Brief content

xxix

xxxi

247

Pa	art 1 Basic concepts of life	
1	The basic molecular themes of life	3
2	Cells and viruses	15
3	Energy considerations in biochemistry	27
Pa	rt 2 Structure and function of proteins and membranes	· · · · · ·
4		47
5	Methods in protein investigation	47 74
6	Enzymes	90
7	The cell membrane and membrane proteins	105
8	Muscle contraction, the cytoskeleton, and	10)
	molecular motors	130
 Pa	rt3 Metabolism	
9	Food digestion, absorption, distribution to the tissues, and appetite control	151
10	Biochemical mechanisms involved in transport, storage, and mobilization of	
	dietary components	168
	Principles of energy release from food	184
12	Glycolysis, the citric acid cycle, and the electron transport system: reactions involved in these pathways	196
13	Energy release from fat	226
14	The synthesis of fat and related compounds	233

15 Synthesis of glucose (gluconeogenesis)

Diseases and medically relevant topics

List of abbreviations

S

16	Strategies for metabolic control and their	
	application to carbohydrate and fat metabolism	255
17	Why should there be an alternative pathway of glucose oxidation? The pentose phosphate	
	pathway	279
18	Raising electrons of water back up the energy	2/9
	scale—photosynthesis	285
19	Amino acid metabolism	295
20	Enzymic protective mechanisms in the body	312
21	Nucleotide synthesis and metabolism	324
Pa	art 4 Information storage and utilization	
22	DNA and genomes	341
23	DNA synthesis, repair, and recombination	356
24	Gene transcription and control	380
25	resis and controlled protein	
	breakdown	408
26	Protein targeting—how proteins are delivered	
	to their cellular destinations	432
	Signal transduction	452
28	Manipulating DNA and genes	482
— Pa	rt 5 The immune system, cell cycle,	The state of the s
	apoptosis, and cancer	
	The immune system	509
30	Cell cycle control, apoptosis, and cancer	524
Fig	ure acknowledgements	538

540

567

569

Answers to problems

Index

Index of diseases and medically relevant topics

Contents

Preface Acknowledgements List of abbreviations

ix xxxi

3

13

14



Summary

Further reading

Part 1 Basic concepts of life

Unity of life at the molecular level	3
Living cells obey the laws of physics and chemistry: the energy cycle in life	3
 ATP (adenosine triphosphate) is the universal energy currency in life 	4
Types of molecule found in living cells	4
Small molecules	5
• The macromolecular constituents of cells	5
Proteins	5
 Catalysis of reactions by enzyme proteins is central to the existence of life 	5
Evolution of proteins	7
Development of new genes	7
DNA (deoxyribonucleic acid)	7
DNA can direct its own replication	8
Junk DNA	9
Molecular recognition by proteins	10
Noncovalent or weak chemical bonds	10
How did it all start?	10
The RNA world	11
The new 'omics' phase of biochemistry and	

Chapter 1 The basic molecular themes of life

Chapter 2 Cells and viruses	15
Cells are the units of all living systems	15
Classification of organisms	15
Prokaryotic cells	15
Cell division in prokaryotes	16
Eukaryotic cells	17
Eukaryotic cell growth and division	20
Stem cells	20
Mitosis and cell division in eukaryotic cells	21
• Meiosis	21
Viruses	23
Genetic material of viruses	24
Some examples of viruses of special interest	24
• Retroviruses	25
Summary	
Further reading	25
Problems	26
	26
Chapter 3 Energy considerations in biochemistry	27
 What determines whether a chemical reaction is 	
possible?	27
• Reversible and irreversible reactions and ΔG values	28
 The importance of irreversible reactions in the strategy of metabolism 	
Why is this metabolic strategy used in the cell?	29
 How are ΔG values obtained? 	29 30
Standard free-energy values and equilibrium constants	30
• Given that a reaction has a negative ΔG value, what	50
determines whether it actually takes place at	
a perceptible rate in the cell?	30
How is food breakdown in cells coupled to drive	

32

32

energy-requiring reactions?

The high-energy phosphate compound

What is a 'high-energy phosphate compound'?

