

Section I Diagnosis and Treatment: General Principles

1	Clinical Approach to Inborn Errors of Metabolism in Pediatrics	3
	<i>Jean-Marie Saudubray, Angela Garcia Cazorla</i>	
1.1	Classification	4
1.1.1	Pathophysiology	4
1.1.2	Clinical Presentation	5
1.2	Antenatal Symptoms	6
1.3	Neonatal and Early Infancy Presentation (<1 year)	8
1.3.1	Clinical Presentation	8
1.3.2	Metabolic Derangements and Diagnostic Tests	14
1.4	Later Onset Acute and Recurrent Attacks (Late Infancy and Beyond)	18
1.4.1	Clinical Presentations	18
1.4.2	Metabolic Derangements and Diagnostic Tests	26
1.5	Chronic and Progressive Neurological Symptoms (Mental Retardation, Developmental Delay, Epilepsy, Neurological Deterioration and Psychiatric Symptoms)	32
1.5.1	Diagnostic Approach to Neurological and Mental Deterioration Related to Age	32
1.5.2	Specific Neurosensorial, Neurophysiological and Neuroradiological Signs and Symptoms (at any Age)	45
1.5.3	Recommended Laboratory Tests in Neurological Syndromes	52
1.6	Specific Organ Signs and Symptoms	55
1.6.1	Cardiology	55
1.6.2	Dermatology	55
1.6.3	Endocrinology	57
1.6.4	Gastroenterology and Nutritional Findings	58
1.6.5	Haematology	61
1.6.6	Hepatology	63
1.6.7	Immunology	64
1.6.8	Myology	65
1.6.9	Nephrology	65
1.6.10	Neurology and Psychiatry	65
1.6.11	Ophthalmologic Signs	65
1.6.12	Orthopedy	66
1.6.13	Pneumology	68
1.6.14	Psychiatry	68
1.6.15	Rheumatology	68
1.6.16	Stomatology	69
	References	69
2	Inborn Errors of Metabolism in Adults: A Diagnostic Approach to Neurological and Psychiatric Presentations	71
	<i>Fanny Mochel, Frédéric Sedel</i>	
2.1	Differences Between Paediatric and Adult Phenotypes	72
2.2	General Approach to IEM in Adulthood	72
2.2.1	Disorders of Energy Metabolism	72
2.2.2	Disorders of Lipid Metabolism	72
2.2.3	Intoxication Syndromes	75
2.2.4	Disorders of Neurotransmitter Metabolism	76
2.2.5	Metal Storage Disorders	76
2.3	Specific Approaches to Neurometabolic Presentations in Adults	76
2.3.1	Encephalopathies/Comas	76
2.3.2	Strokes and Pseudostrokes	77
2.3.3	Movement Disorders	77
2.3.4	Peripheral Neuropathies	77

2.3.5	Leukoencephalopathies	79
2.3.6	Epilepsy	81
2.3.7	Psychiatric Disorders	82
2.3.8	Spastic Paraparesis	84
2.3.9	Cerebellar Ataxia	84
2.3.10	Myopathy	85
2.3.11	Others	87
	References	89
3	Diagnostic Procedures	91
	<i>Guy Touati, Fanny Mochel, Daniel Rabier</i>	
3.1	Introduction	92
3.2	Basal Metabolic Investigation	92
3.2.1	Amino and organic acids	92
3.2.2	Metabolic Profile over the Course of the Day	92
3.3	Metabolomic Approaches: the Example of <i>In Vitro</i> ¹H-NMR Spectroscopy of Body Fluids	100
3.4	Functional Tests	101
3.4.1	Fasting Test	101
3.4.2	Oral Glucose Loading Test	103
3.4.3	Glucagon Test	103
3.4.4	Protein and Allopurinol Loading Test	103
3.4.5	Exercise Test	104
3.5	Next Generation Sequencing and Gene panels	104
3.6	Postmortem Protocol	105
3.6.1	Cells and Tissues for Enzyme Assays	105
3.6.2	Cells and Tissues for Chromosome and DNA Investigations	105
3.6.3	Skin Fibroblasts	105
3.6.4	Body Fluids for Chemical Investigations	105
3.6.5	Autopsy	106
	References	107
4	Emergency Treatments	109
	<i>Manuel Schiff, Fanny Mochel, Carlo Dionisi-Vici</i>	
4.1	Introduction	110
4.2	General Principles	110
4.2.1	Supportive Care	110
4.2.2	Nutrition	110
4.2.3	Specific Therapies	110
4.2.4	Extracorporeal Procedures for Toxin Removal	110
4.3	Emergency Management of Particular Clinical Presentations	111
4.3.1	Neurological Deterioration	111
4.3.2	Liver Failure	114
4.3.3	Neonatal Hypoglycaemia	114
4.3.4	Cardiac Failure	115
4.3.5	Primary Hyperlactataemia	115
4.3.6	Intractable Seizures	115
4.4	Final Considerations	115
	References	115

Section II Disorders of Carbohydrate Metabolism

5	The Glycogen Storage Diseases and Related Disorders	121
	<i>John Walter, Philippe Labrune, Pascal Laforêt</i>	
5.1	Hepatic Glycogenoses	123
5.1.1	Liver Glycogen Storage Disease Type 0 (GSD 0a)	123
5.1.2	Glycogen Storage Disease Type I (GSD I)	123

5.1.3	Glycogen Storage Disease Type III (GSD III)	127
5.1.4	Glycogen Storage Disease Type IV (GSD IV)	128
5.1.5	Glycogen Storage Disease Type VI (GSD VI)	129
5.1.6	Glycogen storage disease type IX (GSD IX)	129
5.1.7	Fanconi-Bickel Syndrome	129
5.2	Muscle and Cardiac Glycogenoses	130
5.2.1	Glycogen Storage Disease Type V (Myophosphorylase Deficiency, McArdle Disease)	130
5.2.2	Disorders of Glycolysis	131
5.2.3	Glycogen Storage Disease Type II (Pompe Disease)	131
5.2.4	Danon Disease (LAMP-2 Deficiency)	132
5.2.5	Glycogen Depletion Syndromes: Muscle Glycogen Synthase Deficiency (Muscle GSD Type 0, GSD 0b) and Glycogenin 1 Deficiency	133
5.2.6	Muscle and Cardiac Glycogenosis with Polyglucosan Bodies Due to <i>RBCK1</i> and <i>GYG1</i> Mutations	133
5.2.7	AMP-activated Protein Kinase (AMPK) Deficiency	134
5.3	Brain Glycogenoses	134
5.3.1	Lafora Disease (Neuronal Laforin/Malin Defects)	134
5.3.2	Adult Polyglucosan Body Disease	135
	References	135
6	Disorders of Galactose Metabolism	139
	<i>Gerard T. Berry, John Walter, Judith L. Fridovich-Keil</i>	
6.1	Galactose-1-Phosphate Uridyltransferase (GALT) Deficiency	141
6.1.1	Clinical Presentation of GALT Deficiency	141
6.1.2	Metabolic Derangement in GALT Deficiency	142
6.1.3	Genetics of GALT Deficiency	142
6.1.4	Diagnostic Tests for GALT Deficiency	142
6.1.5	Treatment and Prognosis for GALT Deficiency	143
6.2	Uridine Diphosphate Galactose 4'-Epimerase (GALE) Deficiency	144
6.2.1	Clinical Presentation of GALE Deficiency	144
6.2.2	Metabolic Derangement in GALE Deficiency	144
6.2.3	Genetics of GALE Deficiency	145
6.2.4	Diagnostic Tests for GALE Deficiency	145
6.2.5	Treatment and Prognosis for GALE Deficiency	145
6.3	Galactokinase (GALK) Deficiency	145
6.3.1	Clinical Presentation of GALK Deficiency	145
6.3.2	Metabolic Derangement in GALK Deficiency	145
6.3.3	Genetics of GALK Deficiency	145
6.3.4	Diagnostic Tests for GALK Deficiency	146
6.3.5	Treatment and Prognosis for GALK Deficiency	146
6.4	Fanconi-Bickel Syndrome	146
6.5	Portosystemic Venous Shunting and Hepatic Arteriovenous Malformations	146
	References	146
7	Disorders of Glycolysis and the Pentose Phosphate Pathway	149
	<i>Mirjam M.C. Wamelink, Vassili Valayannopoulos, Barbara Garavaglia</i>	
7.1	Muscle Phosphofructokinase (PFKM) Deficiency	151
7.1.1	Clinical Presentation	151
7.1.2	Metabolic Derangement	151
7.1.3	Genetics	151
7.1.4	Diagnostic Tests	152
7.2	Aldolase A (ALDOA) Deficiency	152
7.2.1	Clinical Presentation	152
7.2.2	Metabolic Derangement	152
7.2.3	Genetics	152
7.2.4	Diagnostic Tests	152
7.2.5	Treatment and Prognosis	152
7.3	Triosephosphate Isomerase (TPI) Deficiency	152

