Nutritional Biochemistry of the Vitamins
SECOND EDITION

The vitamins are a chemically disparate group of compounds whose only common feature is that they are dietary essentials that are required in small amounts for the normal functioning of the body and maintenance of metabolic integrity. Metabolically, they have diverse functions, such as coenzymes, hormones, antioxidants, mediators of cell signaling, and regulators of cell and tissue growth and differentiation. This book explores the known biochemical functions of the vitamins, the extent to which we can explain the effects of deficiency or excess, and the scientific basis for reference intakes for the prevention of deficiency and promotion of optimum health and well-being. It also highlights areas in which our knowledge is lacking and further research is required. This book provides a compact and authoritative reference volume of value to students and specialists alike in the field of nutritional biochemistry, and indeed all who are concerned with vitamin nutrition, deficiency, and metabolism.

David Bender is a Senior Lecturer in Biochemistry at University College London. He has written seventeen books, as well as numerous chapters and reviews, on various aspects of nutrition and nutritional biochemistry. His research has focused on the interactions between vitamin B₆ and estrogens, which has led to the elucidation of the role of vitamin B₆ in terminating the actions of steroid hormones. He is currently the Editor-in-Chief of Nutrition Research Reviews.
Nutritional Biochemistry of the Vitamins

SECOND EDITION

DAVID A. BENDER
University College London
Contents

List of Figures xvii
List of Tables xxi
Preface xxiii

1 The Vitamins 1
   1.1 Definition and Nomenclature of the Vitamins 2
      1.1.1 Methods of Analysis and Units of Activity 6
      1.1.2 Biological Availability 8
   1.2 Vitamin Requirements and Reference Intakes 10
      1.2.1 Criteria of Vitamin Adequacy and the Stages of Development of Deficiency 10
      1.2.2 Assessment of Vitamin Nutritional Status 12
      1.2.3 Determination of Requirements 17
         1.2.3.1 Population Studies of Intake 17
         1.2.3.2 Depletion/Repletion Studies 18
         1.2.3.3 Replacement of Metabolic Losses 18
         1.2.3.4 Studies in Patients Maintained on Total Parenteral Nutrition 19
      1.2.4 Reference Intakes of Vitamins 19
         1.2.4.1 Adequate Intake 23
         1.2.4.2 Reference Intakes for Infants and Children 23
         1.2.4.3 Tolerable Upper Levels of Intake 24
         1.2.4.4 Reference Intake Figures for Food Labeling 27

2 Vitamin A: Retinoids and Carotenoids 30
   2.1 Vitamin A Vitamers and Units of Activity 31
      2.1.1 Retinoids 31
      2.1.2 Carotenoids 33
      2.1.3 International Units and Retinol Equivalents 35
### Contents

- **2.2 Absorption and Metabolism of Vitamin A and Carotenoids** 35
  - 2.2.1 Absorption and Metabolism of Retinol and Retinoic Acid 35
    - 2.2.1.1 Liver Storage and Release of Retinol 36
    - 2.2.1.2 Metabolism of Retinoic Acid 38
    - 2.2.1.3 Retinoyl Glucuronide and Other Metabolites 39
  - 2.2.2 Absorption and Metabolism of Carotenoids 40
    - 2.2.2.1 Carotene Dioxygenase 41
    - 2.2.2.2 Limited Activity of Carotene Dioxygenase 42
    - 2.2.2.3 The Reaction Specificity of Carotene Dioxygenase 43
  - 2.2.3 Plasma Retinol Binding Protein (RBP) 45
  - 2.2.4 Cellular Retinoid Binding Proteins CRBPs and CRABPs 47
- **2.3 Metabolic Functions of Vitamin A** 49
  - 2.3.1 Retinol and Retinaldehyde in the Visual Cycle 49
  - 2.3.2 Genomic Actions of Retinoic Acid 54
    - 2.3.2.1 Retinoid Receptors and Response Elements 55
  - 2.3.3 Nongenomic Actions of Retinoids 58
    - 2.3.3.1 Retinoylation of Proteins 58
    - 2.3.3.2 Retinoids in Transmembrane Signaling 60
- **2.4 Vitamin A Deficiency (Xerophthalmia)** 61
  - 2.4.1 Assessment of Vitamin A Nutritional Status 64
    - 2.4.1.1 Plasma Concentrations of Retinol and \(\beta\)-Carotene 64
    - 2.4.1.2 Plasma Retinol Binding Protein 65
    - 2.4.1.3 The Relative Dose Response (RDR) Test 66
    - 2.4.1.4 Conjunctival Impression Cytology 66
  - 2.4.2 Vitamin A Requirements and Reference Intakes 66
    - 2.5.1 Toxicity of Vitamin A 68
      - 2.5.1.1 Teratogenicity of Retinoids 70
    - 2.5.2 Pharmacological Uses of Vitamin A, Retinoids, and Carotenoids 71
      - 2.5.2.1 Retinoids in Cancer Prevention and Treatment 71
      - 2.5.2.2 Retinoids in Dermatology 72
      - 2.5.2.3 Carotene 72

### 3 Vitamin D

- **3.1 Vitamin D Vitamers, Nomenclature, and Units of Activity** 78
- **3.2 Metabolism of Vitamin D** 79
  - 3.2.1 Photosynthesis of Cholecalciferol in the Skin 80
  - 3.2.2 Dietary Vitamin D 82
  - 3.2.3 25-Hydroxylation of Cholecalciferol 83
  - 3.2.4 Calcidiol 1\(\alpha\)-Hydroxylase 85
  - 3.2.5 Calcidiol 24-Hydroxylase 85
  - 3.2.6 Inactivation and Excretion of Calcitriol 86
  - 3.2.7 Plasma Vitamin D Binding Protein (Gc-Globulin) 87
3.2.8 Regulation of Vitamin D Metabolism 87
  3.2.8.1 Calcitriol 88
  3.2.8.2 Parathyroid Hormone 88
  3.2.8.3 Calcitonin 88
  3.2.8.4 Plasma Concentrations of Calcium and Phosphate 89

3.3 Metabolic Functions of Vitamin D 89
  3.3.1 Nuclear Vitamin D Receptors 91
  3.3.2 Nongenomic Responses to Vitamin D 92
  3.3.3 Stimulation of Intestinal Calcium and Phosphate Absorption 93
    3.3.3.1 Induction of Calbindin-D 93
  3.3.4 Stimulation of Renal Calcium Reabsorption 94
  3.3.5 The Role of Calcitriol in Bone Metabolism 94
  3.3.6 Cell Differentiation, Proliferation, and Apoptosis 96
  3.3.7 Other Functions of Calcitriol 97
    3.3.7.1 Endocrine Glands 98
    3.3.7.2 The Immune System 98