xvi CONTENTS

What are the structural features of high-energy	
phosphate compounds?	33
• What transports the —® around the cell?	35
How does ATP perform chemical work?	35
Calculation of ΔG value	36
• How does ATP drive other types of work?	37
A note on the relationship between AMP, ADP, and ATP	37
Covalent and noncovalent bonds	37
What causes weak bond formation and breakage?	39
 The vital role of weak bonds in molecular recognition 	39
Appendix: Buffers and pK_a values	39
$ullet$ p K_a values and their relationship to buffers	40
Summary	42
Further reading	42
Problems	42
Chanter / The church	
Chapter 4 The Structure of proteins	47
Chapter 4 The structure of proteins The primary structure of proteins	47
The primary structure of proteins	47
The primary structure of proteins What is a native protein?	
The primary structure of proteins What is a native protein?	47 48
 The primary structure of proteins What is a native protein? What are the basic considerations which determine the folded structure of a protein? 	47 48 48
 The primary structure of proteins What is a native protein? What are the basic considerations which determine the folded structure of a protein? Structures of the 20 amino acids Hydrophobic amino acids 	47 48 48 49
 The primary structure of proteins What is a native protein? What are the basic considerations which determine the folded structure of a protein? Structures of the 20 amino acids Hydrophobic amino acids Hydrophilic amino acids 	47 48 48 49 49
 The primary structure of proteins What is a native protein? What are the basic considerations which determine the folded structure of a protein? Structures of the 20 amino acids Hydrophobic amino acids Hydrophilic amino acids Amino acids for special purposes 	47 48 48 49
 The primary structure of proteins What is a native protein? What are the basic considerations which determine the folded structure of a protein? Structures of the 20 amino acids Hydrophobic amino acids Hydrophilic amino acids Amino acids for special purposes Ionization of amino acids 	47 48 48 49 49 50
 The primary structure of proteins What is a native protein? What are the basic considerations which determine the folded structure of a protein? Structures of the 20 amino acids Hydrophobic amino acids Hydrophilic amino acids Amino acids for special purposes Ionization of amino acids Symbols for amino acids 	47 48 48 49 49 50 50
 The primary structure of proteins What is a native protein? What are the basic considerations which determine the folded structure of a protein? Structures of the 20 amino acids Hydrophobic amino acids Hydrophobic amino acids Amino acids for special purposes Ionization of amino acids Symbols for amino acids The different levels of protein structure—primary 	47 48 48 49 49 50 50 51
 The primary structure of proteins What is a native protein? What are the basic considerations which determine the folded structure of a protein? Structures of the 20 amino acids Hydrophobic amino acids Hydrophilic amino acids Amino acids for special purposes Ionization of amino acids Symbols for amino acids Symbols for amino acids The different levels of protein structure—primary, secondary, tertiary, and quaternary 	47 48 48 49 49 50 50 51
 The primary structure of proteins What is a native protein? What are the basic considerations which determine the folded structure of a protein? Structures of the 20 amino acids	47 48 48 49 49 50 50 51 51
 The primary structure of proteins What is a native protein? What are the basic considerations which determine the folded structure of a protein? Structures of the 20 amino acids Hydrophobic amino acids Hydrophilic amino acids Amino acids for special purposes lonization of amino acids Symbols for amino acids The different levels of protein structure—primary, secondary, tertiary, and quaternary Secondary structure of proteins The α helix 	47 48 48 49 49 50 50 51 51
 The primary structure of proteins What is a native protein? What are the basic considerations which determine the folded structure of a protein? Structures of the 20 amino acids Hydrophobic amino acids Hydrophilic amino acids Amino acids for special purposes lonization of amino acids Symbols for amino acids The different levels of protein structure—primary, secondary, tertiary, and quaternary Secondary structure of proteins The α helix The β-pleated sheet 	47 48 48 49 49 50 50 51 51 51 52 52 52 53
 What is a native protein? What are the basic considerations which determine the folded structure of a protein? Structures of the 20 amino acids Hydrophobic amino acids Hydrophobic amino acids Hydrophilic amino acids Amino acids for special purposes Ionization of amino acids Symbols for amino acids The different levels of protein structure—primary, secondary, tertiary, and quaternary Secondary structure of proteins The \(\alpha\) helix The \(\beta\) pleated sheet Connecting loops 	47 48 48 49 49 50 50 51 51
 What is a native protein? What are the basic considerations which determine the folded structure of a protein? Structures of the 20 amino acids Hydrophobic amino acids Hydrophilic amino acids Amino acids for special purposes Ionization of amino acids Symbols for amino acids The different levels of protein structure—primary, secondary, tertiary, and quaternary Secondary structure of proteins The α helix The β-pleated sheet Connecting loops Tertiary structure of proteins 	47 48 48 49 49 50 50 51 51 51 52 52 52 53
 The primary structure of proteins What is a native protein? What are the basic considerations which determine the folded structure of a protein? Structures of the 20 amino acids Hydrophobic amino acids Hydrophilic amino acids Amino acids for special purposes Ionization of amino acids Symbols for amino acids The different levels of protein structure—primary, secondary, tertiary, and quaternary Secondary structure of proteins The α helix The β-pleated sheet Connecting loops Tertiary structure of proteins How do the three motifs—the α helix, the β-pleated sheet and 	47 48 48 49 49 50 50 51 51 52 52 52 53 54
 What is a native protein? What are the basic considerations which determine the folded structure of a protein? Structures of the 20 amino acids	47 48 48 49 49 50 50 51 51 52 52 52 53 54 54
 What is a native protein? What are the basic considerations which determine the folded structure of a protein? Structures of the 20 amino acids Hydrophobic amino acids Hydrophobic amino acids Amino acids for special purposes lonization of amino acids Symbols for amino acids Symbols for amino acids Symbols for amino acids Symbols for amino acids The different levels of protein structure—primary, secondary, tertiary, and quaternary Secondary structure of proteins The α helix The β-pleated sheet Connecting loops Tertiary structure of proteins How do the three motifs—the α helix, the β-pleated sheet, and connecting loops—make up a protein? What forces hold the tertiary structure in position? Where do the disulphide or S—S covalent bonds come into 	47 48 48 49 49 50 50 51 51 52 52 52 53 54
 What is a native protein? What are the basic considerations which determine the folded structure of a protein? Structures of the 20 amino acids	47 48 48 49 49 50 50 51 51 52 52 52 53 54 54

Protein homologies and evolution	57	
Protein domains	57	
 Domain shuffling 	57	
The problem of protein folding	58	
Membrane proteins	58	
Conjugated proteins	58	
Extracellular matrix proteins	58	
Structure of collagens	59	
Box 4.1 Genetic diseases of collagen	61	
Structure of elastin	61	
Structure of proteoglycans	61	
 Adhesion proteins of the extracellular matrix 	63	
 Integrins are important signalling proteins 	64	
 Myoglobin and haemoglobin—an illustration of how protein structure is related to function 	64	
Myoglobin	65	
Structure of haemoglobin	65	
 Binding of oxygen to haemoglobin 	66	
How is the sigmoidal oxygen saturation curve achieved?	66	
 Binding of oxygen to haemoglobin How is the sigmoidal oxygen saturation curve achieved? Theoretical models to explain protein allosterism Mechanism of the allosteric change in haemoglobin The essential role of 2:3-bisphosphoglycerate (BPG) in 	heoretical models to explain protein allosterism	67
haemoglobin	67	
haemoglobin function	68	
Effect of pH on oxygen binding to haemoglobin	69	
Role of pH changes in oxygen and CO₂ transport	69	
Box 4.2 Sickle cell anaemia and thalassaemias	70	
pH buffering in the blood	71	
Summary	71	
Further reading	72	
Problems	72	
Chapter 5 Methods in protein investigation	74	
Purification of proteins	74	
Column chromatography	75	
SDS polyacrylamide gel electrophoresis	76	
Immunological detection of proteins	77	
Methods of protein sequencing	78	
 The role of databases in protein sequencing 	78	
Deduction of amino acid sequences of proteins		
from the base sequence of genes	79	

Determination of the three-dimensional	
structure of proteins	79
X-ray diffraction	79
Nuclear magnetic resonance	80
 Homology modelling 	80
 An exercise in obtaining a 3-D structure from a protein database 	80
Analysis of proteins by mass spectrometry	80
• Introduction	80
Mass spectrometers consist of three principal components	80
 Ionization methods for protein and peptide MS 	80
Types of mass analyser	81
Quadrupole (Q)	81
Time of flight (TOF) Ion-trap	81 81
Types of mass spectrometer	
Single-analyser mass spectrometers	81 81
Tandem mass spectrometers (MS/MS)	81
 Identification of proteins using MS for peptide 	
mass analysis ('fingerprinting') and database searching	•
Searching	81
Identification of proteins by limited sequencing and database searching	82
 Sequencing a protein by MS 	83
 Molecular-weight determination of proteins 	83
 Analysis of posttranslational modification of proteins 	83
Proteomics and MS	83
Bioinformatics and databases	84
A bioinformatics overview	84
Database website addresses	85
Appendix: An example of how the structure of	
a protein can be obtained from the protein data bank (PDB)	85
Summary	87
Further reading	88
Problems	89
Chapter 6 Enzymes	90
Enzyme catalysis	90
The nature of enzyme catalysis	91
The induced-fit mechanism of enzyme catalysis	92
Enzyme kinetics	93
Hyperbolic kinetics of a 'classical' enzyme	93

