

Brief Contents

Acknowledgements.....	vii
About the authors.....	vii
Preface.....	viii
Learning from this book.....	x
Online resources.....	xii
Contents.....	xiv
Diseases and medically relevant topics.....	xxvii
Abbreviations.....	xxviii

Part 1

Basic concepts of life

Chapter 1 The basic molecular themes of life.....	3
Chapter 2 Cells and viruses.....	24
Chapter 3 Energy considerations in biochemistry.....	36

Part 2

Structure and function of proteins and membranes

Chapter 4 The structure of proteins.....	51
Chapter 5 Methods in protein investigation.....	78
Chapter 6 Enzymes.....	95
Chapter 7 The cell membrane and membrane proteins ...	112
Chapter 8 Muscle contraction, the cytoskeleton, and molecular motors.....	136

Part 3

Metabolism and nutrition

Chapter 9 General principles of nutrition.....	155
Chapter 10 Food digestion, absorption, and distribution to the tissues.....	164
Chapter 11 The storage fuels: mechanisms of transport, storage, and mobilization of carbohydrate and fat.....	181
Chapter 12 Principles of energy release from food.....	199
Chapter 13 Glycolysis, the TCA cycle, and the electron transport system.....	210
Chapter 14 Energy release from fat.....	239
Chapter 15 An alternative pathway of glucose oxidation: the pentose phosphate pathway.....	246

Chapter 16 Synthesis of glucose (gluconeogenesis).....	252
Chapter 17 Synthesis of fat and related compounds.....	260
Chapter 18 Nitrogen metabolism: amino acid metabolism.....	273
Chapter 19 Nitrogen metabolism: nucleotide metabolism.....	289
Chapter 20 Mechanisms of metabolic control and their applications to metabolic integration.....	302
Chapter 21 Raising electrons of water back up the energy scale: photosynthesis.....	330

Part 4

Information storage and utilization

Chapter 22 The genome.....	343
Chapter 23 DNA synthesis, repair, and recombination.....	360
Chapter 24 Gene transcription.....	382
Chapter 25 Protein synthesis and controlled protein breakdown.....	395
Chapter 26 Control of gene expression.....	418
Chapter 27 Protein sorting and delivery.....	440
Chapter 28 Manipulating DNA and genes.....	457

Part 5

Cells and tissues

Chapter 29 Cell signalling.....	485
Chapter 30 The cell cycle, cell division, cell death, and cancer.....	515

Part 6

Protective mechanisms against disease

Chapter 31 Blood clotting, xenobiotic metabolism, and reactive oxygen species.....	537
Chapter 32 The immune system.....	547

Answers to problems.....	563
Index of diseases and medically relevant topics.....	591
Index.....	593

Contents

Acknowledgements	vii
About the authors	vii
Preface	viii
Learning from this book	x
Online resources	xii
Diseases and medically relevant topics	xxvii
Abbreviations	xxviii

Part 1

Basic concepts of life

Chapter 1 The basic molecular themes of life	3
■ All life forms are similar at the molecular level	3
■ The energy cycle in life	4
■ The laws of thermodynamics deal with energy	4
■ Energy can be transformed from one state to another	5
ATP (adenosine triphosphate) is the universal energy currency in life	5
■ Some basic chemical concepts relevant to biology	5
Chemical bonding in biological molecules	5
Covalent bonds are formed by atoms sharing pairs of electrons	6
■ Double and single bonds	7
Electronegativity differences cause some covalent bonds to be polar	9
Ions are formed when atoms completely gain or lose electrons	10
Some polar groups can ionize in water	10
Noncovalent bonds are electrostatic interactions	10
Ionic bonds	10
Hydrogen bonds	10
van der Waals interactions	11
Hydrophobic interactions	11
■ Functional groups determine the characteristic reactions of biological molecules	11
■ Types of molecules found in living cells	12
Small molecules	12
Macromolecules are made by polymerization of smaller units	13
Protein and nucleic acid molecules have information content	13
■ Proteins	14
Catalysis of reactions by enzyme proteins is central to the existence of life	14
What is the function of enzymes?	15

■ Proteins work by molecular recognition	15
Life is self-assembling due to molecular recognition by proteins	15
Many proteins are molecular machines	15
How can one class of molecule carry out so many tasks?	15
■ Evolution of proteins	15
Development of new genes	16
■ DNA (deoxyribonucleic acid)	16
DNA directs its own replication	16
Genetic code	16
■ Organization of the genome	18
■ How did life start?	18
The RNA world	18
■ Proteomics and genomics	19
■ Appendix: Buffers and pK_a values	19
pK_a values and their relationship to buffers	20
Summary	21
Further reading	22
Problems	23
Chapter 2 Cells and viruses	24
■ Cells are the units of all living systems	24
What determines the size of cells?	24
■ Classification of organisms	24
Prokaryotic cells	25
Eukaryotic cells	26
Basic types of eukaryotic cells	29
■ Viruses	31
Genetic material of viruses	31
Some examples of viruses of special interest	32
Summary	34
Further reading	35
Problems	35
Chapter 3 Energy considerations in biochemistry	36
■ Energy considerations	36
Energy considerations determine whether a chemical reaction is possible in the cell	36
Reversible and irreversible reactions and ΔG values	38
The importance of irreversible reactions in the strategy of metabolism	38
What is the significance of irreversible reactions in a metabolic pathway?	38
How are ΔG values obtained?	39