3.4 Vitamin D Deficiency – Rickets and Osteomalacia 98
  3.4.1 Nonnutritional Rickets and Osteomalacia 99
  3.4.2 Vitamin D-Resistant Rickets 100
  3.4.3 Osteoporosis 101
    3.4.3.1 Glucocorticoid-Induced Osteoporosis 102

3.5 Assessment of Vitamin D Status 103

3.6 Requirements and Reference Intakes 104
  3.6.1 Toxicity of Vitamin D 105
  3.6.2 Pharmacological Uses of Vitamin D 106

4 Vitamin E: Tocopherols and Tocotrienols 109
  4.1 Vitamin E Vitamers and Units of Activity 109
  4.2 Metabolism of Vitamin E 113
  4.3 Metabolic Functions of Vitamin E 115
    4.3.1 Antioxidant Functions of Vitamin E 116
      4.3.1.1 Prooxidant Actions of Vitamin E 118
      4.3.1.2 Reaction of Tocopherol with Peroxynitrite 119
    4.3.2 Nutritional Interactions Between Selenium and Vitamin E 121
    4.3.3 Functions of Vitamin E in Cell Signaling 122
  4.4 Vitamin E Deficiency 122
    4.4.1 Vitamin E Deficiency in Experimental Animals 122
    4.4.2 Human Vitamin E Deficiency 125
  4.5 Assessment of Vitamin E Nutritional Status 125
  4.6 Requirements and Reference Intakes 127
    4.6.1 Upper Levels of Intake 128
    4.6.2 Pharmacological Uses of Vitamin E 128
      4.6.2.1 Vitamin E and Cancer 129
      4.6.2.2 Vitamin E and Cardiovascular Disease 129
5 Vitamin K

5.1 Vitamin K Vitamers

5.2 Metabolism of Vitamin K

5.2.1 Bacterial Biosynthesis of Menaquinones

5.3 The Metabolic Functions of Vitamin K

5.3.1 The Vitamin K-Dependent Carboxylase

5.3.2 Vitamin K-Dependent Proteins in Blood Clotting

5.3.3 Osteocalcin and Matrix Gla Protein

5.3.4 Vitamin K-Dependent Proteins in Cell Signaling – Gas6

5.4 Vitamin K Deficiency

5.4.1 Vitamin K Deficiency Bleeding in Infancy

5.5 Assessment of Vitamin K Nutritional Status

5.6 Vitamin K Requirements and Reference Intakes

5.6.1 Upper Levels of Intake

5.6.2 Pharmacological Uses of Vitamin K

6 Vitamin B₁ – Thiamin

6.1 Thiamin Vitamers and Antagonists

6.2 Metabolism of Thiamin

6.2.1 Biosynthesis of Thiamin

6.3 Metabolic Functions of Thiamin

6.3.1 Thiamin Diphosphate in the Oxidative Decarboxylation of Oxoacids

6.3.1.1 Regulation of Pyruvate Dehydrogenase Activity

6.3.1.2 Thiamin-Responsive Pyruvate Dehydrogenase Deficiency

6.3.1.3 2-Oxoglutarate Dehydrogenase and the γ-Aminobutyric Acid (GABA) Shunt

6.3.1.4 Branched-Chain Oxo-acid Decarboxylase and Maple Syrup Urine Disease

6.3.2 Transketolase

6.3.3 The Neuronal Function of Thiamin Triphosphate

6.4 Thiamin Deficiency

6.4.1 Dry Beriberi

6.4.2 Wet Beriberi

6.4.3 Acute Pernicious (Fulminating) Beriberi – Shoshin Beriberi

6.4.4 The Wernicke–Korsakoff Syndrome

6.4.5 Effects of Thiamin Deficiency on Carbohydrate Metabolism

6.4.6 Effects of Thiamin Deficiency on Neurotransmitters

6.4.6.1 Acetylcholine

6.4.6.2 5-Hydroxytryptamine

6.4.7 Thiaminases and Thiamin Antagonists
Contents

6.5 Assessment of Thiamin Nutritional Status 167
6.5.1 Urinary Excretion of Thiamin and Thiochrome 167
6.5.2 Blood Concentration of Thiamin 167
6.5.3 Erythrocyte Transketolase Activation 168
6.6 Thiamin Requirements and Reference Intakes 169
6.6.1 Upper Levels of Thiamin Intake 169
6.6.2 Pharmacological Uses of Thiamin 169

7 Vitamin B₂ – Riboflavin 172
7.1 Riboflavin and the Flavin Coenzymes 172
7.2 The Metabolism of Riboflavin 175
7.2.1 Absorption, Tissue Uptake, and Coenzyme Synthesis 175
7.2.2 Riboflavin Binding Protein 177
7.2.3 Riboflavin Homeostasis 178
7.2.4 The Effect of Thyroid Hormones on Riboflavin Metabolism 178
7.2.5 Catabolism and Excretion of Riboflavin 179
7.2.6 Biosynthesis of Riboflavin 181
7.3 Metabolic Functions of Riboflavin 183
7.3.1 The Flavin Coenzymes: FAD and Riboflavin Phosphate 183
7.3.2 Single-Electron-Transferring Flavoproteins 184
7.3.3 Two-Electron-Transferring Flavoprotein Dehydrogenases 185
7.3.4 Nicotinamide Nucleotide Disulfide Oxidoreductases 185
7.3.5 Flavin Oxidases 186
7.3.6 NADPH Oxidase, the Respiratory Burst Oxidase 187
7.3.7 Molybdenum-Containing Flavoprotein Hydroxylases 188
7.3.8 Flavin Mixed-Function Oxidases (Hydroxylases) 189
7.3.9 The Role of Riboflavin in the Cryptochromes 190
7.4 Riboflavin Deficiency 190
7.4.1 Impairment of Lipid Metabolism in Riboflavin Deficiency 191
7.4.2 Resistance to Malaria in Riboflavin Deficiency 192
7.4.3 Secondary Nutrient Deficiencies in Riboflavin Deficiency 193
7.4.4 Iatrogenic Riboflavin Deficiency 194
7.5 Assessment of Riboflavin Nutritional Status 196
7.5.1 Urinary Excretion of Riboflavin 196
7.5.2 Erythrocyte Glutathione Reductase (EGR) Activation Coefficient 197
7.6 Riboflavin Requirements and Reference Intakes 197
7.7 Pharmacological Uses of Riboflavin 198