Allosteric enzymes

	CONTENTS	xv i
General properties of enzymes	95	
Nomenclature of enzymes	95	
• Isozymes	95	
Enzyme cofactors and activators	95	
• Effect of pH on enzymes	96	
Effect of temperature on enzymes	96	
Effect of inhibitors on enzymes	97	
Reversible and irreversible inhibitors Competitive and noncompetitive inhibitors	97 97	
What are the structural features of enzyme proteins that confer catalytic activity on them?	t 98	
Mechanism of the chymotrypsin reaction	98	
The catalytic triad of the active centre	98	
 The reactions at the catalytic centre of chymotrypsin 	99	
 What is the function of the aspartate residue of the catalytic triad? 		
Other serine proteases	101	
A brief description of other types of protease	101	
	101	
Summary	102	
Further reading Problems	103	
Fioneins	104	
Chapter 7 The cell membrane and membrane proteins	105	
Basic lipid architecture of membranes	105	
The polar lipid constituents of cell membranes	105	
Glycerophospholipids	106	
 What are the polar groups attached to the phosphatidic acid? 		
Sphingolipids	107	
Membrane lipid nomenclature	108	
Why are there so many different types of	109	
membrane lipid?	110	
 The fatty acid components of membrane lipids 	110	
• What is cholesterol doing in membranes?	111	
 The self-sealing character of the lipid bilayer 	111	
 Permeability characteristics of the lipid bilayer 	112	
Membrane proteins and membrane design	112	
Structures of integral membrane proteins	112	
 Anchoring of peripheral membrane proteins to membranes 		
• Glycoproteins	114	
- discoproteins	114	

CONTENTS

Functions of membranes	115
	_
Transport of substances in and out of the cell Active transport	115
Active transport	115
Calculation of energy required for transport	115
Mechanism of the Na $^+/K^+$ pump	115
Box 7.1 Cardiac glycosides	116
Symport systems	117
Antiport systems Uniport systems	117
Passive transport or facilitated diffusion	117 118
Gated ion channels	118
Mechanism of the selectivity of the potassium channel	118
Nerve-impulse transmission	120
Box 7.2 Cholinesterase inhibitors and Alzheimer's disease	
The acetylcholine-gated Na $^+/K^+$ channel or acetylcholine receptor	121 121
How does acetylcholine binding to a membrane receptor	121
result in a nerve impulse?	121
How is the initial signal propagated along nerve axons?	122
Mechanism for ensuring that the nerve impulse only goes forward	124
Mechanism of control of the voltage-gated Na† and K+ channels	124
 Myelinated neurons permit more rapid nerve-impulse transmission 	125
Why doesn't the Na ⁺ /K ⁺ pump conflict with the	
propagation of action potentials?	125
 Role of the cell membrane in maintaining the shape of the cell 	125
 Cell-cell interactions—tight junctions, gap junctions, and cellular adhesive proteins 	126
Box 7.3 Membrane-targeted antibiotics	127
Summary	127
Further reading	128
Problems	
	129
Chapter 8 Muscle contraction, the cytoskeleton, and molecular motors	120
	130
Muscle contraction	130
A reminder of conformational changes in proteins	130
Types of muscle cell and their energy supply	130
Structure of skeletal striated muscle	131
Structure of the myofibril	131
How does the sarcomere shorten?	131
Structure and action of thick and thin filaments	132
 How does the myosin head convert the energy of ATP 	
hydrolysis into mechanical force on the actin filament?	133
Mechanism of the conformational changes in the myosin head	133
Box 8.1 Muscular dystrophy	134

How is contraction in voluntary striated muscle controlled?	136
• How does Ca ²⁺ trigger contraction?	136
Box 8.2 Malignant hyperthermia	138
How does smooth muscle differ in structure and control from striated muscle? • Control of smooth muscle contractions	138 138
How does Ca ²⁺ control smooth muscle contraction?	138
The cytoskeleton	139
Molecular motors and movements in cells	139
The role of actin and myosin in nonmuscle cells	139
 Structural role of actin and its involvement in cell movement Mechanism of contraction in nonmuscle cells 	140 140
 The role of actin and myosin in intracellular transport of vesicles 	141
Microtubules, cell movement, and intracellular transport	141
Microtubules and intracellular transport	142
Molecular motors: kinesins and dyneins Role of microtubules in cell movement	142 143
Role of microtubules in mitosis	143
Intermediate filaments	143
Box 8.3 Effects of drugs on the cytoskeleton	144
Summary	144
Further reading	145
Part 3 Metabolism	146
Chapter 9 Food digestion, absorption, distribution to the tissues, and appetite control	151
Chemistry of foodstuffs	151
Digestion and absorption	152
Anatomy of the digestive tract	152
What are the energy considerations in digestion and absorption?	152
 A major problem in digestion—why doesn't the body digest itself? 	153
Zymogen or proenzyme production	153
Protection of intestinal epithelial cells by mucous	153

Glucose traffic in the body Mechanism of glycogen synthesis	168 168
Chapter 10 Biochemical mechanisms involved in transport, storage, and mobilization of dietary components	168
Problems	167
Further reading	166
Summary	165
Can hormones be used therapeutically to control obesity?	165
How do these hormones control appetite? Can be manage he used the rapputically to control obesity?	164
Hormones which control appetite	164
Regulation of food intake: appetite control	164
The emergency situation—fight or flight	164
Prolonged fasting or starvation	163
Postprandial conditionFasting condition	163
by hormones • Postprandial condition	163 163
Overall control of fuel distribution in the body	
Characteristics of different tissues in terms of energy metabolism	161
Storage of fat in the body Are amino acids stored by the body?	160
Glucose storage as glycogen	160 160
• How are the different food components stored in cells?	160
Storage of food components in the body	160
 Outline of fuel distribution and utilization by the different tissues of the body 	160
Digestion of other components of food Outling of final distribution and utilization but he	159
• Chylomicrons	158
Resynthesis of TAG in intestinal cells	158
Digestion and absorption of fat	157
Absorption of monosaccharides	157
Digestion of lactose	156
Digestion of starch	156
Digestion of carbohydrates	155
Absorption of amino acids into the bloodstream	155
 Activation of the pancreatic proenzymes 	154
Completion of protein digestion in the small intestine	154
Pepsin, the proteolytic enzyme of the stomach	153
 HCl production in the stomach 	153

How is energy injected into the process?

