

151424

Fernandes
Saudubray
van den Berghe
Walter



Inborn Metabolic Diseases

4th Edition

Diagnosis
and Treatment

 Springer

Contents

I Diagnosis and Treatment: General Principles	
1 A Clinical Approach to Inherited Metabolic Diseases	3
<i>Jean-Marie Saudubray, Isabelle Desguerre, Frédéric Sedel, Christiane Charpentier</i>	
Introduction	5
1.1 Classification of Inborn Errors of Metabolism	5
1.1.1 Pathophysiology	5
1.1.2 Clinical Presentation	6
1.2 Acute Symptoms in the Neonatal Period and Early Infancy (<1 Year)	6
1.2.1 Clinical Presentations	6
1.2.2 Metabolic Derangements and Diagnostic Tests	10
1.3 Later Onset Acute and Recurrent Attacks (Late Infancy and Beyond)	11
1.3.1 Clinical Presentations	11
1.3.2 Metabolic Derangements and Diagnostic Tests	19
1.4 Chronic and Progressive General Symptoms/Signs	24
1.4.1 Gastrointestinal Symptoms	24
1.4.2 Muscle Symptoms	26
1.4.3 Neurological Symptoms	26
1.4.4 Specific Associated Neurological Abnormalities	33
1.5 Specific Organ Symptoms	39
1.5.1 Cardiology	39
1.5.2 Dermatology	39
1.5.3 Dysmorphology	41
1.5.4 Endocrinology	41
1.5.5 Gastroenterology	42
1.5.6 Hematology	42
1.5.7 Hepatology	43
1.5.8 Immune System	44
1.5.9 Myology	44
1.5.10 Nephrology	45
1.5.11 Neurology	45
1.5.12 Ophthalmology	45
1.5.13 Osteology	46
1.5.14 Pneumology	46
1.5.15 Psychiatry	47
1.5.16 Rheumatology	47
1.5.17 Stomatology	47
1.5.18 Vascular Symptoms	47
References	47
2 Newborn Screening for Inborn Errors of Metabolism	49
<i>Bridget Wilcken</i>	
2.1 Introduction	51
2.2 General Aspects of Newborn Screening	51
2.2.1 Aims and Criteria	51
2.2.2 Sensitivity, Specificity, and Positive Predictive Value	51
2.2.3 Technical Aspects of Newborn Screening Tests	51
2.2.4 Range of Possibilities from Early Detection	52
2.2.5 Tandem Mass Spectrometry	52
2.3 Screening for Individual Inborn Errors of Metabolism	53
2.3.1 Phenylketonuria	53
2.3.2 Galactosaemias	54
2.3.3 Aminoacidopathies	54
2.3.4 Organic Acid Disorders	55
2.3.5 Fatty Acid Oxidation Disorders	55
2.3.6 Other Neonatal Screening Programmes	57
References	57
3 Diagnostic Procedures: Function Tests and Postmortem Protocol	59
<i>Guy Touati, Jan Huber, Jean-Marie Saudubray</i>	
3.1 Introduction	61
3.2 Functional Tests	61
3.2.1 Metabolic Profile over the Course of the Day	61
3.2.2 Fasting Test	62
3.2.3 Glucose Loading Test	65
3.2.4 Galactose Loading Test	65
3.2.5 Fructose Loading Test	65
3.2.6 Protein and Allopurinol Loading Test	66
3.2.7 Fat Loading Test	66
3.2.8 Tetrahydrobiopterin Test	66
3.2.9 Exercise Test	67
3.3 Postmortem Protocol	68
3.3.1 Cells and Tissues for Enzyme Assays	68
3.3.2 Cells and Tissues for Chromosome and DNA Investigations	68
3.3.3 Skin Fibroblasts	68
3.3.4 Body Fluids for Chemical Investigations	68
3.3.5 Imaging	68
3.3.6 Autopsy	69
References	69
4 Emergency Treatments	71
<i>Viola Prietsch, Hélène Ogier de Baulny, Jean-Marie Saudubray</i>	
4.1 General Principles	73
4.1.1 Supportive Care	73