8 Niacin 200
8.1 Niacin Vitamers and Nomenclature 201
8.2 Niacin Metabolism 203
8.2.1 Digestion and Absorption 203
8.2.1.1 Unavailable Niacin in Cereals 203
8.2.2 Synthesis of the Nicotinamide Nucleotide Coenzymes 203
8.2.3 Catabolism of NAD(P) 205
8.2.4 Urinary Excretion of Niacin Metabolites 206
8.3 The Synthesis of Nicotinamide Nucleotides from Tryptophan 208
  8.3.1 Picolinate Carboxylase and Nonenzymic Cyclization to Quinolinic Acid 210
8.3.2 Tryptophan Dioxygenase 211
  8.3.2.1 Saturation of Tryptophan Dioxygenase with Its Heme Cofactor 211
  8.3.2.2 Induction of Tryptophan Dioxygenase by Glucocorticoid Hormones 211
  8.3.2.3 Induction Tryptophan Dioxygenase by Glucagon 212
  8.3.2.4 Repression and Inhibition of Tryptophan Dioxygenase by Nicotinamide Nucleotides 212
8.3.3 Kynurenine Hydroxylase and Kynureninase 212
  8.3.3.1 Kynurenine Hydroxylase 213
  8.3.3.2 Kynureninase 213
8.4 Metabolic Functions of Niacin 214
  8.4.1 The Redox Function of NAD(P) 214
  8.4.1.1 Use of NAD(P) in Enzyme Assays 215
  8.4.2 ADP-Ribosyltransferases 215
  8.4.3 Poly(ADP-ribose) Polymerases 217
  8.4.4 cADP-Ribose and Nicotinic Acid Adenine Dinucleotide Phosphate (NAADP) 219
8.5 Pellagra – A Disease of Tryptophan and Niacin Deficiency 221
  8.5.1 Other Nutrient Deficiencies in the Etiology of Pellagra 222
  8.5.2 Possible Pellagragenic Toxins 223
  8.5.3 The Pellagragenic Effect of Excess Dietary Leucine 223
  8.5.4 Inborn Errors of Tryptophan Metabolism 224
  8.5.5 Carcinoid Syndrome 224
  8.5.6 Drug-Induced Pellagra 225
8.6 Assessment of Niacin Nutritional Status 225
  8.6.1 Tissue and Whole Blood Concentrations of Nicotinamide Nucleotides 226
  8.6.2 Urinary Excretion of N^1-Methyl Nicotinamide and Methyl Pyridone Carboxamide 226
8.7 Niacin Requirements and Reference Intakes 227
  8.7.1 Upper Levels of Niacin Intake 228
8.8 Pharmacological Uses of Niacin 229

9 Vitamin B₆ 232
  9.1 Vitamin B₆ Vitamers and Nomenclature 233
  9.2 Metabolism of Vitamin B₆ 234
    9.2.1 Muscle Pyridoxal Phosphate 236
    9.2.2 Biosynthesis of Vitamin B₆ 236
  9.3 Metabolic Functions of Vitamin B₆ 236
    9.3.1 Pyridoxal Phosphate in Amino Acid Metabolism 237
      9.3.1.1 α-Decarboxylation of Amino Acids 239
9.3.1.2 Racemization of the Amino Acid Substrate 241
9.3.1.3 Transamination of Amino Acids (Aminotransferase Reactions) 241
9.3.1.4 Steps in the Transaminase Reaction 242
9.3.1.5 Transamination Reactions of Other Pyridoxal Phosphate Enzymes 243
9.3.1.6 Transamination and Oxidative Deamination Catalyzed by Dihydroxyphenylalanine (DOPA) Decarboxylase 243
9.3.1.7 Side-Chain Elimination and Replacement Reactions 244
9.3.2 The Role of Pyridoxal Phosphate in Glycogen Phosphorylase 244
9.3.3 The Role of Pyridoxal Phosphate in Steroid Hormone Action and Gene Expression 245

9.4 Vitamin B₆ Deficiency 246
9.4.1 Enzyme Responses to Vitamin B₆ Deficiency 247
9.4.2 Drug-Induced Vitamin B₆ Deficiency 249
9.4.3 Vitamin B₆ Dependency Syndromes 250

9.5 The Assessment of Vitamin B₆ Nutritional Status 250
9.5.1 Plasma Concentrations of Vitamin B₆ 251
9.5.2 Urinary Excretion of Vitamin B₆ and 4-Pyridoxic Acid 251
9.5.3 Coenzyme Saturation of Transaminases 252
9.5.4 The Tryptophan Load Test 252
9.5.4.1 Artifacts in the Tryptophan Load Test Associated with Increased Tryptophan Dioxygenase Activity 253
9.5.4.2 Estrogens and Apparent Vitamin B₆ Nutritional Status 254
9.5.5 The Methionine Load Test 255

9.6 Vitamin B₆ Requirements and Reference Intakes 256
9.6.1 Vitamin B₆ Requirements Estimated from Metabolic Turnover 256
9.6.2 Vitamin B₆ Requirements Estimated from Depletion/Repletion Studies 257
9.6.3 Vitamin B₆ Requirements of Infants 259
9.6.4 Toxicity of Vitamin B₆ 259
9.6.4.1 Upper Levels of Vitamin B₆ Intake 260

9.7 Pharmacological Uses of Vitamin B₆ 261
9.7.1 Vitamin B₆ and Hyperhomocysteinemia 261
9.7.2 Vitamin B₆ and the Premenstrual Syndrome 262
9.7.3 Impaired Glucose Tolerance 262
9.7.4 Vitamin B₆ for Prevention of the Complications of Diabetes Mellitus 263
9.7.5 Vitamin B₆ for the Treatment of Depression 264
9.7.6 Antihypertensive Actions of Vitamin B₆ 264

9.8 Other Carbonyl Catalysts 265
9.8.1 Pyruvoyl Enzymes 266
9.8.2 Pyrroloquinoline Quinone (PQQ) and Tryptophan Tryptophylquinone (TTQ) 266
9.8.3 Quinone Catalysts in Mammalian Enzymes 268
## 10 Folate and Other Pterins and Vitamin B<sub>12</sub>