	CONTENTS	xix
G-1-P is converted to the activated form, UDPG Adding branches to glycogen	170 170	
Breakdown of glycogen to release glucose into the blood Removing branches from glycogen	171 172	
Key issues in the interconversion of glucose and glycoger	•	
Why does liver have glucokinase and the other tissues hexokinase?	173	
What happens to other sugars absorbed from the intestine? Colorte a match the color and the co	173	
Galactose metabolism Box 10.1 Uridyl transferase deficiency and galactosaemia	174	
,		
Amino acid traffic in the body (in terms of fuel logistics) Fat and cholesterol traffic in the body	176 176	
Uptake of fat from chylomicrons into cells	176	
Logistics of fat and cholesterol movement in the body	176	
An overview	176	
Utilization of cholesterol in the body	177	
 Lipoproteins involved in fat and cholesterol movement in the body 	178	
Apolipoproteins	179	
 Mechanism of TAG and cholesterol transport from the liver and the reverse cholesterol transport in the body 	179	
The role of HDL in cholesterol transport How does cholesterol exit cells to be picked up by HDL?	179 179	
Cholesterol homeostasis in cells	180	
Box 10.2 Inhibitors of cholesterol synthesis	181	
Release of FFA from adipose cells	181	
How are FFA carried in the blood?	181	
Summary	182	
Further reading	182	
Problems	183	
Chapter 11 Principles of energy release from food	184	
Biological oxidation and hydrogen-transfer systems	184	
NAD —an important electron carrier	185	
FAD and FMN are also electron carriers	186	
Energy release from glucose	186	
The main stages of glucose oxidation	186	
Stage 1 in the release of energy from glucose; glycolysis Appropria glycolysis	186	
Anaerobic glycolysis	186	
 Stage 2 of glucose oxidation: the citric acid cycle How is pyruvate fed into the citric acid cycle? 	188 188	
What is coenzyme A?	188	
Oxidative decarboxylation of pyruvate	189	

XX CONTENTS

Stage 3 of glucose oxidation: electron transport to oxygen	189
 The electron transport chain—a hierarchy of electron carriers 	189
Redox potentials Determination of redox potentials	189
Electrons are transported in a stepwise fashion	190
Calculation of the relationship between	190
the ΔG^{0} value and the E'_{0} value	19
Energy release from oxidation of fat	19
Energy release from oxidation of amino acids	19:
The interconvertibility of fuels	192
Box 11.1 A survey of vitamins	194
Summary	194
Problems	19!
Chapter 12 Glycolysis, the citric acid cycle, and the electron transport system: reactions	Manus dan yan yan
involved in these pathways	19
Stage 1—glycolysis	196
Glucose or glycogen?	190
Why use ATP here at the beginning of glycolysis?	197
Why is glucose-6-phosphate converted to fructose-6-phosphate?	197
Splitting fructose bisphosphate to two C_3 compounds	197
• A note on the $\Delta G^{0\prime}$ and ΔG values for the aldolase reaction	198
 Interconversion of dihydroxyacetone phosphate and glyceraldehyde-3-phosphate 	199
 Gyceraldehyde-3-phosphate dehydrogenase— an oxidation linked to ATP synthesis 	199
The final steps in glycolysis	200
 The ATP balance sheet from glycolysis 	202
 Reoxidation of cytoplasmic NADH from glycolysis by 	
electron shuttle systems	202
The glycerol phosphate shuttle The malate–aspartate shuttle	202
Transport of pyruvate into the mitochondria	203
Conversion of pyruvate to acetyl-CoA—a preliminary step before the citric acid cycle	203
Components involved in the pyruvate	
dehydrogenase reaction	204
Stage 2—the citric acid cycle	205
The citric acid cycle as a water-splitting machine	205
• A simplified version of the citric acid cycle	205
Mechanisms of the citric acid cycle reactions	206
The synthesis of citrate	206
Conversion of citrate to α -ketoglutarate	206

Where does it take place? Nature of the electron carriers in the chain Arrangement of the electron carriers	211 211 212
 Oxidative phosphorylation—the generation of ATP coupled to electron transport 	213
The chemiosmotic theory of oxidative phosphorylation	214
• How are protons ejected?	214
The Q cycle in complex III ejects protons from mitochondria Complex IV also creates a proton gradient	215 216
 ATP synthesis by ATP synthase is driven by the proton gradient 	216
• Structure of ATP synthase	217
The F1 unit and its role in the conversion of ADP+ P_i to ATP Activities of the enzyme catalytic centres on the F_i subunit Structure of the F_o unit and its role	217 217 219
• Mechanism by which proton flow causes rotation of F ₀	219
 Transport of ADP into mitochondria and ATP out 	221
The balance sheet of ATP production by electron	
 Yield of ATP from the oxidation of a molecule of glucose to CO₂ and H₂O 	222
 Is ATP production the only use that is made of the potential energy in the proton-motive force? 	222
Box 12.1 Inhibitors of oxidative phosphorylation	223
Summary	223
Further reading	224
Problems	224
Chapter 12 Engrave values of five fet	226
Chapter 13 Energy release from fat Mechanism of acetyl-CoA formation from fatty acids	220
'Activation' of fatty acids by formation of fatty	,
acyl-CoA derivatives	227
 Transport of fatty acyl-CoA derivatives into mitochondria 	227