■ Standard free energy values and equilibrium constants	39
■ The release and utilization of free energy from food	40
■ ATP is the universal energy intermediate in all life	40
■ High- and low-energy phosphates	40
■ What are the structural features of high-energy phosphate compounds?	41
■ The structure of ATP	42
■ What transports the H^+ around the cell?	42
■ How does ATP drive chemical work?	43
■ How does ATP drive other types of work?	45
■ High-energy phosphoryl groups are transferred by enzymes known as kinases	45
■ Energy considerations in covalent and noncovalent bonds	45
■ Noncovalent bonds are the basis of molecular recognition and self-assembly of life forms	46
■ Noncovalent bonds are also important in the structures of individual protein molecules and other macromolecules	46
Summary	47
Further reading	47
Problems	48

Part 2

Structure and function of proteins and membranes

Chapter 4 The structure of proteins	51
■ Structures of the 20 amino acids used in protein synthesis	51
■ Symbols for amino acids	52
■ Aliphatic amino acids	52
■ Aromatic amino acids	52
■ Ionized hydrophilic amino acids	53
■ Uncharged polar hydrophilic amino acids	53
■ Two amino acids with unusual properties	53
■ The different levels of protein structure—primary, secondary, tertiary, and quaternary	54
■ Primary structure of proteins	54
■ Secondary structure of proteins	56
■ Tertiary structure of proteins	58
■ Quaternary structure of proteins	61
■ Protein homologies and evolution	61
■ Protein domains	62
■ Domain shuffling	62
■ Membrane proteins	63
■ Conjugated proteins and posttranslational modifications of proteins	63
■ Extracellular matrix proteins (fibrous proteins)	63

■ Structure of collagens	63
■ Structure of elastin	65
■ Structure of proteoglycans	66
■ Integrins connect the extracellular matrix to the interior of the cell	68
■ Myoglobin and haemoglobin illustrate how protein structure is related to function	69
■ Myoglobin	69
■ Structure of haemoglobin	70
■ Binding of oxygen to haemoglobin	70
■ Theoretical models to explain protein allostery	71
■ Mechanism of the allosteric change in haemoglobin	72
■ The essential role of 2,3-bisphosphoglycerate (BPG) in haemoglobin function	73
■ Effect of pH on oxygen binding to haemoglobin	74
Summary	75
Further reading	76
Problems	77

Chapter 5 Methods in protein investigation	78
■ Purification of proteins	78
■ Column chromatography	79
■ SDS polyacrylamide gel electrophoresis (SDS-PAGE)	81
■ Nondenaturing polyacrylamide gel electrophoresis	82
■ The principles of mass spectrometry	83
■ Mass spectrometers consist of three principal components	83
■ Ionization methods for protein and peptide mass spectrometry	84
■ Types of mass analysers	84
■ Types of mass spectrometers	84
■ Applications of mass spectrometry	85
■ Molecular weight determination of proteins	85
■ Identification of proteins using mass spectrometry without sequencing	85
■ Identification of proteins by limited sequencing and database searching	86
■ Analysis of posttranslational modification of proteins	86
■ Methods of sequencing protein	86
■ Classical methods	86
■ Sequencing by mass spectrometry	86
■ Sequence prediction of proteins from gene DNA sequences	87
■ Determination of the three-dimensional structure of proteins	87

■ X-ray diffraction	87	■ What is cholesterol doing in membranes?	117
■ Nuclear magnetic resonance spectroscopy	87	■ The self-sealing character of the lipid bilayer	118
■ Homology modelling	89	■ Permeability characteristics of the lipid bilayer	118
■ Proteomics	89	■ Membrane proteins and membrane structure	119
■ Bioinformatics and databases	91	■ Structures of integral membrane proteins	120
Summary	93	■ Anchoring of peripheral membrane proteins to membranes	121
Further reading	93	■ Glycoproteins	121
Problems	94	■ Functions of membranes	122
Chapter 6 Enzymes	95	■ Membrane transport	122
■ Enzyme catalysis	95	■ Passive transport or facilitated diffusion	125
■ The nature of enzyme catalysis	96	■ Gated ion channels	125
■ The induced-fit mechanism of enzyme catalysis	97	■ Mechanism of the selectivity of the potassium channel	126
■ Enzyme kinetics	98	■ Nerve-impulse transmission	127
■ Hyperbolic kinetics of a 'classical' enzyme	98	■ How does acetylcholine binding to a membrane receptor result in a nerve impulse?	129
■ Allosteric enzymes	100	■ Myelinated neurons permit more rapid nerve-impulse transmission	132
■ General properties of enzymes	102	■ Role of the cell membrane in maintaining the shape of the cell	132
■ Nomenclature of enzymes	102	■ Cell-cell interactions—tight junctions, gap junctions, and cellular adhesive proteins	134
■ Isozymes	102	Summary	134
■ Enzyme cofactors and activators	102	Further reading	135
■ Covalent modification of enzymes	103	Problems	135
■ Effect of pH on enzymes	103	Chapter 8 Muscle contraction, the cytoskeleton, and molecular motors	136
■ Effect of temperature on enzymes	103	■ Muscle contraction	136
■ Effect of inhibitors on enzymes	103	■ A reminder of conformational changes in proteins	136
■ Competitive and noncompetitive inhibitors	103	■ Types of muscle cell and their energy supply	136
■ Mechanism of enzyme catalysis	104	■ Structure of skeletal striated muscle	137
■ Mechanism of the chymotrypsin reaction	105	■ How does the myosin head convert the energy of ATP hydrolysis into mechanical force on the actin filament?	139
■ The catalytic triad of the active site	105	■ Control of voluntary striated muscle	140
■ The reactions at the catalytic site of chymotrypsin	106	■ How does Ca^{2+} trigger contraction?	140
■ What is the function of the aspartate residue of the catalytic triad?	107	■ Smooth muscle differs in structure and control from striated muscle	141
■ Other serine proteases	108	■ Control of smooth muscle contractions	141
■ A brief description of other types of protease	109	■ The cytoskeleton	143
Summary	109	■ An overview	143
Further reading	110	■ The cytoskeleton is in a constant dynamic state	144
Problems	110	■ The role of actin and myosin in nonmuscle cells	144
Chapter 7 The cell membrane and membrane proteins	112	■ Assembly and collapse of actin filaments	145
■ Basic lipid architecture of membranes	112	■ The role of actin and myosin in cell movement	147
■ The polar lipid constituents of cell membranes	112	■ The role of actin and myosin in intracellular transport of vesicles	147
■ What are the polar groups attached to the phosphatidic acid?	114		
■ Membrane lipid nomenclature	116		
■ What is the advantage of having so many different types of membrane lipid?	116		
■ The fatty acid components of membrane lipids	117		