4.1.2	Nutrition	73
4.1.3	Specific Therapies	73
4.1.4	Extracorporeal Procedures for Toxin Removal	73
4.2	Emergency Management of Particular Clinical Presentations	74
4.2.1	Neurological Deterioration	74
4.2.2	Liver Failure	77
4.2.3	Neonatal Hypoglycemia	77
4.2.4	Cardiac Failure	78
4.2.5	Primary Hyperlactatemia	78
4.2.6	Intractable Convulsions	78
4.3	Final Considerations	78
	References	78
5	Treatment: Present Status and New Trends	81
	<i>John H. Walter, J. Ed Wraith</i>	
5.1	Introduction	83
5.2	Reducing the Load on the Affected Pathway	83
5.2.1	Substrate Reduction by Dietary Restriction	83
5.2.2	Substrate Reduction by Inhibition of Enzymes Within the Pathway	83
5.3	Correcting Product Deficiency	84
5.3.1	Replenishing Depleted Products	84
5.3.2	Increasing Substrate Supply	84
5.3.3	Providing Alternative Substrates	85
5.4	Decreasing Metabolite Toxicity	85
5.4.1	Removing Toxic Metabolites	85
5.4.2	Blocking the Effects of Toxic Metabolites	85
5.5	Stimulating Residual Enzyme	85
5.5.1	Co-Enzyme Treatment	85
5.5.2	Enzyme Enhancement Therapy	86
5.6	Transplantation	87
5.6.1	Hematopoietic Stem Cell Transfer	87
5.6.2	Other Organ Transplantation	87
5.7	Pharmacologic Enzyme Replacement	88
5.7.1	Gaucher Disease	88
5.7.2	Fabry Disease	88
5.7.3	Mucopolysaccharidosis Type I	88
5.7.4	Mucopolysaccharidosis Type VI	88
5.7.5	Pompe Disease	88
5.7.6	Other Disorders	88
5.8	Gene Therapy	89
5.8.1	Gene Transfer	89
5.8.2	Pharmacological Gene Therapy	89
5.9	Conclusions	89
	References	96

II Disorders of Carbohydrate Metabolism

6	The Glycogen Storage Diseases and Related Disorders	101
	<i>G. Peter A. Smit, Jan Peter Rake, Hasan O. Akman, Salvatore DiMauro</i>	
6.1	The Liver Glycogenoses	103
6.1.1	Glycogen Storage Disease Type I (Glucose-6-Phosphatase or Translocase Deficiency)	103
6.1.2	Glycogen Storage Disease Type III (Debranching Enzyme Deficiency)	108
6.1.3	Glycogen Storage Disease Type IV (Branching Enzyme Deficiency)	109
6.1.4	Glycogen Storage Disease Type VI (Glycogen Phosphorylase Deficiency)	111
6.1.5	Glycogen Storage Disease Type IX (Phosphorylase Kinase Deficiency)	111
6.1.6	Glycogen Storage Disease Type 0 (Glycogen Synthase Deficiency)	112
6.2	The Muscle Glycogenoses	112
6.2.1	Glycogen Storage Disease Type V (Myophosphorylase Deficiency)	113
6.2.2	Glycogen Storage Disease Type VII (Phosphofructokinase Deficiency)	113
6.2.3	Phosphoglycerate Kinase Deficiency	114
6.2.4	Glycogen Storage Disease Type X (Phosphoglycerate Mutase Deficiency)	114
6.2.5	Glycogen Storage Disease Type XII (Aldolase A Deficiency)	114
6.2.6	Glycogen Storage Disease Type XIII (β -Enolase Deficiency)	115
6.2.7	Glycogen Storage Disease Type XI (Lactate Dehydrogenase Deficiency)	115
6.2.8	Muscle Glycogen Storage Disease Type 0 (Glycogen Synthase Deficiency)	115
6.3	The Generalized Glycogenoses and Related Disorders	115
6.3.1	Glycogen Storage Disease Type II (Acid Maltase Deficiency)	115
6.3.2	Danon Disease	116
6.3.3	Lafora Disease	116
	References	116
7	Disorders of Galactose Metabolism	121
	<i>Gerard T. Berry, Stanton Segal, Richard Gitzelmann</i>	
7.1	Deficiency of Galactose-1-Phosphate Uridyltransferase	123
7.1.1	Clinical Presentation	123
7.1.2	Metabolic Derangement	123
7.1.3	Genetics	123
7.1.4	Diagnostic Tests	124
7.1.5	Treatment and Prognosis	124