7.3.1	Clinical Presentation	152
7.3.2	Metabolic Derangement	152
7.3.3	Genetics	153
7.3.4	Diagnostic Tests	153
7.3.5	Treatment and Prognosis	153
7.4	Phosphoglycerate Kinase (PGK) Deficiency	153
7.4.1	Clinical Presentation	153
7.4.2	Metabolic Derangement	153
7.4.3	Genetics	153
7.4.4	Diagnostic Tests	153
7.4.5	Treatment and Prognosis	153
7.5	Phosphoglycerate Mutase (PGAM) Deficiency	154
7.5.1	Clinical Presentation	154
7.5.2	Metabolic Derangement	154
7.5.3	Genetics	154
7.5.4	Diagnostic Tests	154
7.5.5	Treatment and Prognosis	154
7.6	Enolase Deficiency	154
7.6.1	Clinical Presentation	154
7.6.2	Metabolic Derangement	154
7.6.3	Genetics	154
7.6.4	Diagnostic Tests	154
7.6.5	Treatment and Prognosis	155
7.7	Lactate Dehydrogenase (LDH) Deficiency	155
7.7.1	Clinical Presentation	155
7.7.2	Metabolic Derangement	155
7.7.3	Genetics	155
7.7.4	Diagnostic Tests	155
7.7.5	Treatment and Prognosis	155
7.8	Glycerol Kinase Deficiency (GKD)	155
7.8.1	Clinical Presentation	155
7.8.2	Metabolic Derangement	155
7.8.3	Genetics	156
7.8.4	Diagnostic Tests	156
7.8.5	Treatment and Prognosis	156
7.9	Ribose-5-Phosphate Isomerase (RPI) Deficiency	156
7.9.1	Clinical Presentation	156
7.9.2	Metabolic Derangement	156
7.9.3	Genetics	157
7.9.4	Diagnostic Tests	157
7.9.5	Treatment and Prognosis	157
7.10	Transaldolase (TALDO) Deficiency	157
7.10.1	Clinical Presentation	157
7.10.2	Metabolic Derangement	157
7.10.3	Genetics	157
7.10.4	Diagnostic Tests	157
7.10.5	Treatment and Prognosis	158
7.11	Transketolase (TKT) Deficiency	158
7.11.1	Clinical Presentation	158
7.11.2	Metabolic Derangement	158
7.11.3	Genetics	158
7.11.4	Diagnostic Tests	158
7.11.5	Treatment and Prognosis	158
7.12	Sedoheptulokinase (SHPK) Deficiency	158
7.12.1	Clinical Presentation	158
7.12.2	Metabolic Derangement	159
7.12.3	Genetics	159

7.12.4	Diagnostic Tests	159
7.12.5	Treatment and Prognosis	159
	References	159
8	Disorders of Fructose Metabolism	161
	<i>Beat Steinmann, René Santer</i>	
8.1	Essential Fructosuria	163
8.1.1	Clinical Presentation	163
8.1.2	Metabolic Derangement	163
8.1.3	Genetics	163
8.1.4	Diagnosis	163
8.1.5	Treatment and Prognosis	163
8.2	Hereditary Fructose Intolerance	163
8.2.1	Clinical Presentation	163
8.2.2	Metabolic Derangement	164
8.2.3	Genetics	164
8.2.4	Diagnosis	164
8.2.5	Differential Diagnosis	165
8.2.6	Treatment and Prognosis	165
8.3	Fructose-1,6-Bisphosphatase Deficiency	165
8.3.1	Clinical Presentation	165
8.3.2	Metabolic Derangement	166
8.3.3	Genetics	166
8.3.4	Diagnosis	166
8.3.5	Differential Diagnosis	167
8.3.6	Treatment and Prognosis	167
	References	167
9	Congenital Hyperinsulinism	169
	<i>Jean-Baptiste Arnoux, Pascale de Lonlay</i>	
9.1	Clinical Presentation	171
9.2	Metabolic Derangement	172
9.3	Genetics	172
9.4	Diagnostic Tests	172
9.5	Treatment and Prognosis	173
9.6	Long-term Medical Management	174
9.7	Prognosis	174
	References	174
10	Disorders of Glucose Transport	175
	<i>René Santer, Jörg Klepper</i>	
10.1	Congenital Glucose/Galactose Malabsorption (SGLT1 Deficiency)	177
10.1.1	Clinical Presentation	177
10.1.2	Metabolic Derangement	177
10.1.3	Genetics	177
10.1.4	Diagnostic Tests	177
10.1.5	Treatment and Prognosis	178
10.2	Renal Glucosuria (SGLT2 Deficiency)	178
10.2.1	Clinical Presentation	178
10.2.2	Metabolic Derangement	178
10.2.3	Genetics	178
10.2.4	Diagnostic Tests	178
10.2.5	Treatment and Prognosis	178
10.3	Glucose Transporter-1 Deficiency (GLUT1 Deficiency)	178
10.3.1	Clinical Presentation	178
10.3.2	Metabolic Derangement	179
10.3.3	Genetics	179
10.3.4	Diagnostic Tests	179

10.3.5	Treatment and Prognosis	179
10.4	Fanconi-Bickel Syndrome (GLUT2 Deficiency)	180
10.4.1	Clinical Presentation	180
10.4.2	Metabolic Derangement	180
10.4.3	Genetics	180
10.4.4	Diagnostic Tests	180
10.4.5	Treatment and Prognosis	181
10.5	Arterial Tortuosity Syndrome (GLUT10 Deficiency)	181
10.5.1	Clinical Presentation	181
10.5.2	Metabolic Derangement	181
10.5.3	Genetics	181
10.5.4	Diagnostic Tests	181
10.5.5	Treatment and Prognosis	181
	References	182

Section III Disorders of Mitochondrial Energy Metabolism

11	Disorders of Pyruvate Metabolism and the Tricarboxylic Acid Cycle	187
	<i>Linda J. De Meirleir, Angels Garcia-Cazorla, Michele Brivet</i>	
11.1	Pyruvate Carboxylase Deficiency	189
11.1.1	Clinical Presentation	189
11.1.2	Metabolic Derangement	189
11.1.3	Genetics	190
11.1.4	Diagnostic Tests	190
11.1.5	Treatment and Prognosis	190
11.2	Phosphoenolpyruvate Carboxykinase Deficiency	192
11.3	Pyruvate Dehydrogenase Complex Deficiency	192
11.3.1	Clinical Presentation	192
11.3.2	Metabolic Derangement	193
11.3.3	Genetics	193
11.3.4	Diagnostic Tests	193
11.3.5	Treatment and Prognosis	194
11.4	Dihydrolipoamide Dehydrogenase Deficiency (DLD)	194
11.4.1	Clinical Presentation	194
11.4.2	Metabolic Derangement	194
11.4.3	Genetics	194
11.4.4	Diagnostic Tests	194
11.4.5	Treatment and Prognosis	194
11.5	2-Ketoglutarate Dehydrogenase Complex Deficiency (KDHC)	195
11.5.1	Clinical Presentation	195
11.5.2	Metabolic Derangement	195
11.5.3	Genetics	195
11.5.4	Diagnostic Tests	195
11.5.5	Treatment and Prognosis	195
11.6	Fumarase Deficiency	195
11.6.1	Clinical Presentation	195
11.6.2	Metabolic Derangement	195
11.6.3	Genetics	196
11.6.4	Diagnostic Tests	196
11.6.5	Treatment and Prognosis	196
11.7	Succinate Dehydrogenase Deficiency	196
11.7.1	Clinical Presentation	196
11.7.2	Metabolic Derangement	196
11.8	Other Krebs Cycle Disorders	196
11.9	Pyruvate Transporter Defect	197
11.10	Protein-bound lipoic acid defect and defects in cofactors	197
	References	197