■ Microtubules, cell movement, and intracellular transport	147
■ Molecular motors: kinesins and dyneins	148
■ Role of microtubules in cell movement	149
■ Role of microtubules and molecular motors in mitosis	149
■ Intermediate filaments	150
Summary	151
Further reading	152
Problems	152

Part 3

Metabolism and nutrition

Chapter 9 General principles of nutrition	155
■ The requirement for energy and nutrients	155
■ Protein	156
■ Fats	156
■ Carbohydrates	157
■ Vitamins	157
■ Guidelines for a healthy diet	160
■ Regulation of food intake	160
■ Hunger, appetite, and satiety	161
■ Integration of hunger and satiety signals by the hypothalamus	161
Summary	162
Further reading	163
Problems	163
Chapter 10 Food digestion, absorption, and distribution to the tissues	164
■ Chemistry of foodstuffs	164
■ Digestion and absorption	165
■ Anatomy of the digestive tract	166
■ What are the energy considerations in digestion and absorption?	166
■ A major question in digestion—why doesn't the body digest itself?	166
■ Digestion of proteins	166
■ HCl production in the stomach	167
■ Pepsin, the proteolytic enzyme of the stomach	167
■ Completion of protein digestion in the small intestine	167
■ Activation of the pancreatic proenzymes	168
■ Absorption of amino acids into the bloodstream	168
■ Digestion of carbohydrates	168
■ Structure of carbohydrates	168
■ Digestion of starch	169
■ Digestion of sucrose	170
■ Digestion of lactose	170
■ Absorption of monosaccharides	170

■ Digestion and absorption of fat	171
■ Resynthesis of TAG in intestinal cells	172
■ Chylomicrons	172
■ Digestion of other components of food	173
■ Storage of food components in the body	173
■ How are food components stored in cells?	174
■ Characteristics of different tissues in terms of energy metabolism	175
■ Overall control of fuel distribution in the body by hormones	177
■ Postprandial condition/absorptive state	178
■ Fasting condition	178
■ Prolonged fasting and starvation	178
■ The emergency situation—fight or flight	179
Summary	179
Further reading	180
Problems	180
Chapter 11 The storage fuels: mechanisms of transport, storage, and mobilization of carbohydrate and fat	181
■ Glucose traffic in the body	181
■ Mechanism of glycogen synthesis	181
■ Breakdown of glycogen to release glucose into the blood	184
■ Key issues in the interconversion of glucose and glycogen	185
■ The liver has glucokinase and the other tissues, hexokinase	185
■ What happens to other sugars absorbed from the intestine?	187
■ Amino acid traffic in the body (in terms of fuel logistics)	188
■ Fat and cholesterol movement in the body: an overview	188
■ Utilization of cholesterol in the body	189
■ Fat and cholesterol traffic in the body: lipoproteins	190
■ Apolipoproteins	190
■ Lipoproteins involved in fat and cholesterol movement in the body	190
■ Metabolism of chylomicrons	191
■ Metabolism of VLDL: TAG and cholesterol transport from the liver	192
■ Mobilization of fat: release of FFA from adipose cells	196
■ How are FFA carried in the blood?	196
Summary	197
Further reading	197
Problems	198