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.1</td>
<td>Folate Vitamers and Dietary Folate Equivalents</td>
<td>271</td>
</tr>
<tr>
<td>10.1.1</td>
<td>Dietary Folate Equivalents</td>
<td>271</td>
</tr>
<tr>
<td>10.2</td>
<td>Metabolism of Folates</td>
<td>273</td>
</tr>
<tr>
<td>10.2.1</td>
<td>Digestion and Absorption of Folates</td>
<td>273</td>
</tr>
<tr>
<td>10.2.2</td>
<td>Tissue Uptake and Metabolism of Folate</td>
<td>274</td>
</tr>
<tr>
<td>10.2.2.1</td>
<td>Poly-γ-glutamylolation of Folate</td>
<td>275</td>
</tr>
<tr>
<td>10.2.3</td>
<td>Catabolism and Excretion of Folate</td>
<td>276</td>
</tr>
<tr>
<td>10.2.4</td>
<td>Biosynthesis of Pterins</td>
<td>276</td>
</tr>
<tr>
<td>10.3</td>
<td>Metabolic Functions of Folate</td>
<td>279</td>
</tr>
<tr>
<td>10.3.1</td>
<td>Sources of Substituted Folates</td>
<td>279</td>
</tr>
<tr>
<td>10.3.1.1</td>
<td>Serine Hydroxymethyltransferase</td>
<td>279</td>
</tr>
<tr>
<td>10.3.1.2</td>
<td>Histidine Catabolism</td>
<td>281</td>
</tr>
<tr>
<td>10.3.1.3</td>
<td>Other Sources of One-Carbon Substituted Folates</td>
<td>283</td>
</tr>
<tr>
<td>10.3.2</td>
<td>Interconversion of Substituted Folates</td>
<td>283</td>
</tr>
<tr>
<td>10.3.2.1</td>
<td>Methylene-Tetrahydrofolate Reductase</td>
<td>284</td>
</tr>
<tr>
<td>10.3.2.2</td>
<td>Disposal of Surplus One-Carbon Fragments</td>
<td>286</td>
</tr>
<tr>
<td>10.3.3</td>
<td>Utilization of One-Carbon Substituted Folates</td>
<td>286</td>
</tr>
<tr>
<td>10.3.3.1</td>
<td>Thymidylate Synthetase and Dihydrofolate Reductase</td>
<td>287</td>
</tr>
<tr>
<td>10.3.3.2</td>
<td>Dihydrofolate Reductase Inhibitors</td>
<td>288</td>
</tr>
<tr>
<td>10.3.3.3</td>
<td>The dUMP Suppression Test</td>
<td>289</td>
</tr>
<tr>
<td>10.3.4</td>
<td>The Role of Folate in Methionine Metabolism</td>
<td>289</td>
</tr>
<tr>
<td>10.3.4.1</td>
<td>The Methyl Folate Trap Hypothesis</td>
<td>291</td>
</tr>
<tr>
<td>10.3.4.2</td>
<td>Hyperhomocysteinemia and Cardiovascular Disease</td>
<td>292</td>
</tr>
<tr>
<td>10.4</td>
<td>Tetrahydrobiopterin</td>
<td>294</td>
</tr>
<tr>
<td>10.4.1</td>
<td>The Role of Tetrahydrobiopterin in Aromatic Amino Acid Hydroxylases</td>
<td>294</td>
</tr>
<tr>
<td>10.4.2</td>
<td>The Role of Tetrahydrobiopterin in Nitric Oxide Synthase</td>
<td>296</td>
</tr>
<tr>
<td>10.5</td>
<td>Molybdopterin</td>
<td>297</td>
</tr>
<tr>
<td>10.6</td>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt; Vitamers and Nomenclature</td>
<td>298</td>
</tr>
<tr>
<td>10.7</td>
<td>Metabolism of Vitamin B&lt;sub&gt;12&lt;/sub&gt;</td>
<td>300</td>
</tr>
<tr>
<td>10.7.1</td>
<td>Digestion and Absorption of Vitamin B&lt;sub&gt;12&lt;/sub&gt;</td>
<td>300</td>
</tr>
<tr>
<td>10.7.2</td>
<td>Plasma Vitamin B&lt;sub&gt;12&lt;/sub&gt; Binding Proteins and Tissue Uptake</td>
<td>301</td>
</tr>
<tr>
<td>10.7.3</td>
<td>Bacterial Biosynthesis of Vitamin B&lt;sub&gt;12&lt;/sub&gt;</td>
<td>303</td>
</tr>
<tr>
<td>10.8</td>
<td>Metabolic Functions of Vitamin B&lt;sub&gt;12&lt;/sub&gt;</td>
<td>303</td>
</tr>
<tr>
<td>10.8.1</td>
<td>Methionine Synthetase</td>
<td>304</td>
</tr>
<tr>
<td>10.8.2</td>
<td>Methylmalonyl CoA Mutase</td>
<td>305</td>
</tr>
<tr>
<td>10.8.3</td>
<td>Leucine Aminomutase</td>
<td>306</td>
</tr>
<tr>
<td>10.9</td>
<td>Deficiency of Folic Acid and Vitamin B&lt;sub&gt;12&lt;/sub&gt;</td>
<td>307</td>
</tr>
<tr>
<td>10.9.1</td>
<td>Megaloblastic Anemia</td>
<td>308</td>
</tr>
<tr>
<td>10.9.2</td>
<td>Pernicious Anemia</td>
<td>308</td>
</tr>
<tr>
<td>10.9.3</td>
<td>Neurological Degeneration in Vitamin B&lt;sub&gt;12&lt;/sub&gt; Deficiency</td>
<td>309</td>
</tr>
<tr>
<td>10.9.4</td>
<td>Folate Deficiency and Neural Tube Defects</td>
<td>310</td>
</tr>
<tr>
<td>10.9.5</td>
<td>Folate Deficiency and Cancer Risk</td>
<td>311</td>
</tr>
<tr>
<td>10.9.6</td>
<td>Drug-Induced Folate Deficiency</td>
<td>312</td>
</tr>
<tr>
<td>10.9.7</td>
<td>Drug-Induced Vitamin B&lt;sub&gt;12&lt;/sub&gt; Deficiency</td>
<td>313</td>
</tr>
</tbody>
</table>
10.10 Assessment of Folate and Vitamin B₁₂ Nutritional Status

