1226	Fibroblastic, Epithelial, and Nonadherent Cells Grow Readily in Culture	1251
<i>S. cerevisiae</i> Cdc28 Is Functionally Equivalent to <i>S. pombe</i> Cdc2	1227	Some Cell Cultures Give Rise to Immortal Cell Lines	1252
S Phase-Promoting Factor Consists of a Catalytic Subunit and G ₁ Cyclin	1228	Certain Factors in Serum Are Required for Long-Term Growth of Cultured Cells	1253
Various Cdc28-Cyclin Heterodimers Regulate Progress through the Cell Cycle in <i>S. cerevisiae</i>	1230	Malignant Transformation Leads to Many Changes in Cultured Cells	1254
Cdc28-G ₁ Cyclin Complexes May Activate Transcription Factors at START	1230	Transcription of Oncogenes Can Trigger Transformation	1258
A Cdk-Cyclin Complex Regulates a DNA Initiation Factor in <i>Xenopus</i>	1231	<i>Oncogenes and Their Proteins: Classification and Characteristics</i>	1258
<i>Cell-Cycle Control in Mammalian Cells</i>	1232	Oncogenes Were Initially Identified in Viruses and Tumor Cell DNA	1258
Mammalian Restriction Point Is Analogous to START in Yeast Cells	1232	Five Types of Proteins Participate in Control of Cell Growth	1259
Multiple Cdks and Cyclins Regulate Passage of Mammalian Cells through the Cell Cycle	1232	Oncoproteins Affect the Cell's Growth-Control Systems in Various Ways	1260
Growth Factor-Induced Expression of Two Classes of Genes Returns G ₀ Mammalian Cells to the Cell Cycle	1235	Apoptosis, or Induced Cell Suicide, Is One Mechanism of Protection Against Cancer	1267
Activity of Transcription Factor E2F Is Required for Entry into S Phase	1236	Oncoproteins Act Cooperatively in Transformation and Tumor Induction	1267
<i>Role of Checkpoints in Cell-Cycle Regulation</i>	1237	Consistent Chromosomal Anomalies Associated with Tumors Point to the Presence of Oncogenes	1268
Presence of Unreplicated DNA Prevents Entry into Mitosis	1238	Inherited Human Propensities to Develop Cancer Point to Tumor-Suppressor Genes	1269
Defects in Assembly of the Mitotic Spindle Prevent Exit from Mitosis	1239	<i>DNA Viruses as Transforming Agents</i>	1270
DNA Damage Prevents Entry into S Phase and Mitosis	1239	DNA Viruses Can Transform Nonpermissive Cells by Random Integration of the Viral Genome into the Host-Cell Genome	1270
<i>Summary</i>	1240	Transformation by DNA Viruses Requires Interaction of a Few Independently Acting Viral Proteins	1271
<i>Review Questions</i>	1242	<i>RNA-Containing Retroviruses as Transforming Agents</i>	1273
<i>References</i>	1243	Virion-Producing Infection Cycle of Retroviruses Requires Integration into the Host-Cell Genome	1273
26 CANCER	1247	Oncogenic Transducing Retroviruses Convert Cellular Proto-Oncogenes into Oncogenes	1275
<i>Characteristics of Tumor Cells</i>	1248		
Malignant Tumor Cells Are Invasive and Can Spread	1248		