7.2	Uridine Diphosphate-Galactose 4'-Epimerase Deficiency	126	9.3.4	Diagnosis	141
7.2.1	Clinical Presentation	126	9.3.5	Differential Diagnosis	141
7.2.2	Metabolic Derangement	126	9.3.6	Treatment and Prognosis	141
7.2.3	Genetics	126		References	142
7.2.4	Diagnostic Tests	127	10	Persistent Hyperinsulinemic Hypoglycemia	143
7.2.5	Treatment and Prognosis	127		<i>Pascale de Lonlay, Jean-Marie Saudubray</i>	
7.3	Galactokinase Deficiency	127	10.1	Clinical Presentation	145
7.3.1	Clinical Presentation	127	10.2	Metabolic Derangement	145
7.3.2	Metabolic Derangement	127	10.3	Genetics	146
7.3.3	Genetics	127	10.4	Diagnostic Tests	146
7.3.4	Diagnostic Tests	127	10.4.1	Diagnostic Criteria	146
7.3.5	Treatment and Prognosis	128	10.4.2	Differentiation of Focal from Diffuse Forms	146
7.4	Fanconi-Bickel Syndrome	128	10.5	Treatment and Prognosis	147
7.5	Portosystemic Venous Shunting and Hepatic Arterio-Venous Malformations	128	10.5.1	Medical Treatment	147
	References	128	10.5.2	Surgical Treatment	147
			10.5.3	Prognosis	147
8	Disorders of the Pentose Phosphate Pathway	131		References	148
	<i>Nanda M. Verhoeven, Cornelis Jakobs</i>		11	Disorders of Glucose Transport	151
8.1	Ribose-5-Phosphate Isomerase Deficiency	133		<i>René Santer, Jörg Klepper</i>	
8.1.1	Clinical Presentation	133	11.1	Congenital Glucose/Galactose Malabsorption (SGLT1 Deficiency)	153
8.1.2	Metabolic Derangement	133	11.1.1	Clinical Presentation	153
8.1.3	Genetics	133	11.1.2	Metabolic Derangement	153
8.1.4	Diagnostic Tests	133	11.1.3	Genetics	153
8.1.5	Treatment and Prognosis	133	11.1.4	Diagnosis	153
8.2	Transaldolase Deficiency	133	11.1.5	Treatment and Prognosis	154
8.2.1	Clinical Presentation	133	11.2	Renal Glucosuria (SGLT2 Deficiency)	154
8.2.2	Metabolic Derangement	134	11.2.1	Clinical Presentation	154
8.2.3	Genetics	134	11.2.2	Metabolic Derangement	154
8.2.4	Diagnostic Tests	134	11.2.3	Genetics	154
8.2.5	Treatment and Prognosis	134	11.2.4	Diagnosis	154
	References	134	11.2.5	Treatment and Prognosis	154
9	Disorders of Fructose Metabolism	135	11.3	Glucose Transporter Deficiency Syndrome (GLUT1 Deficiency)	154
	<i>Beat Steinmann, René Santer, Georges van den Berghe</i>		11.3.1	Clinical Presentation	154
9.1	Essential Fructosuria	137	11.3.2	Metabolic Derangement	155
9.1.1	Clinical Presentation	137	11.3.3	Genetics	155
9.1.2	Metabolic Derangement	137	11.3.4	Diagnosis	155
9.1.3	Genetics	137	11.3.5	Treatment and Prognosis	155
9.1.4	Diagnosis	137	11.4	Fanconi-Bickel Syndrome (GLUT2 Deficiency)	155
9.1.5	Treatment and Prognosis	137	11.4.1	Clinical Presentation	155
9.2	Hereditary Fructose Intolerance	137	11.4.2	Metabolic Derangement	156
9.2.1	Clinical Presentation	137	11.4.3	Genetics	156
9.2.2	Metabolic Derangement	138	11.4.4	Diagnosis	156
9.2.3	Genetics	138	11.4.5	Treatment and Prognosis	156
9.2.4	Diagnosis	138		References	157
9.2.5	Differential Diagnosis	139			
9.2.6	Treatment and Prognosis	139			
9.3	Fructose-1,6-Bisphosphatase Deficiency	140			
9.3.1	Clinical Presentation	140			
9.3.2	Metabolic Derangement	140			
9.3.3	Genetics	141			