 Conversion of fatty acyl-CoA to acetyl-CoA molecules inside the mitochondrion by β-oxidation 	228
Energy yield from fatty acid oxidation	228
Oxidation of unsaturated fat Is the acetyl-CoA derived from fat breakdown always	229
directly fed into the citric acid cycle?	229
How is acetoacetate made from acetyl-CoA?	229
Utilization of acetoacetate	229
Oxidation of odd-numbered carbon-chain fatty acids	230
Peroxisomal oxidation of fatty acids	231
• Where to now?	231
Summary	231
Further reading	232
Problems	232
Chapter 14 The synthesis of fat and	
related compounds	233
Mechanism of fat synthesis	233
 General principles of the process 	233
 Synthesis of malonyl-CoA 	233
• The acyl carrier protein (ACP) and the β -ketoacyl synthase	234
Mechanism of fatty acyl-CoA synthesis	234
Organization of the fatty acid synthesis process	234
 The reductive steps in fatty acid synthesis What is NADP*? 	235
	236
Where does fatty acid synthesis take place?	236
Synthesis of unsaturated fatty acids	237
Box 14.1 Omega fatty acids and diet	238
Synthesis of TAG and membrane lipids from fatty acids	238
Synthesis of new membrane lipid bilayer	238
 Synthesis of glycerophospholipids 	239
 Synthesis of new membrane lipid bilayer 	241
Synthesis of prostaglandins and related compounds	242
 The prostaglandins and thromboxanes 	242
Box 14.2 Nonsteroidal anti-inflammatory drugs (NSAIDs)	243
• Leukotrienes	244
• Synthesis of cholesterol	244
Conversion of cholesterol to steroid hormones	244
Summary	245
Further reading	245
Problems	245

Chapter 15 Synthesis of glucose (gluconeogenesis)	247
Mechanism of glucose synthesis from pyruvate	
What are the sources of pyruvate used by the liver for	247
gluconeogenesis?	248
Synthesis of glucose from glycerol	250
Effects of ethanol metabolism on gluconeogenesis	251
Effect of ethanol metabolism on the NADH/NAD ⁺ ratio in the liver cell	251
Synthesis of glucose via the glyoxylate cycle	252
Summary	253
Further reading	253
Problems	253
Chapter 16 Strategies for metabolic control and their application to carbohydrate and fat metabolism	255
Why are controls necessary?	255
 The potential danger of futile cycles in metabolism 	256
How are enzyme activities controlled?	257
 Metabolic control by varying the amounts of enzymes is not instantaneous 	257
 Metabolic control by regulation of the activities of enzymes in the cell 	257
• Which enzymes in metabolic pathways are regulated?	257
The nature of control enzymes	258
Allosteric control of enzymes	258
 The mechanism of allosteric control of enzymes 	258
What causes the sigmoidal response of reaction velocity to substrate concentration?	259
Reversibility of allosteric control	
 Allosteric control is a tremendously powerful metabolic concept 	259 259
Allosteric enzymes often have multiple allosteric modulators	260
Control of enzyme activity by phosphorylation	260
Protein kinases and phosphatases	260
 Control by phosphorylation usually depends on chemical signals from other cells 	261
General aspects of the hormonal control of metabolism	261
How do glucagon, epinephrine, and insulin work?	261
What is a second messenger?	261
The second messenger for glucagon and epinephrine is cyclic AMP (cAMP)	262

xxii CONTENTS

 Control of glucose uptake into cells Control of glycogen metabolism Control of glycogen breakdown in muscle Mechanism of muscle phosphorylase activation by cAMP Control of glycogen breakdown in the liver Reversal of phosphorylase activation in muscle and liver 	
Control of glycogen breakdown in muscle Mechanism of muscle phosphorylase activation by cAMP Control of glycogen breakdown in the liver	264
Mechanism of muscle phosphorylase activation by cAMPControl of glycogen breakdown in the liver	
 Control of glycogen breakdown in the liver 	264
	265
Reversal of phosphorylase activation in muscle and live	266
 Reversal of phosphorylase activation in muscle and liver 	266
 Control of glycogen synthase 	267
cAMP causes inactivation of glycogen synthase Mechanism of insulin activation of glycogen synthase	267
How does insulin inactivate GSK3?	267 267
Control of glycolysis and gluconeogenesis	268
Allosteric controls	268
Hormonal control of glycolysis and gluconeogenesis	269
Control of glycolysis and gluconeogenesis pathways by fructose-2:6-bisphosphate (F-2:6-BP)	
Control of pyruvate kinase	269 270
Glucocorticoid stimulation of gluconeogenesis	270
Control of pyruvate dehydrogenase, the citric acid	
cycle, and oxidative phosphorylation	271
ontrols of fatty acid oxidation and synthesis	272
Nonhormonal controls	272
Hormonal controls on fat metabolism	273
Regulation of the cellular ATP level by AMP-activated protein kinase	273
Insulin and diabetes	274
A concluding note on metabolic control analysis	275
ummary	276
urther reading	277
roblems	278
hapter 17 Why should there be an lternative pathway of glucose oxidation? he pentose phosphate pathway	om amendenskeningsvegov,
	279
he oxidative section produces equal amounts of bose-5-phosphate and NADPH	279
The nonoxidative section and its purpose	279
Conversion of surplus ribose-5-phosphate to glucose-6-phosphate	280
Glucose-6-phosphate to ribose-5-phosphate production without NADPH generation	281
Where does the complete oxidation of glucose	
come into all of this?	282

Summary	283
Further reading Problems	284 284
Chapter 18 Raising electrons of water back up	and the second second second second
the energy scale—photosynthesis	285
Overview	285
 Site of photosynthesis—the chloroplast 	286
The light-dependent reactions of photosynthesis	286
 The photosynthetic apparatus and its organization in the thylakoid membrane 	286
• How is light energy captured?	287
 Mechanism of light-dependent reduction of NADP⁺ 	288
Photosystem II	288
Photosystem I	288
The water-splitting centre of PSII	289
How is ATP generated?	289
An explanatory note	290
The 'dark reactions' of photosynthesis	290
 How is CO₂ converted to carbohydrate? 	290
Getting from 3-phosphoglycerate to glucose	290
3-Phosphoglycerate is formed from ribulose-1:5-bisphosphate Where does the ribulose-1:5-bisphosphate come from?	290 291
Has evolution slipped up a bit?	291
• The C ₄ pathway	292
Summary	293
Further reading	294
Problems	294
Chapter 19 Amino acid metabolism	295
Nitrogen balance of the body	296
General metabolism of amino acids	296
 Aspects of amino acid metabolism 	296
 Glutamate dehydrogenase has a central role in the deamination of amino acids 	227
Mechanism of transamination reactions	297 298
Special deamination mechanisms for serine and cysteine	298
Fate of the keto acid or carbon skeletons of deaminated amino acids	299
Genetic errors in amino acid metabolism cause diseases	300
Phenylketonuria	300
Maple syrup disease	301