Chapter 12 Principles of energy release from food	199		
■ Overview of glucose metabolism	199	■ The electron transport chain	223
■ Biological oxidation and hydrogen-transfer systems	199	■ Oxidative phosphorylation: the generation of ATP coupled to electron transport	225
■ Energy release from glucose	201	■ How are protons ejected?	227
■ The main stages of glucose oxidation	201	■ ATP synthesis by ATP synthase is driven by the proton gradient	228
■ Stage 1 in the release of energy from glucose: glycolysis	201	■ Structure of ATP synthase	229
■ Stage 2 of glucose oxidation: the TCA cycle	202	■ The F_1 unit and its role in the conversion of ADP + P_i to ATP	229
■ Stage 3 of glucose oxidation: electron transport to oxygen	204	■ Structure of the F_0 unit and its role	231
■ The electron transport chain: a hierarchy of electron carriers	204	■ Mechanism by which proton flow causes rotation of F_0	231
■ Energy release from oxidation of fat	205	■ Transport of ADP into mitochondria and ATP out	233
■ Energy release from oxidation of amino acids	207	■ Re-oxidation of cytosolic NADH from glycolysis by electron shuttle systems	233
■ The interconvertibility of fuels	207	■ The balance sheet of ATP production by electron transport	234
Summary	208	■ Yield of ATP from the oxidation of a molecule of glucose to CO_2 and H_2O	235
Further reading	209	■ Is ATP production the only use that is made of the potential energy in the proton-motive force?	235
Problems	209	Summary	236
Chapter 13 Glycolysis, the TCA cycle, and the electron transport system	210	Further reading	237
■ Stage 1: glycolysis	210	Problems	237
■ Glucose or glycogen? It depends on the location	210	Chapter 14 Energy release from fat	239
■ ATP is needed at the beginning of glycolysis	210	■ Mechanism of acetyl-CoA formation from fatty acids	240
■ Interconversion of dihydroxyacetone phosphate and glyceraldehyde-3-phosphate	213	■ 'Activation' of fatty acids by formation of fatty acyl-CoA derivatives	240
■ Glyceraldehyde-3-phosphate dehydrogenase: an oxidation linked to ATP synthesis	213	■ Transport of fatty acyl-CoA derivatives into mitochondria	240
■ The final steps in glycolysis	214	■ Conversion of fatty acyl-CoA into acetyl-CoA molecules inside the mitochondrion by β -oxidation	241
■ Anaerobic glycolysis	215	■ Energy yield from fatty acid oxidation	241
■ The ATP balance sheet from glycolysis	215	■ Oxidation of unsaturated fat	242
■ Transport of pyruvate into the mitochondria	215	■ Oxidation of odd-numbered carbon-chain fatty acids	242
■ Conversion of pyruvate into acetyl-CoA: a preliminary step before the TCA cycle	215	■ Ketogenesis in starvation and type 1 diabetes mellitus	243
■ Components involved in the pyruvate dehydrogenase reaction	217	■ How is acetoacetate made from acetyl-CoA?	243
■ Stage 2: the TCA cycle	217	■ Peroxisomal oxidation of fatty acids	244
■ A simplified version of the TCA cycle	218	■ Where to now?	244
■ Mechanisms of the TCA cycle reactions	218	Summary	244
■ Generation of GTP coupled to splitting of succinyl-CoA	220	Further reading	245
■ What determines the direction of the TCA cycle?	221	Problems	245
■ Stoichiometry of the cycle	222	Chapter 15 An alternative pathway of glucose oxidation: the pentose phosphate pathway	246
■ How is the concentration of TCA cycle intermediates maintained?	222	■ The pentose phosphate pathway has two main parts	246
■ Stage 3: the electron transport chain that conveys electrons from NADH and $FADH_2$ to oxygen	223		

■ The oxidative part produces equal amounts of ribose-5-phosphate and NADPH	247	Summary	271
■ Conversion of surplus ribose-5-phosphate into glucose-6-phosphate	247	Further reading	272
■ Conversion of glucose-6-phosphate into ribose-5-phosphate without NADPH generation	249	Problems	272
■ Generation of NADPH without net production of ribose-5-phosphate	249	Chapter 18 Nitrogen metabolism:	
■ Why is the pentose phosphate pathway so important in the erythrocyte?	249	amino acid metabolism	273
Summary	251	■ Nitrogen balance in the body	274
Further reading	251	■ General metabolism of amino acids	274
Problems	251	■ Aspects of amino acid metabolism	274
Chapter 16 Synthesis of glucose (gluconeogenesis)	252	■ Glutamate dehydrogenase has a central role in the deamination of amino acids	275
■ Mechanism of glucose synthesis from pyruvate	252	■ What happens to the amino group after deamination? The urea cycle	277
■ What are the sources of pyruvate or oxaloacetate used by the liver for gluconeogenesis?	254	■ Mechanism of arginine synthesis	278
■ Synthesis of glucose from glycerol	255	■ Conversion of citrulline to arginine	278
■ Synthesis of glucose from propionate	256	■ Transport of the amino nitrogen from extrahepatic tissues to the liver	279
■ Effects of ethanol metabolism on gluconeogenesis	256	■ Diseases due to urea cycle deficiencies	280
■ Synthesis of glucose via the glyoxylate cycle in bacteria and plants	257	■ Alternatives to urea formation exist in different animals	280
Summary	258	■ Fate of the oxo-acid or carbon skeletons of deaminated amino acids	280
Further reading	259	■ Genetic errors in amino acid metabolism cause diseases	281
Problems	259	■ Methionine and transfer of methyl groups	282
Chapter 17 Synthesis of fat and related compounds	260	■ Synthesis of amino acids	283
■ Mechanism of fat synthesis	260	■ Synthesis of glutamate	283
■ General principles of the process	260	■ Synthesis of aspartic acid and alanine	283
■ Synthesis of malonyl-CoA is the first step	260	■ Synthesis of serine	283
■ The acyl carrier protein (ACP) and the β -ketoacyl synthase	261	■ Synthesis of glycine	283
■ Mechanism of fatty acyl-CoA synthesis	261	■ Haem and its synthesis from glycine	283
■ Organization of the process of fatty acid synthesis	261	■ Destruction of haem	284
■ The reductive steps in fatty acid synthesis	263	■ Synthesis of adrenaline and noradrenaline	285
■ Fatty acid synthesis takes place in the cytosol	263	Summary	287
■ Synthesis of unsaturated fatty acids	265	Further reading	288
■ Synthesis of TAG and membrane lipids from fatty acids	265	Problems	288
■ Synthesis of new membrane lipid bilayer	266	Chapter 19 Nitrogen metabolism:	
■ Synthesis of glycerophospholipids	266	nucleotide metabolism	289
■ Synthesis of new membrane lipid bilayer	268	■ Structure and nomenclature of nucleotides	289
■ Synthesis of prostaglandins and related compounds	269	■ The sugar component of nucleotides	289
■ The prostaglandins and thromboxanes	270	■ The base component of nucleotides	290
■ Leukotrienes	270	■ Attachment of the bases in nucleotides	290
■ Synthesis of cholesterol	270	■ Synthesis of purine and pyrimidine nucleotides	291
■ Conversion of cholesterol into steroid hormones	271	■ Purine nucleotides	291
		■ The purine salvage pathway	295
		■ Formation of uric acid from purines	296
		■ Control of purine nucleotide synthesis	296
		■ Synthesis of pyrimidine nucleotides	297
		■ How are deoxyribonucleotides formed?	297