III Disorders of Mitochondrial Energy Metabolism

12 Disorders of Pyruvate Metabolism and the Tricarboxylic Acid Cycle	161		
<i>Linda J. De Meirleir, Rudy Van Coster, Willy Lissens</i>			
12.1 Pyruvate Carboxylase Deficiency	163	14.1.3 Succinyl-CoA 3-Oxoacid CoA Transferase Deficiency	193
12.2 Phosphoenolpyruvate Carboxykinase Deficiency	165	14.1.4 Mitochondrial Acetoacetyl-CoA Thiolase Deficiency	193
12.3 Pyruvate Dehydrogenase Complex Deficiency . .	167	14.2 Metabolic Derangement	194
12.4 Dihydrolipoamide Dehydrogenase Deficiency . .	169	14.3 Genetics	194
12.5 2-Ketoglutarate Dehydrogenase Complex Deficiency	169	14.4 Diagnostic Tests	194
12.6 Fumarase Deficiency	170	14.4.1 Mitochondrial 3-Hydroxy-3-Methylglutaryl-CoA Synthase Deficiency	194
12.7 Succinate Dehydrogenase Deficiency	171	14.4.2 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency	194
12.8 Pyruvate Transporter Defect	172	14.4.3 Succinyl-CoA 3-Oxoacid CoA Transferase Deficiency	195
References	172	14.4.4 Mitochondrial Acetoacetyl-CoA Thiolase Deficiency	195
		14.5 Treatment and Prognosis	195
13 Disorders of Mitochondrial Fatty Acid Oxidation and Related Metabolic Pathways 175		14.6 Cytosolic Acetoacetyl-CoA Thiolase Deficiency . .	195
<i>Charles A. Stanley, Michael J. Bennett, Ertan Mayatepek</i>			
13.1 Introduction	177	References	196
13.2 Clinical Presentation	177	15 Defects of the Respiratory Chain	197
13.2.1 Carnitine Cycle Defects	177	<i>Arnold Munnich</i>	
13.2.2 β -Oxidation Defects	179	15.1 Clinical Presentation	199
13.2.3 Electron Transfer Defects	180	15.1.1 Fetuses	199
13.2.4 Ketogenesis Defects	180	15.1.2 Neonates	199
13.3 Genetics	180	15.1.3 Infants	201
13.4 Diagnostic Tests	181	15.1.4 Children and Adults	201
13.4.1 Disease-Related Metabolites	181	15.2 Metabolic Derangement	201
13.4.2 Tests of Overall Pathway	182	15.3 Genetics	202
13.4.3 Enzyme Assays	183	15.3.1 Mutations in Mitochondrial DNA	203
13.4.4 Prenatal Diagnosis	183	15.3.2 Mutations in Nuclear DNA	203
13.5 Treatment and Prognosis	184	15.3.3 Genetic Analysis of Respiratory Chain Deficiencies	203
13.5.1 Management of Acute Illness	184	15.3.4 Genetic Counseling and Prenatal Diagnosis . . .	204
13.5.2 Long-term Diet Therapy	184	15.4 Diagnostic Tests	204
13.5.3 Carnitine Therapy	184	15.4.1 Screening Tests	204
13.5.4 Other Therapy	184	15.4.2 Enzyme Assays	204
13.5.5 Prognosis	185	15.4.3 Histopathological Studies	206
13.6 Rare Related Disorders	187	15.4.4 Magnetic Resonance Spectroscopy of Muscle and Brain	207
13.6.1 Transport Defect of Fatty Acids	187	15.5 Treatment and Prognosis	207
13.6.2 Defects in Leukotriene Metabolism	187	References	208
References	188	16 Creatine Deficiency Syndromes	211
14 Disorders of Ketogenesis and Ketolysis	191	<i>Sylvia Stöckler-Ipsiroglu, Gajja S. Salomons</i>	
<i>Andrew A.M. Morris</i>			
14.1 Clinical Presentation	193	16.1 Clinical Presentation	213
14.1.1 Mitochondrial 3-Hydroxy-3-Methylglutaryl-CoA Synthase Deficiency	193	16.1.1 Guanidinoacetate Methyltransferase Deficiency	213
14.1.2 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency	193	16.1.2 Arginine:Glycine Amidinotransferase Deficiency	213
		16.1.3 SLC6A8 Deficiency	213
		16.2 Metabolic Derangement	214
		16.3 Genetics	214
		16.4 Diagnostic Tests	214
		16.4.1 MRS of Brain	214