10.10.1 Plasma and Erythrocyte Concentrations of Folate and Vitamin B₁₂

10.10.2 The Schilling Test for Vitamin B₁₂ Absorption

10.10.3 Methylmalonic Aciduria and Methylmalonic Acidemia

10.10.4 Histidine Metabolism – the FIGLU Test

10.10.5 The dUMP Suppression Test

10.11 Folate and Vitamin B₁₂ Requirements and Reference Intakes

10.11.1 Folate Requirements

10.11.2 Vitamin B₁₂ Requirements

10.11.3 Upper Levels of Folate Intake

10.12 Pharmacological Uses of Folate and Vitamin B₁₂

11 Biotin (Vitamin H)

11.1 Metabolism of Biotin

11.1.1 Bacterial Synthesis of Biotin

11.1.1.1 The Importance of Intestinal Bacterial Synthesis of Biotin

11.2 The Metabolic Functions of Biotin

11.2.1 The Role of Biotin in Carboxylation Reactions

11.2.1.1 Acetyl CoA Carboxylase

11.2.1.2 Pyruvate Carboxylase

11.2.1.3 Propionyl CoA Carboxylase

11.2.1.4 Methylcrotonyl CoA Carboxylase

11.2.2 Holocarboxylase Synthetase

11.2.2.1 Holocarboxylase Synthetase Deficiency

11.2.3 Biotinidase

11.2.3.1 Biotinidase Deficiency

11.2.4 Enzyme Induction by Biotin

11.2.5 Biotin in Regulation of the Cell Cycle

11.3 Biotin Deficiency

11.3.1 Metabolic Consequences of Biotin Deficiency

11.3.1.1 Glucose Homeostasis in Biotin Deficiency

11.3.1.2 Fatty Liver and Kidney Syndrome in Biotin-Deficient Chicks

11.3.1.3 Cot Death

11.3.2 Biotin Deficiency In Pregnancy

11.4 Assessment of Biotin Nutritional Status

11.5 Biotin Requirements

11.6 Avidin

12 Pantothenic Acid

12.1 Pantothenic Acid Vitamers

12.2 Metabolism of Pantothenic Acid

12.2.1 The Formation of CoA from Pantothenic Acid

12.2.1.1 Metabolic Control of CoA Synthesis
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.2.2 Catabolism of CoA</td>
<td>350</td>
</tr>
<tr>
<td>12.2.3 The Formation and Turnover of ACP</td>
<td>350</td>
</tr>
<tr>
<td>12.2.4 Biosynthesis of Pantothenic Acid</td>
<td>351</td>
</tr>
<tr>
<td>12.3 Metabolic Functions of Pantothenic Acid</td>
<td>352</td>
</tr>
<tr>
<td>12.4 Pantothenic Acid Deficiency</td>
<td>353</td>
</tr>
<tr>
<td>12.4.1 Pantothenic Acid Deficiency in Experimental Animals</td>
<td>353</td>
</tr>
<tr>
<td>12.4.2 Human Pantothenic Acid Deficiency – The Burning Foot Syndrome</td>
<td>354</td>
</tr>
<tr>
<td>12.5 Assessment of Pantothenic Acid Nutritional Status</td>
<td>355</td>
</tr>
<tr>
<td>12.6 Pantothenic Acid Requirements</td>
<td>355</td>
</tr>
<tr>
<td>12.7 Pharmacological Uses of Pantothenic Acid</td>
<td>356</td>
</tr>
<tr>
<td>13 Vitamin C (Ascorbic Acid)</td>
<td>357</td>
</tr>
<tr>
<td>13.1 Vitamin C Vitamers and Nomenclature</td>
<td>358</td>
</tr>
<tr>
<td>13.1.1 Assay of Vitamin C</td>
<td>359</td>
</tr>
<tr>
<td>13.2 Metabolism of Vitamin C</td>
<td>359</td>
</tr>
<tr>
<td>13.2.1 Intestinal Absorption and Secretion of Vitamin C</td>
<td>361</td>
</tr>
<tr>
<td>13.2.2 Tissue Uptake of Vitamin C</td>
<td>361</td>
</tr>
<tr>
<td>13.2.3 Oxidation and Reduction of Ascorbate</td>
<td>362</td>
</tr>
<tr>
<td>13.2.4 Metabolism and Excretion of Ascorbate</td>
<td>363</td>
</tr>
<tr>
<td>13.3 Metabolic Functions of Vitamin C</td>
<td>364</td>
</tr>
<tr>
<td>13.3.1 Dopamine β-Hydroxylase</td>
<td>365</td>
</tr>
<tr>
<td>13.3.2 Peptidyl Glycine Hydroxylase (Peptide α-Amidase)</td>
<td>366</td>
</tr>
<tr>
<td>13.3.3 2-Oxoglutarate–Linked Iron-Containing Hydroxylases</td>
<td>367</td>
</tr>
<tr>
<td>13.3.4 Stimulation of Enzyme Activity by Ascorbate In Vitro</td>
<td>369</td>
</tr>
<tr>
<td>13.3.5 The Role of Ascorbate in Iron Absorption and Metabolism</td>
<td>369</td>
</tr>
<tr>
<td>13.3.6 Inhibition of Nitrosamine Formation by Ascorbate</td>
<td>370</td>
</tr>
<tr>
<td>13.3.7 Pro- and Antioxidant Roles of Ascorbate</td>
<td>371</td>
</tr>
<tr>
<td>13.3.7.1 Reduction of the Vitamin E Radical by Ascorbate</td>
<td>371</td>
</tr>
<tr>
<td>13.3.8 Ascorbic Acid in Xenobiotic and Cholesterol Metabolism</td>
<td>371</td>
</tr>
<tr>
<td>13.4 Vitamin C Deficiency – Scurvy</td>
<td>372</td>
</tr>
<tr>
<td>13.4.1 Anemia in Scurvy</td>
<td>373</td>
</tr>
<tr>
<td>13.5 Assessment of Vitamin C Status</td>
<td>374</td>
</tr>
<tr>
<td>13.5.1 Urinary Excretion of Vitamin C and Saturation Testing</td>
<td>374</td>
</tr>
<tr>
<td>13.5.2 Plasma and Leukocyte Concentrations of Ascorbate</td>
<td>374</td>
</tr>
<tr>
<td>13.5.3 Markers of DNA Oxidative Damage</td>
<td>376</td>
</tr>
<tr>
<td>13.6 Vitamin C Requirements and Reference Intakes</td>
<td>376</td>
</tr>
<tr>
<td>13.6.1 The Minimum Requirement for Vitamin C</td>
<td>376</td>
</tr>
<tr>
<td>13.6.2 Requirements Estimated from the Plasma and Leukocyte Concentrations of Ascorbate</td>
<td>378</td>
</tr>
<tr>
<td>13.6.3 Requirements Estimated from Maintenance of the Body Pool of Ascorbate</td>
<td>378</td>
</tr>
<tr>
<td>13.6.4 Higher Recommendations</td>
<td>379</td>
</tr>
<tr>
<td>13.6.4.1 The Effect of Smoking on Vitamin C Requirements</td>
<td>380</td>
</tr>
</tbody>
</table>
Contents