■ Medical effects of folate deficiencies	298	Muscle and liver PFK2 enzymes are different	315
■ Thymidylate synthesis is targeted by anticancer agents such as methotrexate	299	Fructose metabolism and its control differs from that of glucose	316
Summary	300	Control of pyruvate dehydrogenase, the TCA cycle, and oxidative phosphorylation	317
Further reading	301	■ Controls of fatty acid oxidation and synthesis	318
Problems	301	Nonhormonal controls	318
Chapter 20 Mechanisms of metabolic control and their applications to metabolic integration	302	Degradation of acetyl-CoA carboxylase is another type of control of fat metabolism	318
■ Why are controls necessary?	302	Hormonal controls on fat metabolism	318
■ The potential danger of futile cycles in metabolism	302	■ Responses to metabolic stress	319
■ How are enzyme activities controlled?	303	Response to low ATP concentrations by AMP-activated protein kinase	319
■ Metabolic control by varying the quantities of enzymes is relatively slow	303	Response of cells to oxygen deprivation	320
■ Metabolic control by regulation of the activities of enzymes in the cell can be very rapid	304	Mechanism of the response to hypoxia	320
Which enzymes in metabolic pathways are regulated?	304	■ Integration of metabolism: the fed and fasting state, and diabetes mellitus	320
The nature of control of enzymes	304	Metabolism in the fed state	321
■ Allosteric control of enzymes	304	Metabolism in the fasting state	322
The mechanism of allosteric control of enzymes and its reversibility	305	Metabolism in prolonged starvation	323
Allosteric control is a tremendously powerful metabolic concept	305	Metabolism in type 1 diabetes mellitus	324
■ Control of enzyme activity by phosphorylation	305	Summary	326
Protein kinases and phosphatases are key players in control mechanisms	305	Further reading	329
Control by phosphorylation usually depends on chemical signals from other cells	306	Problems	329
■ General aspects of the hormonal control of metabolism	306	Chapter 21 Raising electrons of water back up the energy scale: photosynthesis	330
How do glucagon, adrenaline, and insulin work?	306	■ Overview	330
What is a second messenger?	307	Site of photosynthesis: the chloroplast	330
The intracellular second messenger for glucagon and adrenaline is cyclic AMP	307	■ The light-dependent reactions of photosynthesis	331
■ Control of carbohydrate metabolism	308	The photosynthetic apparatus and its organization in the thylakoid membrane	331
Control of glucose uptake into cells	308	How is light energy captured?	332
■ Control of glycogen metabolism	310	Mechanism of light-dependent reduction of NADP ⁺	333
Control of glycogen breakdown in muscle	310	Photosystem II	333
Mechanism of muscle phosphorylase activation by cAMP	311	Photosystem I	333
Control of glycogen degradation in the liver	312	How is ATP generated?	334
Reversal of phosphorylase activation in muscle and liver	312	■ The 'dark reactions' of photosynthesis: the Calvin cycle	335
The switchover from glycogen degradation to glycogen synthesis	312	How is CO ₂ converted into carbohydrate?	335
Mechanism of insulin activation of glycogen synthase	313	Rubisco has an apparent efficiency problem	336
Control of glycolysis and gluconeogenesis	314	The C ₄ pathway	337
		Summary	338
		Further reading	338
		Problems	338
		Part 4	
		Information storage and utilization	
		Chapter 22 The genome	343