16.4.2	Metabolic Screening	214	18.2.3	Genetics	239
16.4.3	DNA Diagnostics	215	18.2.4	Diagnostic Tests	239
16.4.4	Functional Tests/Enzymatic Diagnostics	215	18.2.5	Treatment and Prognosis	239
16.4.5	Prenatal Diagnosis	215	18.3	Hereditary Tyrosinaemia Type III	239
16.5	Treatment and Prognosis	215	18.3.1	Clinical Presentation	239
16.5.1	GAMT Deficiency	215	18.3.2	Metabolic Derangement	239
16.5.2	AGAT Deficiency	216	18.3.3	Genetics	240
16.5.3	SLC6A8 Deficiency	216	18.3.4	Diagnostic Tests	240
	References	216	18.3.5	Treatment and Prognosis	240
			18.4	Transient Tyrosinaemia	240
			18.5	Alkaptonuria	240
			18.5.1	Clinical Presentation	240
			18.5.2	Metabolic Derangement	241
			18.5.3	Genetics	241
			18.5.4	Diagnostic Tests	241
			18.5.5	Treatment and Prognosis	241
			18.6	Hawkinsinuria	241
			18.6.1	Clinical Presentation	241
			18.6.2	Metabolic Derangement	241
			18.6.3	Genetics	241
			18.6.4	Diagnostic Tests	241
			18.6.5	Treatment and Prognosis	242
				References	242
IV Disorders of Amino Acid Metabolism and Transport					
17	Hyperphenylalaninaemia	221	19	Branched-Chain Organic Acidurias/Acidemias	245
	<i>John H. Walter, Philip J. Lee, Peter Burgard</i>			<i>Udo Wendel, Hélène Ogier de Baulny</i>	
17.1	Introduction	223	19.1	Maple Syrup Urine Disease, Isovaleric Aciduria, Propionic Aciduria, Methylmalonic Aciduria	247
17.2	Phenylalanine Hydroxylase Deficiency	223	19.1.1	Clinical Presentation	247
17.2.1	Clinical Presentation	223	19.1.2	Metabolic Derangement	249
17.2.2	Metabolic Derangement	223	19.1.3	Genetics	250
17.2.3	Genetics	223	19.1.4	Diagnostic Tests	251
17.2.4	Diagnostic Tests	224	19.1.5	Treatment and Prognosis	251
17.2.5	Treatment and Prognosis	224	19.2	3-Methylcrotonyl Glycinuria	256
17.3	Maternal Phenylketonuria	227	19.2.1	Clinical Presentation	256
17.3.1	Clinical Presentation	227	19.2.2	Metabolic Derangement	256
17.3.2	Metabolic Derangement	227	19.2.3	Genetics	257
17.3.3	Management	227	19.2.4	Diagnostic Tests	257
17.3.4	Prognosis	228	19.2.5	Treatment and Prognosis	257
17.4	Hyperphenylalaninaemia and Disorders of Bipterin Metabolism	229	19.3	3-Methylglutaconic Aciduria Type I	257
17.4.1	Clinical Presentation	229	19.4	Short/Branched-Chain Acyl-CoA Dehydrogenase Deficiency	258
17.4.2	Metabolic Derangement	229	19.5	2-Methyl-3-Hydroxybutyryl-CoA Dehydrogenase Deficiency	258
17.4.3	Genetics	229	19.6	Isobutyryl-CoA Dehydrogenase Deficiency	259
17.4.4	Diagnostic Tests	229	19.7	3-Hydroxyisobutyric Aciduria	259
17.4.5	Treatment	230	19.8	Malonic Aciduria	259
17.4.6	Outcome	230	19.8.1	Clinical Presentation	259
	References	231	19.8.2	Metabolic Derangement	259
			19.8.3	Genetics	259
18	Disorders of Tyrosine Metabolism	233	19.8.4	Diagnostic Tests	260
	<i>Anupam Chakrapani, Elisabeth Holme</i>		19.8.5	Treatment and Prognosis	260
18.1	Hereditary Tyrosinaemia Type I (Hepatorenal Tyrosinaemia)	235		References	260
18.1.1	Clinical Presentation	235			
18.1.2	Metabolic Derangement	235			
18.1.3	Genetics	236			
18.1.4	Diagnostic Tests	236			
18.1.5	Treatment and Prognosis	237			
18.2	Hereditary Tyrosinaemia Type II (Oculocutaneous Tyrosinaemia, Richner-Hanhart Syndrome)	238			
18.2.1	Clinical Presentation	238			
18.2.2	Metabolic Derangement	239			