Alcaptonuria

Methionine and transfer of methyl groups	301
What are the methyl groups transferred to?	302
Synthesis of amino acids	302
Synthesis of glutamic acid	302
Synthesis of aspartic acid and alanine	302
• Synthesis of serine	302
• Synthesis of glycine	303
Haem and its synthesis from glycine	303
Destruction of haem	303
Box 19.1 Acute intermittent porphyria	304
Synthesis of epinephrine and norepinephrine	304
The urea cycle	305
Mechanism of arginine synthesis	306
Conversion of citrulline to arginine	307
How is the amino nitrogen transported from	507
extrahepatic tissues to the liver to be converted	
into urea?	308
Transport of ammonia in the blood as glutamine Transport of amino nitrogen in the blood as alanine	308
	309
Diseases due to urea cycle deficiencies Alters et in each urea formation exist in different animals.	309
Alternatives to urea formation exist in different animals	309
Summary	310
Further reading	310
Problems	311
Chapter 20 Enzymic protective mechanisms in the body	312
Blood clotting	312
What are the signals that clot formation is needed?	313
How does thrombin cause thrombus (clot) formation?	313
Keeping clotting in check	314
Rat poison, blood clotting, and vitamin K	315
Protection against ingested foreign chemicals (xenobiotics)	315
Cytochrome P450	316
Medical significance of P450s	316
Secondary modification—addition of a polar group to	
products of the P450 attack	316
The glucuronidation system	316 316
The glutathione S-transferase system	_
Multidrug resistance	317

Protection of the body against its own proteases

	CONTENTS	xxii
Protection against reactive oxygen species	318	
Mopping up oxygen free radicals with vitamins C and E	319	
 Enzymic destruction of superoxide by superoxide dismutase 	319	
The glutathione peroxidase–glutathione reductase strategy	319	
Protection against hypoxia (low oxygen levels)	320	
Mechanism of the hypoxia response	320	
,		
Summary	321	
Further reading Problems	322	
Problems	323	
Chapter 21 Nucleotide synthesis and	retire til viville kilosik siler vikiletillitet til til	
metabolism	324	
Structure and nomenclature of nucleotides	324	
The sugar component of nucleotides	324	
 The base component of nucleotides 	325	
Nomenclature	325	
Structure of the bases	325	
Attachment of the bases in nucleotides	325	
Synthesis of purine and pyrimidine nucleotides	326	
Purine nucleotides	326	
PRPP—the ribotidation agent	326	
• The <i>de novo</i> purine nucleotide synthesis pathway	327	
The one-carbon transfer reaction in purine nucleotide synthesis	277	
Where does the formyl group in N ¹⁰ -formyl FH ₂ come from?	327 329	
How are ATP and GTP produced from AMP and GMP?	329	
The purine salvage pathway	330	
What is the physiological role of the purine salvage pathway?	331	
 Formation of uric acid from purines 	331	
Control of purine nucleotide synthesis	332	
 Synthesis of pyrimidine nucleotides 	332	
How are deoxyribonucleotides formed?	333	
Thymidylate synthesis—conversion of dUMP to dTMP	333	
Medical effects of folate deficiencies	335	
Thymidylate synthesis is targeted by anticancer		
agents such as the antifolate, methotrexate	335	
Vitamin B_{12} deficiency in cells and the folate methyl trap	335	
Summary	336	
Further reading	336	
Problems	336	



Part 4 Information storage

Chapter 22 DNA and genomes	341
What are nucleic acids?	341
The primary structure of DNA	341
What are the bases in DNA?	342
 Attachment of the bases to deoxyribose 	342
 The physical properties of the polynucleotide components 	342
Structure of the polynucleotide of DNA	
• Why deoxyribose? Why not ribose?	342
The DNA double helix	343 344
Complementary base pairing	344
• DNA chains are antiparallel; what does this mean?	346
How is the DNA packed into a nucleus?	348
 How does the described structure of DNA correlate with the compact eukaryotic chromosomes visible in the light microscope? 	
The mitochondrial genome	349 350
What is a gene in molecular terms?	350
 Some variations on the 'standard' gene 	351
 Size and organization of genomes 	351
Organization of the human genome	351
Repetitive DNA sequences	351
Transposon movement	352
 Noncoding RNAs are challenging the basic dogma of molecular genetics 	352
Discovery of microgenes for small noncoding RNAs	352
RNA interference (RNAi)	
Where are we now?	353 353
Summary	353
urther reading	354
	254

What is a gene in molecular terms?	359
 Some variations on the 'standard' gene 	35
 Size and organization of genomes 	35
Organization of the human genome	35:
 Repetitive DNA sequences 	351
 Transposon movement 	352
 Noncoding RNAs are challenging the basic dogma of molecular genetics 	352
Discovery of microgenes for small noncoding RNAs	352
RNA interference (RNAi)Where are we now?	353 353
Summary Further reading	353 354
Problems	355

356

356

357

Chapter 23 DNA synthesis, repair,

Control of initiation of DNA replication in E. coli

Overall principle of DNA replication

and recombination

Initiation and regulation of DNA replication in eukaryotes	357
Unwinding the DNA double helix and supercoiling	358
 How are positive supercoils removed ahead of the replicative fork? 	359
The basic enzymic reaction catalysed by DNA polymerases	-4-
How does a new strand get started?	361 362
The polarity problem in DNA replication	362
Mechanism of Okazaki fragment synthesis	-
Enzyme complex at the replicative fork in <i>E. coli</i>	363 364
The DNA sliding clamp and the clamp loading mechanism	364 364
 Processing the Okazaki fragments 	364
How is fidelity achieved in DNA replication?	366
Exonucleolytic proofreading	368
Methyl-directed mismatch repair	368
Repair of DNA damage in <i>E</i> . coli	369
Repair of double-strand breaks	370
The machinery in the eukaryotic replicative fork	371
 The problem of replicating the ends of eukaryotic 	
chromosomes	371
How is telomeric DNA synthesized? Telomere shortening correlates with ageing	373 373
DNA damage repair in eukaryotes	373
s the mechanism described above the only way in which DNA is synthesized?	3,3
DNA synthesis by reverse transcription	374
Homologous recombination	374
	375
Mechanism of homologous recombination in E. coli Formation of cross-over junctions by single-strand invasion	375
Separation of the duplexes	376 376
Recombination in eukaryotes	377
iummary	377
urther reading	377 377
roblems	378
hapter 24 Gene transcription and control	380
lessenger RNA	380
The structure of RNA	380
How is mRNA synthesized?	380
Some general properties of mRNA	381