13.6.5 Safety and Upper Levels of Intake of Vitamin C 380
13.6.5.1 Renal Stones 380
13.6.5.2 False Results in Urine Glucose Testing 381
13.6.5.3 Rebound Scurvy 381
13.6.5.4 Ascorbate and Iron Overload 382
13.7 Pharmacological Uses of Vitamin C 382
13.7.1 Vitamin C in Cancer Prevention and Therapy 382
13.7.2 Vitamin C in Cardiovascular Disease 383
13.7.3 Vitamin C and the Common Cold 383

14 Marginal Compounds and Phytonutrients 385
14.1 Carnitine 385
14.1.1 Biosynthesis and Metabolism of Carnitine 386
14.1.2 The Possible Essentiality of Carnitine 388
14.1.3 Carnitine as an Ergogenic Aid 388
14.2 Choline 389
14.2.1 Biosynthesis and Metabolism of Choline 389
14.2.2 The Possible Essentiality of Choline 391
14.3 Creatine 392
14.4 Inositol 393
14.4.1 Phosphatidylinositol in Transmembrane Signaling 394
14.4.2 The Possible Essentiality of Inositol 394
14.5 Taurine 396
14.5.1 Biosynthesis of Taurine 396
14.5.2 Metabolic Functions of Taurine 398
14.5.2.1 Taurine Conjugation of Bile Acids 398
14.5.2.2 Taurine in the Central Nervous System 398
14.5.2.3 Taurine and Heart Muscle 399
14.5.3 The Possible Essentiality of Taurine 399
14.6 Ubiquinone (Coenzyme Q) 400
14.7 Phytonutrients: Potentially Protective Compounds in Plant Foods 401
14.7.1 Allyl Sulfur Compounds 401
14.7.2 Flavonoids and Polyphenols 402
14.7.3 Glucosinolates 403
14.7.4 Phytoestrogens 404

Bibliography 409
Index 463
List of Figures

1.1. Derivation of reference intakes of nutrients. .............................. 22
1.2. Derivation of requirements or reference intakes for children. ....... 24
1.3. Derivation of reference intake (RDA) and tolerable upper level (UL) for a nutrient. ............................................................. 25
2.1. Major physiologically active retinoids. ...................................... 32
2.2. Major dietary carotenoids. ...................................................... 34
2.3. Oxidative cleavage of $\beta$-carotene by carotene dioxygenase. .... 41
2.4. Potential products arising from enzymic or nonenzymic symmetrical or asymmetric oxidative cleavage of $\beta$-carotene. ....... 44
2.5. Role of retinol in the visual cycle. ........................................... 51
2.6. Interactions of all-trans- and 9-cis-retinoic acids (and other active retinoids) with retinoid receptors. ................................. 56
2.7. Retinoylation of proteins by retinoyl CoA. .............................. 59
2.8. Retinoylation of proteins by 4-hydroxyretinoic acid. ............... 60
3.1. Vitamin D vitamers. .............................................................. 78
3.2. Synthesis of calcitriol from 7-dehydrocholesterol in the skin. .... 81
3.3. Metabolism of calcitriol to yield calcitriol and 24-hydroxycalcidiol. 84
4.1. Vitamin E vitamers. .............................................................. 110
4.2. Stereochemistry of $\alpha$-tocopherol. ...................................... 112
4.3. Reaction of tocopherol with lipid peroxides. ............................... 114
4.4. Resonance forms of the vitamin E radicals. ............................. 117
4.5. Role of vitamin E as a chain-perpetuating prooxidant. ............... 118
4.6. Reactions of $\alpha$- and $\gamma$-tocopherol with peroxynitrite. ........ 119
5.1. Vitamin K vitamers. .............................................................. 132
5.2. Reaction of the vitamin K-dependent carboxylase. .................. 137
5.3. Intrinsic and extrinsic blood clotting cascades. ....................... 140
6.1. Thiamin and thiamin analogs. ............................................... 149
6.2. Reaction of the pyruvate dehydrogenase complex. ................. 154
6.3. GABA shunt as an alternative to $\alpha$-ketoglutarate dehydrogenase in the citric acid cycle. ..................................................... 157
# List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.4</td>
<td>Role of transketolase in the pentose phosphate pathway.</td>
<td>160</td>
</tr>
<tr>
<td>7.1</td>
<td>Riboflavin, the flavin coenzymes and covalently bound flavins in proteins.</td>
<td>173</td>
</tr>
<tr>
<td>7.2</td>
<td>Products of riboflavin metabolism.</td>
<td>180</td>
</tr>
<tr>
<td>7.3</td>
<td>Biosynthesis of riboflavin in fungi.</td>
<td>182</td>
</tr>
<tr>
<td>7.4</td>
<td>One- and two-electron redox reactions of riboflavin.</td>
<td>184</td>
</tr>
<tr>
<td>7.5</td>
<td>Reaction of glutathione peroxidase and glutathione reductase.</td>
<td>186</td>
</tr>
<tr>
<td>7.6</td>
<td>Drugs that are structural analogs of riboflavin and may cause deficiency.</td>
<td>195</td>
</tr>
<tr>
<td>8.1</td>
<td>Niacin vitamers, nicotinamide and nicotinic acid, and the nicotinamide nucleotide coenzymes.</td>
<td>202</td>
</tr>
<tr>
<td>8.2</td>
<td>Synthesis of NAD from nicotinamide, nicotinic acid, and quinolinic acid.</td>
<td>204</td>
</tr>
<tr>
<td>8.3</td>
<td>Metabolites of nicotinamide and nicotinic acid.</td>
<td>207</td>
</tr>
<tr>
<td>8.4</td>
<td>Pathways of tryptophan metabolism.</td>
<td>209</td>
</tr>
<tr>
<td>8.5</td>
<td>Redox function of the nicotinamide nucleotide coenzymes.</td>
<td>215</td>
</tr>
<tr>
<td>8.6</td>
<td>Reactions of ADP-ribosyltransferase and poly(ADP-ribose) polymerase.</td>
<td>216</td>
</tr>
<tr>
<td>8.7</td>
<td>Reactions catalyzed by ADP ribose cyclase.</td>
<td>220</td>
</tr>
<tr>
<td>9.1</td>
<td>Interconversion of the vitamin B₆ vitamers.</td>
<td>233</td>
</tr>
<tr>
<td>9.2</td>
<td>Reactions of pyridoxal phosphate-dependent enzymes with amino acids.</td>
<td>238</td>
</tr>
<tr>
<td>9.3</td>
<td>Transamination of amino acids.</td>
<td>241</td>
</tr>
<tr>
<td>9.4</td>
<td>Tryptophan load test for vitamin B₆ status.</td>
<td>248</td>
</tr>
<tr>
<td>9.5</td>
<td>Methionine load test for vitamin B₆ status.</td>
<td>255</td>
</tr>
<tr>
<td>9.6</td>
<td>Quinone catalysts.</td>
<td>267</td>
</tr>
<tr>
<td>10.1</td>
<td>Folate vitamers.</td>
<td>272</td>
</tr>
<tr>
<td>10.2</td>
<td>Biosynthesis of folic acid and tetrahydrobiopterin</td>
<td>277</td>
</tr>
<tr>
<td>10.3</td>
<td>One-carbon substituted tetrahydrofolic acid derivatives.</td>
<td>280</td>
</tr>
<tr>
<td>10.4</td>
<td>Sources and uses of one-carbon units bound to folate.</td>
<td>281</td>
</tr>
<tr>
<td>10.5</td>
<td>Reactions of serine hydroxymethyltransferase and the glyoxyl cleavage system.</td>
<td>281</td>
</tr>
<tr>
<td>10.6</td>
<td>Catabolism of histidine – basis of the FIGLU test for folate status.</td>
<td>282</td>
</tr>
<tr>
<td>10.7</td>
<td>Reaction of methylene-tetrahydrofolate reductase.</td>
<td>284</td>
</tr>
<tr>
<td>10.8</td>
<td>Synthesis of thymidine monophosphate.</td>
<td>287</td>
</tr>
<tr>
<td>10.9</td>
<td>Metabolism of methionine.</td>
<td>290</td>
</tr>
<tr>
<td>10.10</td>
<td>Role of tetrahydrobiopterin in aromatic amino acid hydroxylases.</td>
<td>295</td>
</tr>
<tr>
<td>10.11</td>
<td>Reaction of nitric oxide synthase.</td>
<td>297</td>
</tr>
<tr>
<td>10.12</td>
<td>Vitamin B₁₂.</td>
<td>299</td>
</tr>
<tr>
<td>10.13</td>
<td>Reactions of propionyl CoA carboxylase and methylmalonyl CoA mutase.</td>
<td>305</td>
</tr>
<tr>
<td>11.1</td>
<td>Metabolism of biotin.</td>
<td>325</td>
</tr>
<tr>
<td>11.2</td>
<td>Biotin metabolites.</td>
<td>326</td>
</tr>
</tbody>
</table>
# List of Figures