28 Disorders of Cobalamin and Folate Transport and Metabolism 341
David S. Rosenblatt, Brian Fowler

28.1 Disorders of Absorption and Transport of Cobalamin 343

28.1.1 Hereditary Intrinsic Factor Deficiency 343

28.1.2 Defective Transport of Cobalamin by Enterocytes (Imerslund-Gräsbeck Syndrome) 343

28.1.3 Haptocorrin (R Binder) Deficiency 344

28.1.4 Transcobalamin Deficiency 344

28.2 Disorders of Intracellular Utilization of Cobalamin 345

28.2.1 Combined Deficiencies of Adenosylcobalamin and Methylcobalamin 345

28.2.2 Adenosylcobalamin Deficiency 347

28.2.3 Methylcobalamin Deficiency 348

28.3 Disorders of Absorption and Metabolism of Folate 351

28.3.1 Hereditary Folate Malabsorption 351

28.3.2 Glutamate-Formiminotransferase Deficiency . . . 351

28.3.3 Methylenetetrahydrofolate Reductase Deficiency 352

References 353

VI Neurotransmitter and Small Peptide Disorders

29 Disorders of Neurotransmission 357
Jaak Jaeken, Cornelis Jakobs, Peter T. Clayton, Ron A. Wevers

29.1 Inborn Errors of Gamma Amino Butyric Acid Metabolism 361

29.1.1 Gamma Amino Butyric Acid Transaminase Deficiency 361

29.1.2 Succinic Semialdehyde Dehydrogenase Deficiency 362

29.2 Inborn Defects of Receptors and Transporters of Neurotransmitters 362

29.2.1 Hyperekplexia 362

29.2.2 GABA Receptor Mutation 363

29.2.3 Mitochondrial Glutamate Transport Defect 363

29.3 Inborn Errors of Monoamine Metabolism 365

29.3.1 Tyrosine Hydroxylase Deficiency 365

29.3.2 Aromatic L-Aminoacid Decarboxylase Deficiency 365

29.3.3 Dopamine β -Hydroxylase Deficiency 366

29.3.4 Monoamine Oxidase-A Deficiency 366

29.3.5 Guanosine Triphosphate Cyclohydrolase-I Deficiency 367

29.4 Inborn Disorders Involving Pyridoxine and Pyridoxal Phosphate 369

29.4.1 Pyridoxine-Responsive Epilepsy 369

29.4.2 Pyridox(am)ine 5'-Phosphate Oxidase Deficiency 370

References 371

30 Disorders in the Metabolism of Glutathione and Imidazole Dipeptides 373
Ellinor Ristoff, Agne Larsson, Jaak Jaeken

30.1 Disorders in the Metabolism of Glutathione . . . 375

30.1.1 γ -Glutamylcysteine Synthetase Deficiency 375

30.1.2 Glutathione Synthetase Deficiency 375

30.1.3 γ -Glutamyl Transpeptidase Deficiency 377

30.1.4 5-Oxoprolinase Deficiency 377

30.1.5 Secondary 5-Oxoprolinuria 377

30.2 Disorders of Imidazole Dipeptides 378

30.2.1 Serum Carnosinase Deficiency 378

30.2.2 Homocarnosinosis 378

30.2.3 Prolidase Deficiency 378

References 379

31 Trimethylaminuria and Dimethylglycine Dehydrogenase Deficiency 381
Valerie Walker, Ron A. Wevers

31.1 Trimethylaminuria (Fish Odour Syndrome) 383

31.1.1 Clinical Presentation 383

31.1.2 Metabolic Derangement 383

31.1.3 Genetics 383

31.1.4 Diagnostic Tests 383

31.1.5 Treatment 383

31.2 Dimethylglycine Dehydrogenase Deficiency . . . 384

31.2.1 Clinical Presentation 384

31.2.2 Metabolic Derangement 384

31.2.3 Genetics 384

31.2.4 Diagnostic Tests 384

31.2.5 Treatment 384

References 384

VII Disorders of Lipid and Bile Acid Metabolism

32 Dyslipidemias 389
Annabelle Rodriguez-Oquendo, Peter O. Kwiterovich, Jr.

32.1 Overview of Plasma Lipid and Lipoprotein Metabolism 391

32.1.1 Exogenous Lipoprotein Metabolism 391

32.1.2 Endogenous Lipoprotein Metabolism 392

32.1.3 Reverse Cholesterol Transport and High Density Lipoproteins 393

32.1.4 Lipid Lowering Drugs 394

32.2 Disorders of Exogenous Lipoprotein Metabolism 394

32.2.1 Lipoprotein Lipase Deficiency 394

32.2.2 Apo C-II Deficiency 395

32.3 Disorders of Endogenous Lipoprotein Metabolism 395

32.3.1 Disorders of VLDL Overproduction 396

32.3.2 Disorders of LDL Removal 397

32.4	Disorders of Endogenous and Exogenous Lipoprotein Transport	399	34.4	Cerebrotendinous Xanthomatosis (Sterol 27-Hydroxylase Deficiency)	426
32.4.1	Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)	399	34.5	α -Methylacyl-CoA Racemase Deficiency	427