12	Disorders of Mitochondrial Fatty Acid Oxidation & Riboflavin Metabolism	201
	<i>Andrew A.M. Morris, Ute Spiekerkoetter</i>	
12.1	Disorders of Mitochondrial Fatty Acid Oxidation	203
12.2	Clinical Presentations	203
12.2.1	Fatty Acid Transport Defects	203
12.2.2	Carnitine Cycle Defects	203
12.2.3	β -Oxidation Defects	205
12.2.4	Electron Transfer Defects	206
12.2.5	Other Potential Defects	206
12.3	Metabolic Derangement	206
12.4	Genetics	207
12.5	Diagnostic Tests	207
12.5.1	Abnormal Metabolites	207
12.5.2	<i>In Vitro</i> Studies	209
12.5.3	Fasting Studies	209
12.5.4	Prenatal Diagnosis	209
12.5.5	Newborn Screening	209
12.6	Treatment and Prognosis	209
12.6.1	Management of Acute Illness	209
12.6.2	Long Term Dietary Management	209
12.6.3	Drug Treatment	210
12.6.4	Monitoring	210
12.6.5	Prognosis	211
12.7	Defects of Riboflavin Transport & Metabolism	211
12.7.1	Brown-Vialetto-van Laere Syndrome	211
12.7.2	RFVT1 Deficiency	212
12.7.3	FAD Synthase and Mitochondrial FAD Transporter Deficiencies	212
	References	212
13	Disorders of Ketogenesis and Ketolysis	215
	<i>Andrew A.M. Morris</i>	
13.1	Ketogenesis Defects	217
13.1.1	Clinical Presentation	217
13.1.2	Metabolic Derangement	217
13.1.3	Genetics	217
13.1.4	Diagnostic Tests	217
13.1.5	Treatment and Prognosis	218
13.2	Defects of Ketone Body Utilization or Transport	218
13.2.1	Clinical Presentation	218
13.2.2	Metabolic Derangement	219
13.2.3	Genetics	219
13.2.4	Diagnostic Tests	219
13.2.5	Treatment and Prognosis	219
13.3	Cytosolic Acetoacetyl-CoA Thiolase Deficiency	220
13.4	Ketogenic Diets	220
	References	220
14	Disorders of Oxidative Phosphorylation	223
	<i>Shamima Rahman, Johannes A. Mayr</i>	
14.1	Clinical Presentation	225
14.1.1	Neonatal and Infantile Presentations	226
14.1.2	Presentation in Childhood and Adolescence	230
14.1.3	Adult-Onset Disorders	231
14.2	Metabolic Derangement	231
14.3	Genetics	232
14.3.1	Mitochondrial DNA Mutations	232
14.3.2	Nuclear Gene Defects	232

14.3.3	Frequency of Mutations	233
14.4	Diagnostic Tests	233
14.4.1	Screening Tests	233
14.4.2	Muscle and Other Tissue Biopsies	235
14.4.3	Molecular Genetic Investigations	238
14.5	Treatment and Prognosis	238
14.5.1	Treatable Disorders	238
14.5.2	Supportive Management	240
14.5.3	Vitamin and Cofactor Cocktails	240
14.5.4	Experimental Approaches	240
14.5.5	Genetic Counselling and Prenatal and Preimplantation Genetic Diagnosis	240
14.5.6	Prognosis	240
	References	241
15	Creatine Deficiency Syndromes	243
	<i>Sylvia Stöckler-Ipsiroglu, Saadet Mercimek-Mahmutoglu, Gajja S. Salomons</i>	
15.1	Clinical Presentation	245
15.1.1	Arginine Glycine Amidinotransferase (AGAT) Deficiency	245
15.1.2	Guanidinoacetate Methyltransferase (GAMT) Deficiency	245
15.1.3	Creatine Transporter (CRTR) Deficiency	245
15.2	Metabolic Derangement	245
15.3	Genetics	246
15.4	Diagnostic Tests	246
15.4.1	<i>In Vivo</i> Brain MRS	246
15.4.2	Metabolite Analysis	246
15.4.3	DNA Analysis	246
15.4.4	Functional Tests	247
15.4.5	Prenatal Diagnosis	247
15.4.6	Newborn Screening	247
15.5	Treatment and Prognosis	247
15.5.1	AGAT Deficiency	247
15.5.2	GAMT Deficiency	247
15.5.3	CRTR Deficiency	247
	References	247

Section IV Disorders of Amino Acid Metabolism and Transport

16	Hyperphenylalaninaemia	251
	<i>Peter Burgard, Robin H. Lachmann, John Walter</i>	
16.1	Phenylalanine Hydroxylase Deficiency	253
16.1.1	Clinical Presentation	253
16.1.2	Metabolic Derangement	253
16.1.3	Genetics	253
16.1.4	Diagnostic Tests	253
16.1.5	Treatment and Prognosis	254
16.2	Maternal PKU	258
16.2.1	Clinical Presentation	258
16.2.2	Metabolic Derangement	258
16.2.3	Treatment and Prognosis	258
16.3	HPA and Disorders of Biopterin Metabolism	259
16.3.1	Clinical Presentation	259
16.3.2	Metabolic Derangement	259
16.3.3	Genetics	259
16.3.4	Diagnostic and Confirmatory Tests	259
16.3.5	Treatment and Prognosis	260
	References	261

17	Disorders of Tyrosine Metabolism	265
	<i>Anupam Chakrapani, Paul Gissen, Patrick McKiernan</i>	
17.1	Hereditary Tyrosinaemia Type I (Hepatorenal Tyrosinaemia)	267
17.1.1	Clinical Presentation	267
17.1.2	Metabolic Derangement	267
17.1.3	Genetics	268
17.1.4	Diagnostic Tests	268
17.1.5	Treatment and Prognosis	269
17.2	Hereditary Tyrosinaemia Type II (Oculocutaneous Tyrosinaemia, Richner-Hanhart Syndrome)	270
17.2.1	Clinical Presentation	270
17.2.2	Metabolic Derangement	270
17.2.3	Genetics	271
17.2.4	Diagnostic Tests	271
17.2.5	Treatment and Prognosis	271
17.3	Hereditary Tyrosinaemia Type III	271
17.3.1	Clinical Presentation	271
17.3.2	Metabolic Derangement	271
17.3.3	Genetics	271
17.3.4	Diagnostic Tests	272
17.3.5	Treatment and Prognosis	272
17.4	Transient Tyrosinaemia	272
17.5	Alkaptonuria	272
17.5.1	Clinical Presentation	272
17.5.2	Metabolic Derangement	272
17.5.3	Genetics	273
17.5.4	Diagnostic Tests	273
17.5.5	Treatment and Prognosis	273
17.6	Hawkinsinuria	273
17.6.1	Clinical Presentation	273
17.6.2	Metabolic Derangement	273
17.6.3	Genetics	273
17.6.4	Diagnostic Tests	273
17.6.5	Treatment and Prognosis	274
	References	274
18	Branched-chain Organic Acidurias/Acidaemias	277
	<i>Manuel Schiff, Hélène Ogier de Baulny, Carlo Dionisi-Vici</i>	
18.1	Maple Syrup Urine Disease, Isovaleric Aciduria, Propionic Aciduria, Methylmalonic Aciduria	279
18.1.1	Clinical Presentation	279
18.1.2	Metabolic Derangement	281
18.1.3	Genetics	282
18.1.4	Diagnostic Tests	283
18.1.5	Treatment and Prognosis	283
18.2	3-Methylcrotonyl Glycinuria	288
18.2.1	Clinical Presentation	288
18.2.2	Metabolic Derangement	288
18.2.3	Genetics	288
18.2.4	Diagnostic Tests	289
18.2.5	Treatment and Prognosis	289
18.3	3-Methylglutaconic Aciduria	289
18.4	Short/Branched Chain Acyl-CoA Dehydrogenase Deficiency	290
18.5	2-Methyl-3-Hydroxybutyryl-CoA Dehydrogenase Deficiency	290
18.6	Isobutyryl-CoA Dehydrogenase Deficiency	290
18.7	3-Hydroxyisobutyric Aciduria	290
18.8	Malonyl-CoA Decarboxylase Deficiency	291
18.9	ACSF3 Deficiency	291
18.10	Enoyl-CoA Hydratase or ECHS1 Deficiency	291
	References	291