 Some essential terminology 	381
 A note on where we go from here 	382
Gene transcription in E. coli	382
• What do we mean by the 5' end of a gene?	383
 Phases of gene transcription 	383
Initiation of transcription in E. coli	383
Separating the DNA strands	384
Termination of transcription	384
The rate of gene transcription initiation in prokaryotes	384
 Control of transcription by different sigma factors 	385
 Gene control in E. coli: the lac operon 	385
• Structure of the <i>E. coli lac</i> operon	386
Gene transcription in eukaryotic cells	387
 Capping the RNA transcribed by RNA polymerase II 	387
 Split genes 	387
Mechanism of splicing	387
Ribozymes and self-splicing of RNA	389
What is the biological status of introns?	390
What is the origin of split genes?	390
Alternative splicing or two (or more) proteins for the price of one gene	390
Mechanism of initiation of eukaryotic gene	
transcription and its control	390
 Unpacking of the DNA for transcription 	390
 A general overview of the differences in the initiation and control of gene transcription in prokaryotes and eukaryotes 	204
Types of eukaryotic genes and their controlling regions	391
Type II eukaryotic gene promoters	392 392
Enhancers	393
Transcription factors (activators)	393
 Most transcription factors themselves are regulated 	394
How do transcription factors promote transcriptional	
initiation?	394
The role of chromatin in eukaryotic gene control How do transcription factors open up gene promoters?	394 394
How is transcription initiated on the opened promoter?	396
Discovery of the mediator	397
The RNA polymerase II of eukaryotic cells	398
Termination of transcription in eukaryotic cells	399
Switching off the gene	399
mRNA stability and the control of gene expression	399
Determinants of mRNA stability and their role in	
gene expression control	399
Role of the polyA tail	399
Structural stability determinants of mRNAs	399

	CONTENTS	XXX
Gene transcription in mitochondria	400	
Genes that do not code for proteins	401	
• The structure of DNA-binding proteins	401	
Helix-turn-helix proteins	401	
Leucine zipper proteins Helix-loop-helix proteins	402	
Zinc finger proteins	402 403	
Summary	403	
Further reading	404	
Problems	406	
Chapter 25 Protein synthesis and controlled protein breakdown	408	
Essential basis of the process of protein synthesis	409	
The genetic code	409	
• How are the codons translated?	410	
Transfer RNA	410	
The wobble mechanism	411	
How are amino acids attached to tRNA molecules?	411	
Proofreading by aminoacyl-tRNA ligases	412	
Ribosomes	413	
Initiation of translation	414	
Initiation of translation in <i>E. coli</i>	414	
Once initiation is achieved, elongation is the next step		
 Cytoplasmic elongation factors in E. coli 	416	
Mechanism of elongation in <i>E. coli</i>	416	
How is accuracy of translation achieved?	416	
·	416	
Mechanism of translocation on the <i>E. coli</i> ribosome	418	
Box 25.1 Effects of antibiotics and toxins on protein synthesis	418	
Termination of protein synthesis in <i>E. coli</i>	419	
Physical structure of the ribosome	419	
• What is a polysome?	420	
Protein synthesis in eukaryotes	420	
Protein synthesis in mitochondria	420	
olding up of the polypeptide chain	421	
Chaperones (heat-shock proteins)	421	
Mechanism of action of molecular chaperones	422	
Enzymes involved in protein folding	423	
rion diseases and protein folding	424	

xxvi CONTENTS

Translational control mechanisms

424

441

Regulation of globin synthesis	424
 Translational control of proteins involved in haem 	, ,
synthesis and iron metabolism	424
Programmed destruction of protein by proteasomes	425
The structure of proteasomes	426
 Selection of proteins for destruction—the ubiquitination system 	427
What determines which proteins are ubiquitinated?	427
The role of proteasomes in the immune system	427
Summary	428
Further reading	426 429
Problems	429
Chapter 26 Protein targeting—how proteins are delivered to their cellular destinations	Distributions, in a considerating,
	432
A preliminary overview of the field	432
 Structure and function of the ER and Golgi apparatus 	433
The importance of the GTP/GDP switch mechanism in protein targeting	
How are proteins translocated through the ER	435
membrane?	435
Mechanism of cotranslational transport through the ER membrane	435
Folding of the polypeptides inside the ER	437
Glycosylation of proteins in the ER lumen and Golgi apparatus	437
Vesicles involved in protein translocation from	437
the ER and Golgi	437
ysosomes and the mechanism of their formation	
y receptor-mediated endocytosis	438
low are proteins sorted, packaged, and despatched by the Golgi apparatus?	
Proteins to be returned to the ER	439
Proteins destined for lysosomes	439
Proteins to be secreted from the cell	439
Box 26.1 Lysosomal storage disorders	439
,	439
lechanism of COP-coated vesicle formation	440
How does a vesicle find its target membrane?	440
ynthesis of integral membrane proteins and	
neir transport	441

• How is the membrane protein given the

correct orientation?

Posttranslational transport of proteins	
into organelles	442
Transport of proteins into mitochondria	442
Targeting peroxisomal proteins	444
Nuclear-cytoplasmic traffic Why is a bound of the company	444
Why is there a nuclear membrane? The purples may be sayed.	444
The nuclear pore complex Nuclear localization signals	444
Nuclear localization signals Machanian of mulasses and the signal signals.	446
 Mechanism of nuclear-cytoplasmic transport and the role of guanine nucleotide-binding proteins 	446
 Regulation of nuclear transport by cell signals and its role in gene control 	448
Summary	449
Further reading	449
Problems	451
	(males agriculture sacces de constitue)
Chapter 27 Signal transduction	452
Overview	452
Organization of this chapter	454
What are the signalling molecules?	454
 Neurotransmitters 	454
• Hormones	454
 Cytokines and growth factors 	455
Growth factors/cytokines and the cell cycle	456
 Vitamin D₃ and retinoic acid 	456
Intracellular receptor-mediated responses	456
Box 27.1 The glucocorticoid receptor and	
anti-inflammatory drugs	457
Classification of types of membrane receptor signalling systems	458
Binding domains of signal transduction proteins	
Terminating signals	459 460
Examples of signal transduction pathways	460
Signal transduction pathways from tyrosine	
kinase receptors	461
• The Ras pathway	461
 Mechanism of the Ras signalling pathway 	461
Concept of the GTP/GDP switch mechanism, illustrated by	, 6 •
the Ras pathway The MAP kinase cascade in the Ras pathway	461 462
Nomenclature of the protein kinases of the Ras pathway	463
Concept of the role of protein phosphatases, illustrated by	•
the Ras pathway	463