■ A brief overview	343	■ Initiation and regulation of DNA replication in eukaryotes	361
■ The structures of DNA and RNA	343	■ Unwinding the DNA double helix and supercoiling	361
■ DNA is chemically a very simple molecule	343	■ How are positive supercoils removed ahead of the replication fork?	362
■ DNA and RNA are both nucleic acids	344	■ The basic enzymic reaction catalysed by DNA polymerases	364
■ The primary structure of DNA	344	■ How does a new strand get started?	365
■ There are four different nucleotide bases in DNA	344	■ The polarity problem in DNA replication	365
■ Attachment of the bases to deoxyribose	344	■ Mechanism of Okazaki fragment synthesis	366
■ The physical properties of the polynucleotide components	345	■ Enzyme complex at the replication fork in <i>E. coli</i>	366
■ Structure of the polynucleotide of DNA	345	■ Processing the Okazaki fragments	368
■ Deoxyribose makes DNA more stable than RNA	346	■ The machinery in the eukaryotic replication fork	369
■ Thymine instead of uracil allows DNA repair	346	■ Telomeres solve the problem of replicating the ends of eukaryotic chromosomes	369
■ The DNA double helix	347	■ How is telomeric DNA synthesized?	370
■ Complementary base pairing	347	■ Telomeres stabilize the ends of linear chromosomes	371
■ DNA chains are antiparallel; what does this mean?	350	■ Telomere shortening correlates with ageing	371
■ Base pairing in RNA	350	■ How is fidelity achieved in DNA replication?	371
■ Genome organization	351	■ Exonucleolytic proofreading	372
■ The prokaryotic genome	351	■ Methyl-directed mismatch repair	372
■ Plasmids	351	■ Repair of DNA damage in <i>E. coli</i>	373
■ The eukaryotic genome: chromosomes	351	■ DNA damage repair in eukaryotes	375
■ The mitochondrial genome	351	■ Homologous recombination	375
■ The structure of protein-coding genes	352	■ Mechanism of homologous recombination	375
■ What is a gene?	352	■ Recombination in eukaryotes	379
■ Protein-coding regions of genes in eukaryotes are split up into different sections	352	■ Replication of mitochondrial DNA	379
■ Gene duplication facilitates evolution of new genes	353	■ DNA synthesis by reverse transcription in retroviruses	379
■ Most of the human genome does not encode proteins	354	Summary	380
■ Mobile genetic elements	354	Further reading	381
■ Repetitive DNA sequences	355	Problems	381
■ RNA-coding genes	355	Chapter 24 Gene transcription	382
■ Pseudogenes	355	■ Messenger RNA	382
■ Genome packaging	356	■ The structure of RNA	382
■ The prokaryotic genome is compacted in the cell	356	■ How is mRNA synthesized?	382
■ How is eukaryotic DNA packed into a nucleus?	356	■ Some general properties of mRNA	383
■ The tightness of DNA packaging changes during the cell cycle	356	■ Some essential terminology	383
■ The tightness of DNA packing can regulate gene activity	357	■ Gene transcription in <i>E. coli</i>	384
Summary	358	■ Phases of gene transcription	384
Further reading	359	■ The rate of gene transcription initiation in prokaryotes	386
Problems	359	■ Control of transcription by different sigma factors	386
Chapter 23 DNA synthesis, repair, and recombination	360	■ Gene transcription in eukaryotic cells	386
■ Overall principle of DNA replication	360	■ Eukaryotic RNA polymerases	386
■ Control of initiation of DNA replication in <i>E. coli</i>	361	■ How is transcription initiated at eukaryotic promoters?	387

■ Type II eukaryotic gene promoters	387	■ Protein folding and prion diseases	412
■ Elongation of the transcript requires Pol II modification	388	■ Programmed destruction of protein by proteasomes	413
■ Capping the RNA transcribed by RNA polymerase II	388	■ Introduction	413
■ Split genes and RNA splicing	389	■ The structure of proteasomes	413
■ Ribozymes and self-splicing of RNA	391	■ Proteins destined for destruction in proteasomes are marked by ubiquitination	414
■ Termination of transcription in eukaryotic cells: 3' polyadenylation	391	■ The role of proteasomes in the immune system	415
■ Editing of mRNAs	392	Summary	415
■ Transcription of nonprotein-coding genes	392	Further reading	416
■ Gene transcription in mitochondria	393	Problems	416
Summary	393	Chapter 26 Control of gene expression	418
Further reading	394	■ Levels of regulation	418
Problems	394	■ Gene control in <i>E. coli</i> : the <i>lac</i> operon	418
Chapter 25 Protein synthesis and controlled protein breakdown	395	■ Structure of the <i>E. coli lac</i> operon	419
■ Essential basis of the process of protein synthesis	395	■ Transcriptional regulation in eukaryotes	420
■ The genetic code	396	■ A general overview of the differences in the initiation and control of gene transcription in prokaryotes and eukaryotes	420
■ A preliminary simplified look at the chemistry of peptide synthesis	396	■ DNA elements involved in eukaryotic gene control	421
■ ATP and GTP hydrolysis in translation	397	■ Transcription factors can be classified by protein motifs that are involved in DNA binding	422
■ How are the codons translated?	397	■ How do eukaryotic transcription factors influence transcription?	425
■ Transfer RNA	398	■ Most transcription factors are themselves regulated	426
■ The wobble mechanism	398	■ Transcription repressors	426
■ How are amino acids attached to tRNA molecules?	399	■ The role of chromatin in eukaryotic gene control	427
■ Ribosomes	400	■ DNA methylation and epigenetic control	429
■ Initiation of translation	402	■ Gene control after transcription is initiated: an overview	429
■ Initiation of translation in <i>E. coli</i>	402	■ Gene control post-transcription initiation in prokaryotes	430
■ Initiation factors in <i>E. coli</i>	403	■ Attenuation in the <i>E. coli trp</i> operon	430
■ Once initiation is achieved, elongation is the next step	404	■ Bacterial riboswitches	430
■ Elongation factors in <i>E. coli</i>	404	■ mRNA stability and the control of gene expression	431
■ Mechanism of elongation in <i>E. coli</i>	404	■ Determinants of eukaryotic mRNA stability and their role in gene expression control	432
■ How is accuracy of translation achieved?	405	■ Translational control mechanisms in eukaryotes	433
■ Mechanism of translocation on the <i>E. coli</i> ribosome	406	■ Translational control in iron homeostasis and haem synthesis	433
■ Termination of protein synthesis in <i>E. coli</i>	407	■ Regulation of globin synthesis by translation initiation factor eIF2	434
■ Physical structure of the ribosome	407	■ Small RNAs and RNA interference	434
■ What is a polysome?	408		
■ Protein synthesis in eukaryotes	408		
■ Incorporation of selenocysteine into proteins	410		
■ Protein synthesis in mitochondria	410		
■ Folding up of the polypeptide chain	410		
■ Chaperones (heat shock proteins)	410		
■ Mechanism of action of molecular chaperones	411		
■ Enzymes involved in protein folding	412		