19	Disorders of the Urea Cycle and Related Enzymes	295
	<i>Johannes Häberle, Vicente Rubio</i>	
19.1	Mitochondrial Urea Cycle Disorders	297
19.1.1	Clinical Presentation	297
19.1.2	Metabolic Derangements	298
19.1.3	Genetics	298
19.1.4	Diagnostic Tests	298
19.1.5	Treatment and Prognosis	300
19.2	Cytosolic Urea Cycle Disorders	301
19.2.1	Clinical Presentation	301
19.2.2	Metabolic Derangements	302
19.2.3	Genetics	302
19.2.4	Diagnostic Tests	302
19.2.5	Treatment and Prognosis	303
19.3	Urea Cycle Mitochondrial Transporter Defects	303
19.3.1	Hyperornithinemia, Hyperammonaemia and Homocitrullinuria (HHH) Syndrome	303
19.3.2	Citrin Deficiency	303
19.4	Urea Cycle Defects due to Deficiencies of Ancillary Enzymes	305
19.4.1	Δ^1 -Pyrroline-5-Carboxylate Synthetase (P5CS) Deficiency	305
19.4.2	Carbonic Anhydrase Va (CAVA) Deficiency	305
	References	306
20	Disorders of Sulfur Amino Acid Metabolism	309
	<i>Viktor Kožich, Andrew A. M. Morris, Henk J Blom</i>	
20.1	Methionine S-Adenosyltransferase Deficiency (Mudd's Disease)	311
20.1.1	Clinical Presentation	311
20.1.2	Metabolic Derangement	311
20.1.3	Genetics	311
20.1.4	Diagnostic Tests	311
20.1.5	Treatment and Prognosis	313
20.2	Glycine N-Methyltransferase Deficiency	313
20.2.1	Clinical Presentation	313
20.2.2	Metabolic Derangement	313
20.2.3	Genetics	313
20.2.4	Diagnostic Tests	313
20.2.5	Treatment and Prognosis	313
20.3	S-Adenosylhomocysteine Hydrolase Deficiency	313
20.3.1	Clinical Presentation	313
20.3.2	Metabolic Derangement	313
20.3.3	Genetics	313
20.3.4	Diagnostic Tests	313
20.3.5	Treatment and Prognosis	314
20.4	Adenosine Kinase Deficiency	314
20.5	Cystathionine β-Synthase Deficiency	314
20.5.1	Clinical Presentation	314
20.5.2	Metabolic Derangement	314
20.5.3	Genetics	314
20.5.4	Diagnostic Tests	315
20.5.5	Treatment and Prognosis	316
20.6	Cystathionine γ-Lyase Deficiency	317
20.6.1	Clinical Presentation	317
20.6.2	Metabolic Derangement	317
20.6.3	Genetics	317
20.6.4	Diagnostic Tests	317
20.6.5	Treatment and Prognosis	317
20.7	Molybdenum Cofactor Deficiency	317
20.7.1	Clinical Presentation	317

20.7.2	Metabolic Derangement	317
20.7.3	Genetics	317
20.7.4	Diagnostic Tests	317
20.7.5	Treatment and Prognosis	317
20.8	Isolated Sulfite Oxidase Deficiency	318
20.8.1	Clinical Presentation	318
20.8.2	Metabolic Derangement	318
20.8.3	Genetics	318
20.8.4	Diagnostic Tests	318
20.8.5	Treatment and Prognosis	318
20.9	Ethylmalonic Encephalopathy	318
20.9.1	Clinical Presentation	318
20.9.2	Metabolic Derangement	318
20.9.3	Genetics	318
20.9.4	Diagnostic Tests	318
20.9.5	Treatment and Prognosis	318
	References	319
21	Disorders of Ornithine and Proline Metabolism	321
	<i>Matthias R. Baumgartner, David Valle, Carlo Dionisi-Vici</i>	
21.1	Hyperornithinaemia Due to Ornithine Aminotransferase Deficiency (Gyrate Atrophy of the Choroid and Retina)	323
21.2	Hyperornithinaemia, Hyperammonaemia and Homocitrullinuria (HHH) Syndrome	325
21.3	Δ^1-Pyrroline-5-Carboxylate Synthetase Deficiency	327
21.4	Δ^1-Pyrroline-5-Carboxylate Reductase Deficiency 1 (PYCR1) and 2 (PYCR2)	328
21.5	Proline Oxidase Deficiency (Hyperprolinaemia Type I)	328
21.6	Δ^1-Pyrroline-5-Carboxylate Dehydrogenase Deficiency (Hyperprolinaemia Type II)	329
21.7	Prolidase Deficiency	329
21.8	Spermine Synthase Deficiency (Snyder Robinson Syndrome)	330
	References	330
22	Cerebral Organic Acid Disorders and Other Disorders of Lysine Catabolism	333
	<i>Georg F. Hoffmann, Stefan Kölker</i>	
22.1	Introduction	335
22.2	Hyperlysinaemia/Saccharopinuria	337
22.2.1	Clinical Presentation	337
22.2.2	Metabolic Derangement	337
22.2.3	Genetics	338
22.2.4	Diagnostic Tests	338
22.2.5	Treatment and Prognosis	338
22.3	Hydroxylysinuria	338
22.4	2-Amino-/2-Oxoadipic Aciduria	338
22.4.1	Clinical Presentation	338
22.4.2	Metabolic Derangement	338
22.4.3	Genetics	339
22.4.4	Diagnostic Tests	339
22.4.5	Treatment and Prognosis	339
22.5	Glutaric Aciduria Type I	339
22.5.1	Clinical Presentation	339
22.5.2	Metabolic Derangement	340
22.5.3	Genetics	340
22.5.4	Diagnostic Tests	340
22.5.5	Treatment and Prognosis	341
22.6	Glutaric Aciduria Type III	342
22.6.1	Clinical Presentation	342
22.6.2	Metabolic Derangement	342
22.6.3	Genetics	342