Nononcogenic Transducing Retroviruses Have Been Constructed Experimentally	1277
Slow-Acting Carcinogenic Retroviruses Can Activate Nearby Cellular Proto-Oncogenes after Integration into the Host-Cell Genome	1278
<i>Human Tumor Viruses</i>	1279
<i>Chemical Carcinogens</i>	1280
Most Chemical Carcinogens Must Undergo Metabolic Conversion to Become Active	1280
The Carcinogenic Effect of Chemicals Depends on Their Interaction with DNA	1284
<i>The Role of Radiation and DNA Repair in Carcinogenesis</i>	1284
Ineffective or Error-Prone Repair of Damaged DNA Perpetuates Mutations	1285
Some Defects in DNA-Repair Systems Are Associated with High Cancer Rates in Humans	1285
<i>The Multicausal, Multistep Nature of Carcinogenesis</i>	1286
Epigenetic Alterations May Occur in Teratocarcinomas	1286
Some Cancer-Inducing Chemicals Act Synergistically	1286
Natural Cancers Result from the Interaction of Multiple Events over Time	1287
<i>Human Cancer</i>	1287
<i>Summary</i>	1288
<i>Review Questions</i>	1289
<i>References</i>	1291
27 IMMUNITY	1295
<i>Overview</i>	1296
Antibodies Bind to Epitopes and Have Two Functional Domains	1297
Antibody Reaction with Antigen Is Reversible	1299
Antibodies Come in Many Classes	1300
Antibodies Are Made by B Lymphocytes	1302
The Immune System Has Extraordinary Versatility	1302
Clonal Selection Theory Underlies All Modern Immunology	1303

The Immune System Has a Memory	1304
Other Parts of the Immune Response Are Carried Out by T Lymphocytes	1306
B Cells and T Cells Have Identifying Surface Markers	1306
Macrophages Play a Central Role in Stimulating Immune Responses	1307
Cells Responsible for the Immune Response Circulate throughout the Body	1308
Tolerance Is a Central Concept of Immunology	1309
Immunopathology Is Disease Caused by the Immune System	1309
<i>Antibodies, B Cells, and the Generation of Diversity</i>	1310
Heavy-Chain Structure Differentiates the Classes of Antibodies	1310
Antibodies Have a Domain Structure	1310
The N-Terminal Domains of H and L Chains Have Highly Variable Structures That Constitute the Antigen-Binding Site	1311
Several Mechanisms Generate Antibody Diversity	1315
DNA Rearrangement Generates Antibody Diversity	1315
A Single Recombination Event Generates Diversity in L Chains	1315
Imprecision of Joining Makes an Important Contribution to Diversity	1318
Lambda Diversity Derives from Multiple Constant Regions	1319
H-Chain Variable Regions Derive from Three Libraries	1319
Recognition Sequences for All Joining Reactions Are Virtually Indistinguishable	1320
The Synthesis of Immunoglobulins Is Like That of Other Extracellular Proteins	1321
<i>The Antigen-Independent Phase of B-Lymphocyte Maturation</i>	1321
B-Lymphocytes Go through an Orderly Process of Gene Rearrangement	1321
The Antigen-Independent Phase Can Generate Cells with 10^{11} Different Specificities	1322

The Immune System Requires Allelic Exclusion	1323
Antibody Gene Rearrangement and Expression Are Controlled by Transcription Factors	1323
<i>T Lymphocytes</i>	1324
There Are Two T-Cell Receptor Molecules	1325
T-Cell Receptors Recognize a Foreign Antigen in Combination with a Self-Molecule	1325
T Cells Are Educated in the Thymus to React with Foreign Proteins but Not Self-Proteins	1329
T Cells Respond to Antigen by Either Killing Cells or Secreting Protein Factors	1330
<i>The Antigen-Dependent Phase of the Immune Response</i>	1332
B-Cell Activation Involves B Cell- T_H Cell Collaboration	1333
Activation Is the Result of Cellular Stimulation	1335
Antibody Secretion by Activated B Cells Entails Many Cellular Changes	1335
The Activation Process Produces Both Plasma Cells and Memory Cells	1335
The Change from Surface Antibody to Secreted Antibody Requires the Synthesis of an Altered H Chain	1335
Antibody Class Switching Also Requires an Altered H Chain	1337
Memory Cells Participate in the Secondary Immune Response	1338
Somatic Mutation of Variable Regions Follows from Activation	1338
Tolerance Is Achieved Partly by Making B Cells Unresponsive	1339
<i>Summary</i>	1340
<i>Review Questions</i>	1341
<i>References</i>	1342
<i>Glossary</i>	G-1
<i>Index</i>	I-1