11.3. Biosynthesis of biotin. 328
12.1. Pantothenic acid and related compounds and coenzyme A. 346
12.2. Biosynthesis of coenzyme A. 347
12.3. Biosynthesis of pantothenic acid. 351
13.1. Vitamin C vitamers. 358
13.2. Biosynthesis of ascorbate. 360
13.3. Redox reactions of ascorbate. 363
13.4. Synthesis of the catecholamines. 365
13.5. Reactions of peptidyl glycine hydroxylase and peptidyl hydroxyglycine α-amidating lyase. 366
13.6. Reaction sequence of prolyl hydroxylase. 368
14.1. Reaction of carnitine acyltransferase. 386
14.2. Biosynthesis of carnitine. 387
14.3. Biosynthesis of choline and acetylcholine. 390
14.4. Catabolism of choline. 391
14.5. Synthesis of creatine. 392
14.6. Formation of inositol trisphosphate and diacylglycerol. 395
14.7. Pathways for the synthesis of taurine from cysteine. 397
14.8. Ubiquinone. 400
14.9. Allyl sulfur compounds allicin and alliin. 402
14.10. Major classes of flavonoids. 403
14.11. Glucosinolates. 404
14.12. Estradiol and the major phytoestrogens. 405
### List of Tables

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>The Vitamins</td>
<td>3</td>
</tr>
<tr>
<td>1.2</td>
<td>Compounds that Were at One Time Assigned Vitamin Nomenclature, But Are Not Considered to Be Vitamins</td>
<td>5</td>
</tr>
<tr>
<td>1.3</td>
<td>Marginal Compounds that Are (Probably) Not Dietary Essentials</td>
<td>6</td>
</tr>
<tr>
<td>1.4</td>
<td>Compounds that Are Not Dietary Essentials, But May Have Useful Protective Actions</td>
<td>7</td>
</tr>
<tr>
<td>1.5</td>
<td>Reference Nutrient Intakes of Vitamins, U.K., 1991</td>
<td>13</td>
</tr>
<tr>
<td>1.6</td>
<td>Population Reference Intakes of Vitamins, European Union, 1993</td>
<td>14</td>
</tr>
<tr>
<td>1.7</td>
<td>Recommended Dietary Allowances and Acceptable Intakes for Vitamins, U.S./Canada, 1997–2001</td>
<td>15</td>
</tr>
<tr>
<td>1.8</td>
<td>Recommended Nutrient Intakes for Vitamins, FAO/WHO, 2001</td>
<td>16</td>
</tr>
<tr>
<td>1.9</td>
<td>Terms that Have Been Used to Describe Reference Intakes of Nutrients</td>
<td>21</td>
</tr>
<tr>
<td>1.10</td>
<td>Toxicity of Vitamins: Upper Limits of Habitual Consumption and Tolerable Upper Limits of Intake</td>
<td>26</td>
</tr>
<tr>
<td>1.11</td>
<td>Labeling Reference Values for Vitamins</td>
<td>27</td>
</tr>
<tr>
<td>2.1</td>
<td>Prevalence of Vitamin A Deficiency among Children under Five</td>
<td>61</td>
</tr>
<tr>
<td>2.2</td>
<td>WHO Classification of Xerophthalmia</td>
<td>63</td>
</tr>
<tr>
<td>2.3</td>
<td>Biochemical Indices of Vitamin A Status</td>
<td>65</td>
</tr>
<tr>
<td>2.4</td>
<td>Reference Intakes of Vitamin A</td>
<td>67</td>
</tr>
<tr>
<td>2.5</td>
<td>Prudent Upper Levels of Habitual Intake</td>
<td>69</td>
</tr>
<tr>
<td>3.1</td>
<td>Nomenclature of Vitamin D Metabolites</td>
<td>79</td>
</tr>
<tr>
<td>3.2</td>
<td>Plasma Concentrations of Vitamin D Metabolites</td>
<td>80</td>
</tr>
<tr>
<td>3.3</td>
<td>Genes Regulated by Calcitriol</td>
<td>90</td>
</tr>
<tr>
<td>3.4</td>
<td>Plasma Concentrations of Calcidiol, Alkaline Phosphatase, Calcium, and Phosphate as Indices of Nutritional Status</td>
<td>104</td>
</tr>
<tr>
<td>3.5</td>
<td>Reference Intakes of Vitamin D</td>
<td>105</td>
</tr>
<tr>
<td>4.1</td>
<td>Relative Biological Activity of the Vitamin E Vitamers</td>
<td>111</td>
</tr>
<tr>
<td>4.2</td>
<td>Responses of Signs of Vitamin E or Selenium Deficiency to Vitamin E, Selenium, and Synthetic Antioxidants in Experimental Animals</td>
<td>123</td>
</tr>
<tr>
<td>Table</td>
<td>Title</td>
<td>Page</td>
</tr>
<tr>
<td>-------</td>
<td>----------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>4.3.</td>
<td>Indices of Vitamin E Nutritional Status</td>
<td>126</td>
</tr>
<tr>
<td>5.1.</td>
<td>Reference Intakes of Vitamin K</td>
<td>146</td>
</tr>
<tr>
<td>6.1.</td>
<td>Indices of Thiamin Nutritional Status</td>
<td>168</td>
</tr>
<tr>
<td>6.2.</td>
<td>Reference Intakes of Thiamin</td>
<td>170</td>
</tr>
<tr>
<td>7.1.</td>
<td>Tissue Flavins in the Rat</td>
<td>176</td>
</tr>
<tr>
<td>7.2.</td>
<td>Urinary Excretion of Riboflavin Metabolites</td>
<td>181</td>
</tr>
<tr>
<td>7.3.</td>
<td>Reoxidation of Reduced Flavins in Flavoprotein Oxidases</td>
<td>187</td>
</tr>
<tr>
<td>7.4.</td>
<td>Reoxidation of Reduced Flavins in Flavin Mixed-Function Oxidases</td>
<td>190</td>
</tr>
<tr>
<td>7.5.</td>
<td>Indices of Riboflavin Nutritional Status</td>
<td>196</td>
</tr>
<tr>
<td>7.6.</td>
<td>Reference Intakes of Riboflavin</td>
<td>198</td>
</tr>
<tr>
<td>8.1.</td>
<td>Indices of Niacin Nutritional Status</td>
<td>227</td>
</tr>
<tr>
<td>8.2.</td>
<td>Reference Intakes of Niacin</td>
<td>228</td>
</tr>
<tr>
<td>9.1.</td>
<td>Pyridoxal Phosphate-Catalyzed Enzyme Reactions of Amino Acids</td>