22.6.4	Diagnostic Tests	342
22.6.5	Treatment and Prognosis	342
22.7	L-2-Hydroxyglutaric Aciduria	342
22.7.1	Clinical Presentation	342
22.7.2	Metabolic Derangement	343
22.7.3	Genetics	343
22.7.4	Diagnostic Tests	343
22.7.5	Treatment and Prognosis	343
22.8	D-2-Hydroxyglutaric Aciduria	343
22.8.1	Clinical Presentation	343
22.8.2	Metabolic Derangement	343
22.8.3	Genetics	344
22.8.4	Diagnostic Tests	344
22.8.5	Treatment and Prognosis	344
22.9	D-2-/L-2-Hydroxyglutaric Aciduria	344
22.9.1	Clinical Presentation	344
22.9.2	Metabolic Derangement	344
22.9.3	Genetics	344
22.9.4	Diagnostic Tests	344
22.9.5	Treatment and Prognosis	344
22.10	N-Acetylaspartic Aciduria (Canavan Disease)	344
22.10.1	Clinical Presentation	344
22.10.2	Metabolic Derangement	345
22.10.3	Genetics	345
22.10.4	Diagnostic Tests	345
22.10.5	Treatment and Prognosis	345
22.11	Aminoacylase 1 Deficiency	345
22.11.1	Diagnostic Tests	346
22.11.2	Treatment and Prognosis	346
22.12	Hypoacetylaspartia and Aspartate-Glutamate Carrier 1 Deficiency	346
	References	346
23	Nonketotic Hyperglycinemia (Glycine Encephalopathy) and Lipoate Deficiency Disorders	349
	<i>Johan L.K. Van Hove, Julia B. Hennermann, Curtis R. Coughlin II</i>	
23.1	Introduction: Definitions	350
23.2	Clinical Presentation	351
23.2.1	Severe Classic NKH	351
23.2.2	Attenuated Classic NKH	351
23.2.3	Lipoate Disorders Including Variant NKH	352
23.3	Metabolic Derangement	352
23.4	Genetics	353
23.5	Diagnostic Tests	353
23.6	Treatment	354
23.7	Prognosis	355
	References	355
24	Disorders of Glutamine, Serine and Asparagine Metabolism	357
	<i>Jaak Jaeken, Johannes Häberle, Olivier Dulac</i>	
24.1	Glutamine Synthetase Deficiency	359
24.2	Inborn Errors of Serine Metabolism	359
24.2.1	3-Phosphoglycerate Dehydrogenase Deficiency	359
24.2.2	Phosphoserine Aminotransferase Deficiency	360
24.2.3	3-Phosphoserine Phosphatase Deficiency	360
24.2.4	Brain Serine Transporter Deficiency	360
24.2.5	Serine Palmitoyltransferase Defects	361
24.3	Asparagine Synthetase Deficiency	361
	References	361

25	Disorders of Amino Acid Transport at the Cell Membrane	363
	<i>Kirsti Nääntö-Salonen, Manuel Schiff, Harri Niimikoski</i>	
25.1	Cystinuria	365
25.1.1	Clinical Presentation	365
25.1.2	Metabolic Derangement	365
25.1.3	Genetics	365
25.1.4	Diagnostic Tests	365
25.1.5	Treatment and Prognosis	366
25.2	Lysinuric Protein Intolerance	367
25.2.1	Clinical Presentation	367
25.2.2	Metabolic Derangement	367
25.2.3	Genetics	368
25.2.4	Diagnostic Tests	368
25.2.5	Treatment and Prognosis	368
25.3	Hartnup Disease	369
25.3.1	Clinical Presentation	369
25.3.2	Metabolic Derangement	369
25.3.3	Genetics	369
25.3.4	Diagnostic Tests	369
25.3.5	Treatment and Prognosis	370
25.4	Asymptomatic Aminoacidurias: Iminoglycinuria and Dicarboxylic Aminoaciduria	370
	References	370

Section V Vitamin-Responsive Disorders

26	Biotin-responsive Disorders	375
	<i>Matthias R. Baumgartner, Terttu Suormala</i>	
26.1	Clinical Presentation	377
26.1.1	Holocarboxylase Synthetase Deficiency	378
26.1.2	Biotinidase Deficiency	378
26.2	Metabolic Derangement	378
26.3	Genetics	379
26.3.1	Holocarboxylase Synthetase Deficiency	379
26.3.2	Biotinidase Deficiency	379
26.4	Diagnostic Tests	379
26.4.1	Holocarboxylase Synthetase Deficiency	380
26.4.2	Biotinidase Deficiency	380
26.4.3	Acquired Biotin Deficiency	380
26.4.4	Prenatal Diagnosis	380
26.5	Treatment and Prognosis	380
26.5.1	Holocarboxylase Synthetase Deficiency	381
26.5.2	Biotinidase Deficiency	381
	References	382
27	Disorders of Cobalamin and Folate Transport and Metabolism	385
	<i>David Watkins, David S. Rosenblatt, Brian Fowler</i>	
27.1	Disorders of Absorption and Transport of Cobalamin	387
27.1.1	Hereditary Intrinsic Factor Deficiency	387
27.1.2	Defective Transport of Cobalamin by Enterocytes (Imerslund-Gräsbeck Syndrome)	387
27.1.3	Haptocorrin (R Binder) Deficiency	388
27.1.4	Transcobalamin Deficiency	388
27.1.5	Transcobalamin Receptor Deficiency	389
27.2	Disorders of Intracellular Utilisation of Cobalamin	389
27.2.1	Combined Deficiencies of Adenosylcobalamin and Methylcobalamin	389
27.2.2	Adenosylcobalamin Deficiency	392
27.2.3	Methylcobalamin Deficiency	392

27.3	Disorders of Absorption and Metabolism of Folate	394
27.3.1	Hereditary Folate Malabsorption	394
27.3.2	Cerebral Folate Deficiency	394
27.3.3	Methylenetetrahydrofolate Dehydrogenase (MTHFD1) Deficiency	395
27.3.4	Dihydrofolate Reductase Deficiency	395
27.3.5	Glutamate Formiminotransferase Deficiency	396
27.3.6	Methylenetetrahydrofolate Reductase Deficiency	396
	References	397
28	Disorders of Thiamine and Pyridoxine Metabolism	401
	<i>Garry Brown, Barbara Plecko</i>	
28.1	Disorders of Thiamine (Vitamin B₁) Metabolism	402
28.1.1	Thiamine Transporter 1 (THTR1) Deficiency	403
28.1.2	Thiamine Transporter 2 (THTR2) Deficiency	404
28.1.3	Thiamine Pyrophosphokinase Deficiency	404
28.1.4	Mitochondrial TPP Transporter Deficiency	405
28.1.5	Thiamine-Responsive α -Ketoacid Dehydrogenase Deficiencies	405
28.1.6	Thiamine-Responsive Pyruvate Dehydrogenase Deficiency	405
28.1.7	Thiamine-Responsive Maple Syrup Urine Disease	406
28.2	Vitamin B₆ Metabolism	407
28.2.1	Antiquitin Deficiency	408
28.2.2	Hyperprolinemia Type II	409
28.2.3	Pyridox(am)ine 5'-phosphate Oxidase (PNPO) Deficiency	410
28.2.4	Congenital Hypophosphatasia	410
28.2.5	Hyperphosphatasia-Mental Retardation Syndrome (HPMRS)	410
28.2.6	Other B ₆ Responsive Disorders	410
	References	411

Section VI Neurotransmitter and Small Peptide Disorders

29	Disorders of Neurotransmission	415
	<i>Ángels García-Cazorla, Rafael Artuch, K. Michael Gibson</i>	
29.1	Inborn Errors of Gamma Amino Butyric Acid Metabolism	417
29.1.1	Gamma Amino Butyric Acid Transaminase Deficiency	417
29.1.2	Succinic Semialdehyde Dehydrogenase Deficiency	418
29.1.3	Homocarnosinosis	418
29.2	Inborn Errors of Receptors and Transporters of Neurotransmitters	419
29.2.1	Hyperekplexia	419
29.2.2	GABA Receptor Mutations	420
29.2.3	Glutamate Receptor Mutations	420
29.2.4	Mitochondrial Glutamate Transporter Defect	420
29.2.5	Dopamine Transporter Defect	421
29.2.6	Brain Dopamine-Serotonin Vesicular Transport Defect	421
29.3	Inborn Errors of Monoamine Metabolism	421
29.3.1	Tyrosine Hydroxylase Deficiency	421
29.3.2	Aromatic L-Aminoacid Decarboxylase Deficiency	422
29.3.3	Dopamine β -Hydroxylase Deficiency	423
29.3.4	Monoamine Oxidase-A Deficiency	423
29.3.5	Guanosine Triphosphate Cyclohydrolase-I Deficiency	424
29.3.6	Sepiapterine Reductase Deficiency	425
	References	425