32.4.2	Hepatic Lipase Deficiency	400	34.6	Oxysterol 7 α -Hydroxylase Deficiency	428
32.5	Disorders of Reduced LDL Cholesterol Levels	400	34.7	Bile Acid Amidation Defect	428
32.5.1	Abetalipoproteinemia	400	34.8	Cholesterol 7 α -Hydroxylase Deficiency	429
32.5.2	Hypobetalipoproteinemia	401	34.9	Disorders of Peroxisome Biogenesis and Peroxisomal β -Oxidation	429
32.5.3	Homozygous Hypobetalipoproteinemia	401		References	429
32.6	Disorders of Reverse Cholesterol Transport	401	VIII Disorders of Nucleic Acid and Heme Metabolism		
32.6.1	Familial Hypoalphalipoproteinemia	401	35	Disorders of Purine and Pyrimidine Metabolism	433
32.6.2	Apolipoprotein A-I Mutations	401		<i>Georges van den Berghe, M.- Françoise Vincent, Sandrine Marie</i>	
32.6.3	Tangier Disease	402	35.1	Inborn Errors of Purine Metabolism	435
32.6.4	Lecithin-Cholesterol Acyltransferase Deficiency	402	35.1.1	Phosphoribosyl Pyrophosphate Synthetase Superactivity	435
32.6.5	Cholesteryl Ester Transfer Protein Deficiency	402	35.1.2	Adenylosuccinase Deficiency	436
32.6.6	Elevated Lipoprotein (a)	403	35.1.3	AICA-Ribosiduria	437
32.7	Guidelines for the Clinical Evaluation and Treatment of Dyslipidemia	403	35.1.4	Muscle AMP Deaminase Deficiency	437
32.7.1	Clinical Evaluation	403	35.1.5	Adenosine Deaminase Deficiency	438
32.7.2	Dietary Treatment, Weight Reduction and Exercise	404	35.1.6	Adenosine Deaminase Superactivity	439
32.7.3	Goals for Dietary and Hygienic Therapy	405	35.1.7	Purine Nucleoside Phosphorylase Deficiency	440
32.7.4	Low Density Lipoprotein-Lowering Drugs	406	35.1.8	Xanthine Oxidase Deficiency	440
32.7.5	Triglyceride Lowering Drugs	407	35.1.9	Hypoxanthine-Guanine Phosphoribosyltransferase Deficiency	441
32.7.6	Combination Pharmacotherapy	408	35.1.10	Adenine Phosphoribosyltransferase Deficiency	442
	Abbreviations	408	35.1.11	Deoxyguanosine Kinase Deficiency	442
	References	408	35.2	Inborn Errors of Pyrimidine Metabolism	445
33	Disorders of Cholesterol Synthesis	411	35.2.1	UMP Synthase Deficiency (Hereditary Orotic Aciduria)	445
	<i>Hans R. Waterham, Peter T. Clayton</i>		35.2.2	Dihydropyrimidine Dehydrogenase Deficiency	445
33.1	Mevalonic Aciduria and Hyper-Immunoglobulinaemia-D and Periodic Fever Syndrome (Mevalonate Kinase Deficiency)	413	35.2.3	Dihydropyrimidinase Deficiency	446
33.2	Smith-Lemli-Opitz Syndrome (7-Dehydrocholesterol Reductase Deficiency)	414	35.2.4	Ureidopropionase Deficiency	446
33.3	X-Linked Dominant Chondrodysplasia Punctata 2 or Conradi-Hünemann Syndrome (Sterol Δ^8 - Δ^7 Isomerase Deficiency)	415	35.2.5	Pyrimidine 5'-Nucleotidase Deficiency	446
33.4	CHILD Syndrome (3 β -Hydroxysteroid C-4 Dehydrogenase Deficiency)	416	35.2.6	Cytosolic 5'-Nucleotidase Superactivity	447
33.5	Desmosterolosis (Desmosterol Reductase Deficiency)	417	35.2.7	Thymidine Phosphorylase Deficiency	447
33.6	Lathosterolosis (Sterol Δ^5 -Desaturase Deficiency)	417	35.2.8	Thymidine Kinase Deficiency	447
33.7	Hypops-Ectopic Calcification-Moth-Eaten (HEM) Skeletal Dysplasia or Greenberg Skeletal Dysplasia (Sterol Δ^{14} -Reductase Deficiency)	418		References	447
33.8	Other Disorders	419	36	Disorders of Heme Biosynthesis	451
	References	419		<i>Norman G. Egger, Chul Lee, Karl E. Anderson</i>	
34	Disorders of Bile Acid Synthesis	421	36.1	X-Linked Sideroblastic Anemia	453
	<i>Peter T. Clayton</i>		36.2	Classification of Porphyrias	453
34.1	Introduction	423	36.3	Diagnosis of Porphyrias	454
34.2	3 β -Hydroxy- Δ^5 -C ₂₇ -Steroid Dehydrogenase Deficiency	423	36.4	5-Aminolevulinic Acid Dehydratase Porphyria	454
34.3	Δ^4 -3-Oxosteroid 5 β -Reductase Deficiency	425	36.5	Acute Intermittent Porphyria	455
			36.6	Congenital Erythropoietic Porphyria (Gunther Disease)	458

36.7	Porphyria Cutanea Tarda	459
36.8	Hepatoerythropoietic Porphyria	460
36.9	Hereditary Coproporphyrinemia and Variegate Porphyria	461
36.10	Erythropoietic Protoporphyrinemia	462
	References	463