the Ras pathway

and a me diacovà pun achaenting recinidas	485
Outline of the dideoxy DNA-sequencing technique	485
Sequencing DNA	
Southern blotting	484
 Detection of specific DNA fragments by nucleic acid hybridization probes 	484
Visualizing the separated pieces	484
Separating DNA pieces	484
Cutting DNA with restriction endonucleases	483
Some preliminary considerations	483
Basic methodologies	483
Chapter 28 Manipulating DNA and genes	482
riobiems	480
Further reading Problems	478
Summary	477
 Activation of a guanylate cyclase by nitric oxide 	477
	475
Signal transduction pathways using cGMP as second messenger	
Transduction of the light signal	474
receptor	473
 Other control roles of calcium Vision: a process dependent on a G-protein-coupled 	472
different second messenger	471
The phosphatidylinositol cascade: another example of a G-protein-coupled receptor which works via a	
Desensitization of the G-protein receptors	471
How does cAMP control gene activities?	470
GTPase-activating proteins (GAPs) regulate G-protein signalling Different types of G-protein receptor	470 470
Control of cAMP levels in cells	469
by cAMP as second messenger	468
Epinephrine signalling—a G-protein pathway mediated	468
Structure of G-protein receptors	468
 Signal transduction pathways Overview 	468
The G-protein-coupled receptors and associated	
Negative control of JAK/STAT pathways	467
 The JAK/STAT pathways: another type of tyrosine kinase-associated signalling system 	466
pathway and insulin signalling	465
• The phosphatidylinositide 3-kinase (PI 3-kinase)	4-4
inhibiting dephosphorylation of proteinsConcept of signal sorting in Ras-type pathways	464 464

Automated DNA sequencing

512

reaction (PCR)	48
Joining DNA to form recombinant molecules	48
Cloning DNA	489
Cloning in plasmids	489
 Cloning using bacteriophage λ as vector 	490
Cloning in cosmids	49
Applications of recombinant DNA technology	49
 Production of human and other proteins 	492
 Preparation of a cDNA library 	492
 Expressing the cDNA in E. coli 	49
Site-directed mutagenesis	494
PCR in forensic science	494
Locating disease-producing genes	495
'Knockout mice' or gene targeting	496
Method of obtaining a specific gene knockout	496
 The embryonic stem (ES) cell system 	496
Gene targeting	498
 Gene silencing by RNA interference (RNAi) 	499
Analysis of multiple gene expression in cells using	
DNA microarrays	499
 Transgenic animals and plants 	500
DNA databases and genomics	501
Summary	502
Further reading	503
Problems	504
Part 5 The immune syst cell cycle, apoptosis, and cancer Chapter 29 The immune system	
Overview	
The problem of autoimmune reactions	509
The cells involved in the immune system	510
• There are two arms to the adaptive immune response	510
	510
Where is the immune system located in the body?	511
Antibody-based or humoral immunity	
• Structure of antibodies	511
	511
 What are the functions of antibodies? The different classes of antibodies 	

• Generation of antibody diversity

xxviii CONTENTS

the bone marrow

Cell-cycle controls

Cell-cycle checkpoints

destruction of cyclins

The G₁ checkpoint

Controls in G₁ are complex

How is DNA damage detected?

The theory of clonal selection

The eukaryotic cell cycle	52
Chapter 30 Cell-cycle control, apoptosis, and cancer	52.
Problems	52
Further reading	52
Monoclonal antibodies Summary	5:
	5
Why does the human immune system reject transplanted human cells?	5
CD proteins reinforce the selectivity of T cell receptors for the two classes of MHC protein	5
 Mechanism of action of cytotoxic (killer T) cells 	5
T cells and cell-mediated immunity	5
Memory cells	5
 Affinity maturation of antibodies 	5
 Role of the MHC proteins in presenting peptides on the outside of cells 	5
Role of helper T cells Activation of helper T cells Activation of B cells by activated helper T cells	
into antibody-secreting cells	!
 B cells must be activated before they can develop 	

· Cytokines and growth factor control in the cell cycle

· Cell-cycle controls depend on the synthesis and

Activation of B cells to produce antibodies

Deletion of potentially self-reacting B cells in

514

514

515

525

525

525

525

525

526

Progression to S phase	
Progression to 3 phase Progression to M phase	526
Mitosis phase	526
· Mittosis priase	526
Apoptosis	527
 An overview of what initiates apoptosis 	527
Mechanism of stress-damage-induced apoptosis	528
The role of caspases in apoptosis	528
Death receptor-mediated activation of apoptosis	528
Cancer	528
General concepts	528
Most normal cells can divide only a limited	
number of times	529
Cancer cells have no limitation on the number of cell divisions they can make	529
Types of abnormal cell multiplication	529
Malignant Darwinism: cancer development involves	
an evolutionary progression of mutations	530
Development of colorectal cancer	530
Mutations cause cancer	530
Tumour promoters	531
 The types of genetic change involved in cancer 	531
Oncogenes	531
How are oncogenes acquired?	532
A note on nomenclature of viral oncogenes	533
Tumour-suppression genes	533
 Mechanism of protection by the p53 gene 	533
 Mechanism of protection by the retinoblastoma gene 	534
Molecular biology advances have potential for	
development of new cancer therapies	534
Summary	534
Further reading	534
Problems	537
Figure acknowledgements	538
Answers to problems	540
Index of diseases and medically relevant topics	567
Index	569
	•

Diseases and relevant topic

Box 4.1 Genetic disease:	s of collagen	61
Box 4.2 Sickle cell anaen	nia and thalassaemias	70
Box 7.1 Cardiac glycosid	es	116
Box 7.2 Cholinesterase in	nhibitors and Alzheimer's disease	121
Box 7.3 Membrane-targe	ted antibiotics	127
Box 8.1 Muscular dystrop	phy	134
Box 8.2 Malignant hyper	thermia	138
Box 8.3 Effects of drugs of	on the cytoskeleton	144
Box 10.1 Uridyl transfera	se deficiency and galactosaemia	175
Box 10.2 Inhibitors of cho	olesterol synthesis	181
Box 11.1 A survey of vitar	mins	194
Box 12.1 Inhibitors of oxi	dative phosphorylation	223

medically s

Box 14.1	Omega fatty acids and diet	238
Box 14.2	Nonsteroidal anti-inflammatory drugs (NSAIDs)	243
Box 17.1	Why do red blood cells have the pentose phosphate pathway?	283
Box 19.1	Acute intermittent porphyria	304
Box 25.1	Effects of antibiotics and toxins on protein synthesis	418
Box 26.1	Lysosomal storage disorders	439
Box 27.1	The glucocorticoid receptor and anti-inflammatory drugs	457
Box 27.2	Some deadly toxins work by increasing or inhibiting dephosphorylation of proteins	464