■ Classes and production of small RNAs in eukaryotes	434	■ Regulation of nuclear transport by cell signals and its role in gene control	454
■ Molecular mechanism of gene silencing by RNAi	436	Summary	455
■ <i>In vivo</i> functions and importance of noncoding RNA	437	Further reading	456
■ The potential medical and practical importance of RNAi	437	Problems	456
Summary	438	Chapter 28 Manipulating DNA and genes	457
Further reading	439	■ Basic methodologies	457
Problems	439	■ Some preliminary considerations	457
Chapter 27 Protein sorting and delivery	440	■ Cutting DNA with restriction endonucleases	458
■ A preliminary overview of the field	440	■ Separating DNA pieces	458
■ Structure and function of the ER and Golgi apparatus	441	■ Visualizing the separated pieces	459
■ The importance of the GTP/GDP switch mechanism in protein targeting	442	■ Detection of specific DNA fragments by nucleic acid hybridization probes	459
■ Translocation of proteins through the ER membrane	443	■ Southern blotting	460
■ Mechanism of cotranslational transport through the ER membrane	443	■ Chemical synthesis of DNA	460
■ Synthesis of integral membrane proteins	445	■ Sequencing DNA	461
■ Folding of the polypeptides inside the ER	445	■ The principle of DNA sequencing by the chain-termination method	461
■ Glycosylation of proteins in the ER lumen and Golgi apparatus	446	■ Amplification of DNA by the polymerase chain reaction	464
■ Proteins for lysosomes	446	■ Analysis of multiple gene expression in cells using DNA microarrays	465
■ Proteins to be returned to the ER	446	■ Joining DNA to form recombinant molecules	466
■ Proteins to be secreted from the cell	446	■ Cloning DNA	466
■ Proteins are sorted, packaged, and despatched from the ER and Golgi by vesicular transport	447	■ Cloning in plasmids	467
■ Mechanism of COP-coated vesicle formation	447	■ Cloning libraries	468
■ How does a vesicle find its target membrane?	447	■ Cloning vectors for larger pieces of DNA	469
■ Clathrin-coated vesicles transport enzymes from the Golgi to form lysosomes	448	■ Applications of recombinant DNA technology	470
■ Posttranslational transport of proteins into organelles	448	■ Working with RNA and cDNA to study gene expression	470
■ Transport of proteins into mitochondria	448	■ Production of human proteins and proteins from other sources	470
■ Mitochondrial matrix proteins are synthesized as preproteins	449	■ Expressing the cDNA in <i>E. coli</i>	471
■ Delivery of proteins to mitochondrial membranes and intermembrane space	450	■ Site-directed mutagenesis	472
■ Nuclear–cytosolic traffic	451	■ PCR in forensic science	472
■ Why is there a nuclear membrane?	451	■ Locating disease-producing genes	473
■ The nuclear pore complex	451	■ Knockout mice	475
■ Nuclear localization signals	452	■ The embryonic stem (ES) cell system	475
■ Importins combine with nuclear localization signals on proteins to be transported into the nucleus	453	■ Gene targeting	475
■ GTP/GDP exchange imparts directionality to nuclear–cytosolic transport	453	■ Stem cells and potential therapy for human diseases	476
		■ Gene therapy	477
		■ Genome editing using CRISPR	478
		■ Transgenic organisms	478
		■ DNA databases and genomics	479
		Summary	480
		Further reading	480
		Problems	481