30	Trimethylaminuria, Dimethylglycine Dehydrogenase Deficiency and Disorders in the Metabolism of Glutathione	429
	<i>Valerie Walker, Ron A Wevers, Ertan Mayatepek</i>	
30.1	Trimethylaminuria (Fish Malodour Syndrome)	431
30.1.1	Clinical Presentation	431
30.1.2	Metabolic Derangement	431
30.1.3	Genetics	431
30.1.4	Diagnostic Tests	432
30.1.5	Treatment	432
30.2	Dimethylglycine Dehydrogenase Deficiency	432
30.2.1	Clinical Presentation	432
30.2.2	Metabolic Derangement	432
30.2.3	Genetics	432
30.2.4	Diagnostic Tests	432
30.2.5	Treatment	433
30.3	Disorders in the Metabolism of Glutathione	433
30.3.1	γ -Glutamylcysteine Synthetase Deficiency	433
30.3.2	Glutathione Synthetase Deficiency	434
30.3.3	γ -Glutamyl Transpeptidase Deficiency	435
30.3.4	5-Oxoprolinase Deficiency	436
30.3.5	Dipeptidase Deficiency	436
30.3.6	Secondary 5-Oxoprolinuria	436
	References	436

Section VII Disorders of Lipid and Bile Acid Metabolism

31	Inborn Errors of Lipoprotein Metabolism Presenting in Childhood	441
	<i>Uma Ramaswami, Steve E Humphries</i>	
31.1	Disorders of Low Density Lipoprotein Metabolism	443
31.2	Disorders of Triglyceride (TG) Metabolism	445
31.3	Disorders of High Density Lipoprotein Metabolism	453
31.4	Disorders of Sterol Storage	453
31.5	Conclusion	453
	References	453
32	Disorders of Isoprenoid/Cholesterol Synthesis	455
	<i>Hans R. Waterham, Peter T. Clayton</i>	
32.1	Mevalonate Kinase Deficiency	457
32.2	Smith-Lemli-Opitz Syndrome (7-Dehydrocholesterol Reductase Deficiency)	458
32.3	Sterol $\Delta 8$ - $\Delta 7$ Isomerase Deficiency	459
32.3.1	X-Linked Dominant Chondrodysplasia Punctata 2 or Conradi-Hünemann Syndrome in Females	459
32.3.2	Hemizygous EBP Deficiency in Males	460
32.4	Deficiency of the C4-Demethylase Complex	460
32.4.1	C4-Methyl Sterol Oxidase Deficiency (SMO Deficiency)	460
32.4.2	Sterol 4 α -Carboxylate 3-Dehydrogenase Deficiency	460
32.5	Desmosterol Reductase Deficiency (Desmosterolosis)	461
32.6	Sterol $\Delta 5$ -Desaturase Deficiency (Lathosterolosis)	461
32.7	Sterol $\Delta 14$ -Reductase Deficiency (Hydrops – Ectopic Calcification – Moth-eaten (HEM) Skeletal Dysplasia or Greenberg Skeletal Dysplasia)	462
	References	463
33	Disorders of Bile Acid Synthesis	465
	<i>Peter T. Clayton</i>	
33.1	3 β -Hydroxy- $\Delta 5$ -C27-Steroid Dehydrogenase Deficiency	467
33.2	$\Delta 4$ -3-Oxosteroid 5 β -Reductase Deficiency	468
33.3	Cerebrotendinous Xanthomatosis (Sterol 27-Hydroxylase Deficiency)	469
33.4	α -Methylacyl-CoA Racemase Deficiency	471

33.5	Oxysterol 7α-Hydroxylase Deficiency	471
33.6	Bile Acid Amidation Defect 1: Bile Acid CoA: Amino Acid N-Acyl Transferase Deficiency	472
33.7	Bile Acid Amidation Defect 2: Bile Acid CoA Ligase Deficiency	472
33.8	Cholesterol 7α-Hydroxylase Deficiency	473
33.9	Disorders of Peroxisome Biogenesis, Peroxisomal Import and Peroxisomal β-Oxidation	473
	References	473
34	Disorders of Intracellular Triglyceride and Phospholipid Metabolism	477
	<i>Foudil Lamari, Jean-Marie Saudubray, Grant A. Mitchell</i>	
34.1	Inborn Errors of the Common Pathway of Acylglycerol and Phospholipid Synthesis	479
34.1.1	Glycerol-3-phosphate Dehydrogenase 1 (GPD1) Deficiency: Autosomal Recessive Hepatic Steatosis and Hypertriglyceridemia	479
34.1.2	Glycerol Kinase Deficiency is described in Chapter 7.	479
34.1.3	1-Acylglycerol-3-Phosphate O-Acyltransferase 2 (AGPAT2) Deficiency: Autosomal Recessive Generalized Congenital Lipodystrophy	479
34.1.4	Phosphatidic Acid Phosphatase (PAP; LIPIN) Deficiencies.	479
34.1.5	Diacylglycerol Kinase Epsilon (DGKE) Deficiency: Atypical Haemolytic Uremic Syndrome.	480
34.2	Inborn Errors of Cytoplasmic Triglyceride Metabolism	480
34.2.1	Diacylglycerol O-Acyl Transferase 1 (DGAT1) Deficiency: Congenital Diarrhea	480
34.2.2	Perilipin 1 Deficiency: Autosomal Dominant Partial Lipodystrophy.	481
34.2.3	Neutral Lipid Storage Diseases (NLSDs): ATGL and CGI-58 Deficiencies	481
34.2.4	Hormone-Sensitive Lipase (HSL) Deficiency; Insulin Resistance, Diabetes	481
34.3	Inborn Errors of Phospholipid Biosynthesis	483
34.4	Choline Kinase β (CHKβ) Deficiency: Congenital Muscular Dystrophy, Megaconial Type	483
34.4.1	Choline-PhosphateCytidylyltransferase α (CCT α) Deficiency: Spondylometaphyseal Dysplasia with Cone-Rod Dystrophy or Congenital Lipodystrophy	483
34.4.2	PhosphatidylserineSynthase 1 (PSS1) Gain of Function (Lenz-Majewski Hyperostotic Dwarfism)	483
34.4.3	Acylglycerol Kinase (AGK) Deficiency: Myopathy, Hypertrophic Cardiomyopathy and Congenital Cataract (Sengers Syndrome)	484
34.4.4	Cardiolipin Remodeling Enzyme Deficiency: X-linked Cardiomyopathy and Neutropenia (Barth Syndrome)	484
34.4.5	<i>SERAC1</i> Mutation: Methylglutaconic Aciduria, Deafness, Hepatic Involvement, Encephalopathy, and Leigh Syndrome (MEGDHEL Syndrome)	485
34.4.6	Mitochondrial Calcium Independent Phospholipase A2 γ (iPLA2 γ): Autosomal Recessive Myopathy, Dystonia and Convulsions (not shown)	485
34.5	Inborn Errors related to Phospholipid Remodeling	485
34.5.1	α/β Hydrolase Domain-Containing Protein 12 (ABHD12) Deficiency: Polyneuropathy, Hearing loss, Ataxia, Retinitis Pigmentosa and Cataract (PHARC syndrome)	485
34.5.2	Phospholipase A2 Deficiency (PLA2G6): Autosomal Recessive Infantile Neuroaxonal Dystrophy, Neurodegeneration with Brain Iron Accumulation	486
34.5.3	Deficiencies of Neuropathy Target Esterase (NTE or PNPLA-6) or Mitochondrial Calcium-independent Phospholipase A2 γ (PNPLA6): Peripheral Neuropathy, Spastic Paraplegia, Chorioretinal Degeneration, Hypogonadotrophic Hypogonadism, Trichomegaly (SPG39, Boucher-Neuhauser, Gordon-Holms, Oliver-McFarlane, Laurence-Moon syndromes) or Mitochondrial Myopathy with Dystonia	486
34.5.4	<i>DDHD1</i> and <i>DDHD2</i> Mutations: Hereditary Spastic Paraplegias 28 and 45	487
34.5.5	<i>CYP2U1</i> Mutation: Spastic Paraplegia with Basal Ganglia Calcification (Hereditary Spastic Paraplegia 56, SPG56)	487
34.5.6	Inborn Errors of Polyphosphoinositide Metabolism	488
	References	488