<td>237</td>
</tr>
<tr>
<td>9.2.</td>
<td>Amines Formed by Pyridoxal Phosphate-Dependent Decarboxylases</td>
<td>240</td>
</tr>
<tr>
<td>9.3.</td>
<td>Transamination Products of the Amino Acids</td>
<td>242</td>
</tr>
<tr>
<td>9.4.</td>
<td>Vitamin B6-Responsive Inborn Errors of Metabolism</td>
<td>250</td>
</tr>
<tr>
<td>9.5.</td>
<td>Indices of Vitamin B6 Nutritional Status</td>
<td>251</td>
</tr>
<tr>
<td>9.6.</td>
<td>Reference Intakes of Vitamin B6</td>
<td>258</td>
</tr>
<tr>
<td>10.1.</td>
<td>Adverse Effects of Hyperhomocysteinemia</td>
<td>293</td>
</tr>
<tr>
<td>10.2.</td>
<td>Indices of Folate and Vitamin B12 Nutritional Status</td>
<td>315</td>
</tr>
<tr>
<td>10.3.</td>
<td>Reference Intakes of Folate</td>
<td>319</td>
</tr>
<tr>
<td>10.4.</td>
<td>Reference Intakes of Vitamin B12</td>
<td>320</td>
</tr>
<tr>
<td>11.1.</td>
<td>Abnormal Urinary Organic Acids in Biotin Deficiency and Multiple Carboxylase Deficiency from Lack of Holo-carboxylase Synthetase or Biotinidase</td>
<td>333</td>
</tr>
<tr>
<td>13.1.</td>
<td>Vitamin C-Dependent 2-Oxoglutarate–linked Hydroxylases</td>
<td>367</td>
</tr>
<tr>
<td>13.2.</td>
<td>Plasma and Leukocyte Ascorbate Concentrations as Criteria of Vitamin C Nutritional Status</td>
<td>375</td>
</tr>
<tr>
<td>13.3.</td>
<td>Reference Intakes of Vitamin C</td>
<td>377</td>
</tr>
</tbody>
</table>
Preface

In the preface to the first edition of this book, I wrote that one stimulus to write it had been teaching a course on nutritional biochemistry, in which my students had raised questions for which I had to search for answers. In the intervening decade, they have continued to stimulate me to try to answer what are often extremely searching questions. I hope that the extent to which helping them through the often conflicting literature has clarified my thoughts is apparent to future students who will use this book and that they will continue to raise questions for which we all have to search for answers.

The other stimulus to write the first edition of this book was my membership of United Kingdom and European Union expert committees on reference intakes of nutrients, which reported in 1991 and 1993, respectively. Since these two committees completed their work, new reference intakes have been published for use in the United States and Canada (from 1997 to 2001) and by the United Nations Food and Agriculture Organization/World Health Organization (in 2001). A decade ago, the concern of those compiling tables of reference intakes was on determining intakes to prevent deficiency. Since then, the emphasis has changed from prevention of deficiency to the promotion of optimum health, and there has been a considerable amount of research to identify biomarkers of optimum, rather than minimally adequate, vitamin status. Epidemiological studies have identified a number of nutrients that appear to provide protection against cancer, cardiovascular, and other degenerative diseases. Large-scale intervention trials with supplements of individual nutrients have, in general, yielded disappointing results, but these have typically been relatively short-term (typically 5–10 years); the obvious experiments would require lifetime studies, which are not technically feasible.

The purpose of this book is to review what we know of the biochemistry of the vitamins, and to explain the extent to which this knowledge explains
the clinical signs of deficiency, the possible benefits of higher intakes than are obtained from average diets, and the adverse effects of excessive intakes.

In the decade since the first edition was published, there have been considerable advances in our knowledge: novel functions of several of the vitamins have been elucidated; and the nutritional biochemist today has to interact with structural biochemists, molecular, cell, and developmental biologists and geneticists, as well as the traditional metabolic biochemist. Despite the advances, there are still major unanswered questions. We still cannot explain why deficiency of three vitamins required as coenzymes in energy-yielding metabolism results in diseases as diverse as fatal neuritis and heart disease of thiamin deficiency, painful cracking of the tongue and lips of riboflavin deficiency, or photosensitive dermatitis, depressive psychosis, and death associated with niacin deficiency.

This book is dedicated in gratitude to those whose painstaking work over almost 100 years since the discovery of the first accessory food factor in 1906 has established the basis of our knowledge, and in hope to those who will attempt to answer the many outstanding questions in the years to come.

David A. Bender
August 2002
London