Part 5

Cells and tissues

Chapter 29 Cell signalling	485	Summary	513
■ Overview	485	Further reading	514
■ Organization of this chapter	487	Problems	514
■ What are the signalling molecules?	487		
■ Neurotransmitters	487	Chapter 30 The cell cycle, cell division, cell death, and cancer	515
■ Cytokines and growth factors	488	■ The eukaryotic cell cycle	515
■ Vitamin D and retinoic acid	489	■ The cell cycle is divided into separate phases	515
■ How do cells detect signals and how do they transmit that information to the interior of the cell?	489	■ The cell cycle phases are tightly controlled	516
■ Responses mediated by intracellular receptors	489	■ Cell cycle controls	516
■ Responses mediated by receptors in the cell membrane	490	■ Cytokines and growth factor control in the cell cycle	516
■ There are three main types of membrane-bound receptors	490	■ Cell cycle checkpoints	517
■ General concepts in cell signalling mechanisms	493	■ Cell cycle controls depend on the synthesis and destruction of cyclins	517
■ Protein phosphorylation	493	■ Controls in G_1 are complex	518
■ Binding domains of signal transduction proteins	493	■ The G_1 checkpoint	518
■ Terminating signals	494	■ How is DNA damage detected?	519
■ Signalling mechanisms in greater detail	494	■ Progression to S phase	519
■ Examples of signal transduction pathways	494	■ Progression to M phase	519
■ Signal transduction pathways from tyrosine kinase receptors	494	■ M phase	520
■ The Ras pathway	494	■ Cell division	520
■ The phosphatidylinositol 3-kinase (PI 3-kinase) pathway and insulin signalling	499	■ Mitosis	520
■ The JAK/STAT pathways: another type of tyrosine kinase-associated signalling system	503	■ Meiosis	521
■ G-protein-coupled receptors and associated signal transduction pathways	504	■ Apoptosis	522
■ Overview	504	■ What is the function of apoptosis?	522
■ cAMP as second messenger: adrenaline signalling: a G-protein pathway	504	■ There are two main pathways that initiate apoptosis	523
■ The phosphatidylinositol cascade: another example of a G-protein-coupled receptor that works via a different second messenger	507	■ Caspase enzymes are the effectors of apoptosis	523
■ Other roles of calcium in regulation of cellular processes	508	■ The intrinsic pathway of apoptosis involves mitochondria	524
■ Vision: a process dependent on a G-protein-coupled receptor	509	■ Regulation of the intrinsic pathway of apoptosis by Bcl-2 proteins	524
■ Signal transduction pathway using cGMP as a second messenger	511	■ The extrinsic pathway of apoptosis involves death receptors on the cell surface	525
■ Membrane receptor-mediated pathways	511	■ Cancer	525
■ Nitric oxide signalling: activation of a soluble cytosolic guanylate cyclase	511	■ Telomere shortening limits the number of times most normal cells can divide	525
■ Overview and summary	512	■ Cancer development involves a progression of mutations	526
		■ Development of colorectal cancer	527
		■ Genetic changes in cancer involve oncogenes and tumour-suppressor genes	528
		■ Oncogenes frequently activate signalling pathways	528
		■ How are oncogenes acquired?	529
		■ Retroviruses can activate or acquire cellular protooncogenes	529

■ Tumour-suppressor genes are cell cycle control genes	530
■ Mechanism of protection by the p53 gene	530
■ Mechanism of protection by the retinoblastoma gene	530
■ Molecular biology advances have potential for development of new cancer therapies	531
Summary	532
Further reading	533
Problems	533

Part 6

Protective mechanisms against disease

Chapter 31 Blood clotting, xenobiotic metabolism, and reactive oxygen species	537
■ Blood clotting (coagulation, thrombus formation)	537
■ What signals the necessity for clot formation?	538
■ How does thrombin cause thrombus formation?	538
■ Keeping clotting in check	539
■ Rat poison, blood clotting, and vitamin K	539
■ Protection against ingested foreign chemicals (xenobiotics)	540
■ Cytochrome P450	540
■ Secondary modification: addition of a polar group to products of the P450 attack	541
■ Medical significance of P450s	542
■ Multidrug resistance	542
■ Protection against reactive oxygen species (ROS)	542
■ Formation of the superoxide anion and other reactive oxygen species	542
■ Mopping up oxygen free radicals with vitamins C and E	543
■ Enzymatic destruction of superoxide by superoxide dismutase	544
■ The glutathione peroxidase–glutathione reductase system	544
Summary	545
Further reading	545
Problems	545

Chapter 32 The immune system	547
■ Overview	547
■ The innate immune response	547
■ The adaptive immune response	547
■ The problem of autoimmune reactions	548
■ The cells involved in the immune system	548
■ What does the adaptive immune response achieve?	548
■ Where is the adaptive immune system located?	548
■ Antibody-based or humoral immunity	549
■ Structure of antibodies (immunoglobulins)	549
■ What are the functions of antibodies?	550
■ There are different classes of antibodies	550
■ Generation of antibody diversity	550
■ Activation of B cells to produce antibodies	552
■ Deletion of potentially self-reacting B cells in the bone marrow	552
■ The theory of clonal selection	552
■ B cells must be activated before they can develop into antibody-secreting cells	552
■ Affinity maturation of antibodies	554
■ Memory cells	555
■ Cell-mediated immunity (cytotoxic T cells)	555
■ Mechanism of action of cytotoxic T cells	556
■ The role of the major histocompatibility complexes (MHCs) in the displaying of peptides on the cell surface	556
■ CD proteins reinforce the selectivity of T cell receptors for the two classes of MHCs	557
■ The immune system needs to be tightly regulated	557
■ Why does the human immune system reject transplanted human cells?	558
■ Monoclonal antibodies	558
■ Humanized monoclonal antibodies	559
Summary	559
Further reading	560
Problems	561
Answers to problems	563
Index of diseases and medically relevant topics	591
Index	593