Section VIII Disorders of Nucleic Acid and Heme Metabolism

35	Disorders of Purine and Pyrimidine Metabolism	495
	<i>Sandrine Marie, Georges van den Bergh and Marie-Françoise Vincent</i>	
35.1	Inborn Errors of Purine Metabolism	497
35.1.1	Phosphoribosyl Pyrophosphate Synthetase Superactivity	497
35.1.2	Phosphoribosyl Pyrophosphate Synthetase Deficiency	497

35.1.3	Adenylosuccinase Deficiency	498
35.1.4	AIICA-Ribosiduria	498
35.1.5	Muscle Adenosine Monophosphate Deaminase 1 Deficiency	498
35.1.6	Adenosine Monophosphate Deaminase 2 and 3 Deficiencies	499
35.1.7	Adenosine Deaminase 1 Deficiency	499
35.1.8	Adenosine Deaminase 2 Deficiency	501
35.1.9	Adenosine Deaminase Superactivity	501
35.1.10	Purine Nucleoside Phosphorylase Deficiency	501
35.1.11	Xanthine Oxidase Deficiency	501
35.1.12	Hypoxanthine-Guanine Phosphoribosyltransferase Deficiency	502
35.1.13	Adenine Phosphoribosyltransferase Deficiency	503
35.1.14	Adenylate Kinase 1 Deficiency	504
35.1.15	Adenylate Kinase 2 Deficiency	504
35.1.16	Adenosine Kinase Deficiency	504
35.1.17	Adenylate Cyclase 5 Mutations	504
35.1.18	IMP Dehydrogenase Mutations	504
35.1.19	Deoxyguanosine Kinase Deficiency	504
35.1.20	Thiopurine Methyltransferase Deficiency	505
35.1.21	Inosine Triphosphatase Deficiency	505
35.2	Inborn Errors of Pyrimidine Metabolism	505
35.2.1	CAD (Carbamoylphosphate Synthetase II, Aspartate Transcarbamylase, Dihydroorotase) Deficiency	505
35.2.2	UMP Synthase Deficiency (Hereditary Orotic Aciduria	505
35.2.3	Miller syndrome (Dihydroorotate Dehydrogenase Deficiency	507
35.2.4	Dihydropyrimidine Dehydrogenase Deficiency	507
35.2.5	Dihydropyrimidinase Deficiency	508
35.2.6	Ureidopropionase Deficiency	508
35.2.7	Pyrimidine 5'-Nucleotidase Deficiency	508
35.2.8	Cytosolic 5'-Nucleotidase Superactivity	508
35.2.9	Thymidine Phosphorylase Deficiency	508
35.2.10	Cytidine Deaminase Deficiency	509
35.2.11	Thymidine Kinase 2 Deficiency	509
	References	509
36	Disorders of Haem Biosynthesis	515
	<i>Charles Marques Lourenço, Karl E. Anderson</i>	
36.1	X-Linked Sideroblastic Anaemia	517
36.2	The Porphyrrias	517
36.2.1	Classification and Diagnosis	517
36.3	5-Aminolevulinic Acid Dehydratase Porphyrria	519
36.4	Acute Intermittent Porphyrria (AIP)	519
36.5	Congenital Erythropoietic Porphyrria (CEP) (Gunther Disease)	521
36.6	Porphyria Cutanea Tarda (PCT)	522
36.7	Hepatoerythropoietic Porphyrria	523
36.8	Hereditary Coproporphyrria and Variegate Porphyrria	523
36.9	Erythropoietic Protoporphyrria and X-Linked Protoporphyrria	524
	References	525

Section IX Disorders of Metal Transport and Metabolism

37	Disorders in the Transport of Copper, Iron, Magnesium, Manganese, Selenium and Zinc	531
	<i>Peter M. van Hasselt, Peter Clayton, Roderick H.J. Houwen</i>	
37.1	Copper	532
37.1.1	Wilson Disease	533
37.1.2	Menkes Disease	535
37.1.3	Other Copper Storage Disorders	536
37.1.4	Other Disturbances of Copper Metabolism with a Low Serum Copper	536

37.2	Iron	537
37.2.1	Systemic Iron Overload Syndromes (Haemochromatosis)	538
37.2.2	Iron Deficiency and Distribution Disorders	539
37.2.3	Neurodegeneration with Brain Iron Accumulation (NBIA)	540
37.3	Magnesium	541
37.3.1	Primary Hypomagnesaemia with Secondary Hypocalcaemia	541
37.3.2	Hypomagnesaemia with Hypercalciuria and Nephrocalcinosis	542
37.3.3	Isolated Dominant Hypomagnesemia	542
37.3.4	Isolated Autosomal Recessive Hypomagnesaemia	543
37.4	Manganese	543
37.4.1	Inherited Manganism Due to Mutations in <i>SLC30A10</i>	543
37.4.2	Manganese Transporter Defect	544
37.5	Selenium	544
37.6	Zinc	544
37.6.1	Acrodermatitis Enteropathica	545
37.6.2	Zinc Deficiency in Breastfed Babies	546
37.6.3	Hyperzincaemia with Hypercalprotectinaemia	546
37.6.4	Autosomal Dominant Hyperzincaemia without Symptoms	546
	References	546

Section X Organelle-Related Disorders: Lysosomes, Peroxisomes, and Golgi and Pre-Golgi Systems

38	Disorders of Sphingolipid Synthesis, Sphingolipidoses, Niemann-Pick Disease Type C and Neuronal Ceroid Lipofuscinoses	551
	<i>Marie T. Vanier, Catherine Caillaud, Thierry Levade</i>	
38.1	Disorders of Sphingolipid Synthesis	553
38.1.1	Serine Palmitoyltransferase (Subunit 1 or 2) Deficiency and HSN1	553
38.1.2	Defects in Ceramide Synthases 1 and 2 and Myoclonic Epilepsy	554
38.1.3	Fatty Acid 2-Hydroxylase Deficiency (SPG35/FAHN)	555
38.1.4	GM3 Synthase Deficiency and Amish Epilepsy Syndrome	555
38.1.5	GM2/GD2 Synthase Deficiency (SPG26)	555
38.1.6	Nonlysosomal β -Glucosidase GBA2 Deficiency: SPG46 and Ataxia	555
38.1.7	Ceramide Synthase 3 and Ultra-Long Chain Fatty Acid ω -Hydroxylase (CYP4F22) Deficiencies: Autosomal Recessive Congenital Ichthyosis (ARCI)	555
38.1.8	Mutations in Ceramide Kinase-Like (CERKL) Gene and Retinal Dystrophy	556
38.1.9	Alkaline Ceramidase 3 (ACER3) Deficiency: Infantile Leukodystrophy	556
38.2	Sphingolipidoses	556
38.2.1	Gaucher Disease	556
38.2.2	Acid Sphingomyelinase-Deficient Niemann-Pick Disease (Type A, Type B and Intermediate Forms)	559
38.2.3	GM1 Gangliosidosis	560
38.2.4	GM2 Gangliosidoses	561
38.2.5	Krabbe Disease	562
38.2.6	Metachromatic Leukodystrophy	563
38.2.7	Fabry Disease	565
38.2.8	Farber Disease / Acid Ceramidase Deficiency	566
38.2.9	Prosaposin Deficiency	566
38.3	Niemann-Pick Disease Type C	566
38.3.1	Clinical Presentation	566
38.3.2	Metabolic Derangement	567
38.3.3	Genetics	568
38.3.4	Diagnostic Tests	568
38.3.5	Treatment and Prognosis	568
38.4	Neuronal Ceroid Lipofuscinoses	568
38.4.1	Clinical Presentation	568
38.4.2	Metabolic Derangement	570
38.4.3	Genetics	571