IX Disorders of Metal Transport

37	Disorders in the Transport of Copper, Zinc and Magnesium	467
	<i>Roderick H.J. Houwen</i>	
37.1	Copper	469
37.1.1	Wilson Disease	469
37.1.2	Menkes Disease	471
37.1.3	Other Copper Storage Disorders	472
37.2	Zinc	472
37.2.1	Acrodermatitis Enteropathica	472
37.2.2	Zinc Deficiency in Breastfed Babies	473
37.2.3	Hyperzincemia with Hypercalprotectinemia	473
37.2.4	Autosomal Dominant Hyperzincemia Without Symptoms	473
37.3	Magnesium	474
37.3.1	Primary Hypomagnesemia with Secondary Hypocalcemia	474
37.3.2	Hypomagnesemia with Hypercalciuria and Nephrocalcinosis	474
37.3.3	Isolated Dominant Hypomagnesemia	475
37.3.4	Isolated Autosomal Recessive Hypomagnesemia	475
37.3.5	Other Metals	475
	References	475

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

38	Disorders of Sphingolipid Metabolism	479
	<i>Marie-Thérèse Vanier</i>	
38.1	Gaucher Disease	481
38.2	Niemann-Pick Disease Type A and B	482
38.3	GM1-Gangliosidosis	484
38.4	GM2-Gangliosidosis	485
38.5	Krabbe Disease	486
38.6	Metachromatic Leukodystrophy	487
38.7	Fabry Disease	489
38.8	Farber Disease	490
38.9	Prosaposin Deficiency	490
38.10	Niemann-Pick Disease Type C	491
	References	492

39	Mucopolysaccharidoses and Oligosaccharidoses	495
	<i>J. Ed Wraith</i>	
39.1	Clinical Presentation	497
39.1.1	Mucopolysaccharidoses	497
39.1.2	Oligosaccharidoses	505
39.2	Metabolic Derangements	506
39.3	Genetics	506
39.4	Diagnostic Tests	506
39.5	Treatment and Prognosis	506
	References	507

40	Peroxisomal Disorders	509
	<i>Bwee Tien Poll-The, Patrick Aubourg, Ronald J.A. Wanders</i>	
40.1	Clinical Presentation	511
40.1.1	Dysmorphism	511
40.1.2	Neurological Dysfunction	512
40.1.3	Hepatic and Gastrointestinal Disease	512
40.2	Metabolic Derangements	514
40.2.1	Peroxisome Biogenesis	514
40.2.2	Metabolic Functions of Peroxisomes	515
40.2.3	Metabolic Abnormalities in the Different Peroxisomal Disorders	518
40.3	Genetics	519
40.4	Diagnostic Tests	519
40.4.1	Diagnostic Group 1	519
40.4.2	Diagnostic Group 2	519
40.4.3	Diagnostic Group 3	519
40.4.4	Diagnostic Group 4	520
40.4.5	Histological Detection	520
40.4.6	Prenatal Diagnosis	520
40.5	Treatment and Prognosis	520
	References	521

41	Congenital Disorders of Glycosylation	523
	<i>Jaak Jaeken</i>	
41.1	Introduction	525
41.2	Congenital Disorders of Protein N-Glycosylation	526
41.2.1	Phosphomannomutase 2 Deficiency (CDG-Ia)	526
41.2.2	Phosphomannose-Isomerase Deficiency (CDG-Ib)	527
41.2.3	Glucosyltransferase I Deficiency (CDG-Ic)	528
41.3	Congenital Disorders of Protein O-Glycosylation	528
41.3.1	Hereditary Multiple Exostoses	528
41.3.2	Walker-Warburg Syndrome	529
41.3.3	Muscle-Eye-Brain Disease	529
41.4	Newly Discovered Disorders	529
41.4.1	COG7 Deficiency	529
41.4.2	GM3 Synthase Deficiency	529
	References	530

42	Cystinosis	531
	<i>Michel Broyer</i>	
42.1	Infantile Cystinosis	533
42.1.1	Clinical Presentation	533
42.1.2	Metabolic Derangement	534
42.1.3	Genetics	535
42.1.4	Diagnostic Tests	535
42.1.5	Treatment	535
42.2	Adolescent Cystinosis	536
42.3	Adult Benign Cystinosis	536
	References	536
43	Primary Hyperoxalurias	539
	<i>Pierre Cochat, Marie-Odile Rolland</i>	
43.1	Primary Hyperoxaluria Type 1	541
43.1.1	Clinical Presentation	541
43.1.2	Metabolic Derangement	542
43.1.3	Genetics	542
43.1.4	Diagnosis	542
43.1.5	Treatment and Prognosis	542
43.2	Primary Hyperoxaluria Type 2	545
43.2.1	Clinical Presentation	545
43.2.2	Metabolic Derangement	545
43.2.3	Genetics	545
43.2.4	Diagnosis	545
43.2.5	Treatment and Prognosis	545
43.3	Non-Type 1 Non-Type 2 Primary Hyperoxaluria	545
	References	545
	Subject Index	547