38.4.4	Diagnostic Tests	571
38.4.5	Treatment and Prognosis	571
	References	571
39	Mucopolysaccharidoses, Oligosaccharidoses and Sialic Acid Disorders	577
	<i>Simon Jones, Frits Wijburg</i>	
39.1	Mucopolysaccharidoses	579
39.1.1	Clinical Presentation	579
39.1.2	Metabolic Derangement	583
39.1.3	Genetics	583
39.1.4	Diagnostic Tests	583
39.1.5	Treatment and Prognosis	583
39.2	Oligosaccharidoses and Mucopolidoses	585
39.2.1	Clinical Presentation	585
39.2.2	Metabolic Derangements	587
39.2.3	Genetics	587
39.2.4	Diagnostic Tests	588
39.2.5	Treatment and Prognosis	588
	References	588
40	Inborn Errors of Non-Mitochondrial Fatty Acid Metabolism Including Peroxisomal Disorders	591
	<i>Ronald J.A. Wanders, Patrick Aubourg, Bwee Tien Poll-The</i>	
40.1	Disorders of Etherphospholipid Biosynthesis	594
40.1.1	Peroxin 7 (PEX7) Deficiency (RCDP Type 1)	594
40.1.2	Glycerone 3-Phosphate Acyltransferase (GNPAT) Deficiency (RCDP type 2)	594
40.1.3	Alkylglycerone 3-Phosphate Synthase (AGPS) Deficiency (RCDP Type 3)	594
40.1.4	PEX5L-Deficiency (RCDP Type 4)	594
40.1.5	Fatty Acyl-CoA Reductase 1 (FAR1) Deficiency	595
40.2	Disorders of Peroxisomal β-Oxidation	595
40.2.1	X-Linked Adrenoleukodystrophy	595
40.2.2	D-Bifunctional Protein (DBP) Deficiency	596
40.2.3	Acyl-CoA Oxidase (ACOX) Deficiency	597
40.2.4	Methyl Acyl-CoA Racemase (AMACR) Deficiency	597
40.2.5	Sterol Carrier Protein-2 (SCPx) Deficiency	598
40.2.6	PMP70 Deficiency	598
40.2.7	Contiguous <i>ABCD1</i> , <i>DXS1357A</i> -Deletion Syndrome (CADD5)	598
40.2.8	Zellweger Spectrum Disorders (ZSD)	598
40.3	Disorders of Peroxisomal Fatty Acid Alpha-Oxidation	599
40.3.1	Adult Refsum Disease (ARD)	599
40.4	The Fatty Acid Chain Elongation Disorders	600
40.4.1	ELOVL4 Deficiency	600
40.4.2	ELOVL5 Deficiency	601
40.4.3	Trans-2,3-Enoyl-CoA Reductase (TER) Deficiency	601
40.4.4	3-Hydroxyacyl-CoA Dehydratase1 (HACD1) Deficiency	601
40.5	Disorders of Eicosanoid Metabolism	601
40.5.1	Primary Hypertrophic Osteoarthropathy Type 1 (PHOAR1): 15-Hydroxy Prostaglandin Dehydrogenase (PGDH) Deficiency and Type 2 (PHOAR2): Prostaglandin Transporter (PGT) Deficiency	601
40.5.2	LTC4-Synthase Deficiency	603
40.6	Remaining Disorders of Fatty Acid Homeostasis	603
40.6.1	Sjögren Larsson Syndrome (SLS)	603
40.6.2	Bile Acid-CoA: Amino Acid N-Acyltransferase (BAAT) Deficiency	604
40.7	Other Peroxisomal Disorders not Involving Fatty Acid Metabolism	604
40.7.1	Oxalurias and Oxalosis: Glyoxylate Detoxification Disorders	604
40.7.2	Pipelic Acidemia	604
40.7.3	Acatalasemia	604
	References	605

41	Congenital Disorders of Glycosylation, Dolichol and Glycosylphosphatidylinositol Metabolism	607
	<i>Jaak Jaeken, Eva Morava</i>	
41.1	Introduction	609
41.2	Congenital Disorders of Protein N-Glycosylation	611
41.2.1	Phosphomannomutase 2 Deficiency (PMM2-CDG)	611
41.2.2	Mannosephosphate Isomerase Deficiency (MPI-CDG)	612
41.2.3	Glucosyltransferase 1 Deficiency (ALG6-CDG)	612
41.2.4	Mannosyltransferase 1 Deficiency (ALG1-CDG)	613
41.2.5	UDP-GlcNAc:Dol-P-GlcNAc-P Transferase Deficiency (DPAGT1-CDG)	613
41.2.6	Golgi α -1-2 Mannosidase 1 Deficiency (MAN1B1-CDG)	614
41.3	Congenital Disorders of Protein O-Glycosylation	614
41.3.1	Progeroid Variant of Ehlers-Danlos Syndrome (B4GALT7-CDG)	614
41.3.2	GALNT3 Deficiency (GALNT3-CDG)	614
41.3.3	Hereditary Multiple Exostoses (EXT1/EXT2-CDG)	614
41.3.4	Cerebro-Ocular Dysplasia-Muscular Dystrophy Syndromes, Types A1, B1, C1/A2, B2, C2 (POMT1/POMT2-CDG)	616
41.3.5	Muscle-Eye-Brain Disease, Types A3, B3, C3 (POMGNT1-CDG)	616
41.3.6	O-Fucose-Specific β -1,3-Glucosyltransferase Deficiency (B3GALTL-CDG)	616
41.4	Defects in Lipid Glycosylation and in Glycosylphosphatidylinositol (GPI) Anchor Biosynthesis	616
41.4.1	GM3 Synthase Deficiency (ST3GAL5-CDG)	616
41.4.2	GM2 Synthase Deficiency (B4GALNT1-CDG)	616
41.4.3	PIGA Deficiency (PIGA-CDG)	616
41.5	Defects in Multiple Glycosylation Pathways and in Other Pathways Including Dolicholphosphate Biosynthesis Defects	616
41.5.1	Hereditary Inclusion Body Myopathy (GNE-CDG)	616
41.5.2	Congenital Myasthenic Syndrome-12 (GFPT1-CDG)	617
41.5.3	Steroid 5- α -Reductase Deficiency (SRD5A3-CDG)	617
41.5.4	COG6 Deficiency (COG6-CDG)	620
41.5.5	Autosomal Recessive Cutis Laxa Type 2 (ATP6V0A2-CDG)	620
41.5.6	Phosphoglucosmutase 1 Deficiency (PGM1-CDG)	620
41.5.7	Golgi Homeostasis Disorders: TMEM199 and CCDC115 Deficiencies	620
41.5.8	Manganese and Zinc Transporter Defect: SLC39A8 Deficiency	620
41.6	Congenital Disorders of Deglycosylation	621
41.6.1	N-glycanase 1 Deficiency	621
41.6.2	Lysosomal Storage Disorders	621
	References	621
42	Cystinosis	623
	<i>Patrick Niaudet</i>	
42.1	Infantile Cystinosis	624
42.1.1	Clinical Presentation	624
42.1.2	Metabolic Derangement	626
42.1.3	Genetics	626
42.1.4	Diagnostic Tests	626
42.1.5	Treatment	626
42.2	Late-Onset Cystinosis	627
42.3	Ocular Cystinosis	628
	References	628

Section XI Appendix

43	Medications Used in the Treatment of Inborn Errors	633
	<i>John Walter</i>	
	Subject Index	643