

# Contents

---

List of Contributors xix

Preface xxvii

PART

---

I

## ANATOMY

### 1. Development of the Autonomic Nervous System

CARYL E. HILL

Pathways and Fate of Neural Crest Cells 3

Factors Operating during Neural Crest Migration 3

Neurite Outgrowth and Target Contact 4

Factors Involved in Neurite Outgrowth and Neuronal Survival 5

Synapse Formation and Neuronal Differentiation 5

Conclusions 5

### 2. Mechanisms of Differentiation of Autonomic Neurons

KWANG-SOO KIM

The Autonomic Nervous System Is Derived from Neural Crest Cells 6

Signaling Molecules Regulate the Developmental Processes of the Autonomic Nervous System 6

Transcriptional Code Underlying the Development and Phenotypic Specification of the Autonomic Nervous System 7

Mash1 7

Phox2 Genes 7

Gata3 8

Activator Protein 2 8

Other Transcriptional Factors 8

Neurotransmitter Phenotypes of the Autonomic Nervous System 9

Noradrenaline Phenotype 9

Control Mechanism of *DBH* Gene Expression Is Closely Related to Autonomic Nervous System Development 9

Cholinergic Phenotype and the Switch of Neurotransmitter Phenotypes by the Target Cell Interactions 9

### 3. Milestones in Autonomic Research

MAX R. BENNETT

Receptors 12

Classical Transmitters: The Discovery of Noradrenaline, Acetylcholine, and Their Receptors 12

The Discovery of New Transmitters, Including Nucleotides, Peptides, and Nitric Oxide 12

Varicosities 12

Varicosities Shown to be the Source of Transmitters 12

Varicosities Have the Capacity to Take Up Transmitters After Their Release 12

Varicosities Possess Receptors That on Activation Modulate Further Transmitter Release 13

Generation of Currents and Second Messengers on Receptor Activation After Transmitter Release from Varicosities 13

Action Potentials, Initiated by the Generation of Junction Potentials, Are Caused by the Influx of Calcium Ions 13

Control of the Influx of Calcium Ions Is a Principal Means of Decreasing Blood Pressure 13

PART

---

II

## PHARMACOLOGY

### 4. Central Autonomic Control

EDUARDO E. BENARROCH

Anatomy of Central Autonomic Areas 17

Forebrain 17

Levels of Integration of Central Autonomic Control 18

Bulbospinal Level	18
Pontomesencephalic Level	18
Forebrain Level	18

## 5. Peripheral Autonomic Nervous System

ROBERT W. HAMILL AND ROBERT E. SHAPIRO

Sympathetic Nervous System	20
Sympathoadrenal Axis and the Adrenal Gland	23
Parasympathetic Nervous System	24
The Concept of Plurichemical Transmission and Chemical Coding	25
Functional Neuroanatomy and Biochemical Pharmacology	27

## 6. The Autonomic Neuroeffector Junction

GEOFFREY BURNSTOCK

Structure of the Autonomic Neuromuscular Junction	29
Varicose Terminal Axons	29
Junctional Cleft	29
Prejunctional and Postjunctional Specialization	30
Muscle Effector Bundles and Gap Junctions	30
Autonomic Neurotransmission	30
Electrophysiology	30
Receptor Localization on Smooth Muscle Cells	31
Model of Autonomic Neuroeffector Junction	32

## 7. Autonomic Neuromuscular Transmission

MAX R. BENNETT

New Transmitters and the Concept of Cotransmitters	34
Varicosities, Vesicle-Associated Proteins, and Calcium Fluxes	34
Ionotropic Receptors Are Localized to the Muscle Membrane at Varicosities	34
Metabotropic and Ionotropic Receptors Are Internalized and Recycled after Binding Transmitter	34
Sources of Intracellular Calcium in Smooth Muscle for Initiating Contraction	35
Modulation of Calcium Influx and the Control of Hypertension	35

## 8. Dopaminergic Neurotransmission

CHRISTOPHER BELL

Transmitter Neurochemistry	36
Transmitter Synthesis	36
Transmitter Storage and Release	36
Transmitter Recycling	36
Future Questions	37

## 9. Dopamine Receptors

AKI LAAKSO AND MARC G. CARON

Structural and Functional Characteristics of Dopamine Receptors	39
Gene Structure	39
Receptor Structure	39
Signal Transduction	40
D1-like Receptors	40
D2-like Receptors	41
Oligomerization	41
Pharmacology	42
Distribution	42
Distribution in the Brain	42
D1 Receptors	42
D2 Receptors	42
D3 Receptors	42
D4 Receptors	43
D5 Receptors	43
Dopamine Receptors in the Periphery	43
Regulation	43

## 10. Noradrenergic Neurotransmission

DAVID S. GOLDSTEIN

Noradrenergic Innervation of the Cardiovascular System	44
Norepinephrine: The Sympathetic Neurotransmitter	45
Norepinephrine Synthesis	45
Storage	46
Release	46
Disposition	47

## 11. $\alpha_1$ -Adrenergic Receptors

ROBERT M. GRAHAM

Subtypes	50
Structure and Signaling	50
Ligand Binding and Activation	50
Regulation	52
Vascular Subtypes	52

## 12. $\alpha_2$ -Adrenergic Receptors

LEE E. LIMBIRD

## 13. $\beta$ -Adrenergic Receptors

STEPHEN B. LIGGETT

Signaling of $\beta$ -AR Subtypes	57
Regulation of $\beta$ -AR Function	57
Polymorphisms of $\beta$ -AR	58

## 14. Purinergic Neurotransmission

GEOFFREY BURNSTOCK

Sympathetic Nerves	61
Parasympathetic Nerves	61
Sensory-Motor Nerves	62
Intramural (Intrinsic) Nerves	63
Skeletal Neuromuscular Junctions	63
Synaptic Purinergic Transmission in Ganglia and Brain	64
Glial Cells	64
Plasticity of Expression of Purinergic Cotransmitters	64
Long-Term (Trophic) Signaling	64
P2X <sub>3</sub> Receptors and Nociception	64
Future Developments	64

## 15. Adenosine Receptors and Autonomic Regulation

ITALO BIAGGIONI

Postsynaptic Antiadrenergic Effects of Adenosine	66
Presynaptic Effects of Adenosine on Efferent Nerves and Ganglionic Transmission	66
Adenosine and Central Autonomic Regulation	66
Neuroexcitatory Actions of Adenosine on Afferent Pathways	67
Integrated View of Adenosine and Cardiovascular Autonomic Regulation	67

## 16. Acetylcholine and Muscarinic Receptors

B. V. RAMA SASTRY AND DAVID ROBERTSON

Acetylcholine Synthesis and Metabolism: Drug Mechanisms	70
Acetylcholine Receptors	70
Muscarinic Agonists	71
Muscarinic Autonomic Effects of Acetylcholine	71
Muscarinic Antagonists	72

## 17. Nicotinic Acetylcholine Receptors: Structure and Functional Properties

PALMER TAYLOR

Structural Considerations	73
Subtype Diversity of Nicotinic Receptors	73
Electrophysiologic Events Associated with Receptor Activation	74
Distribution of Nicotinic Receptors	76

## 18. Acetylcholinesterase and Its Inhibitors

ALBERT ENZ

Mechanism of Action	77
Acetylcholinesterase Inhibitors	77
Pharmacologic Actions of Acetylcholinesterase Inhibition	77
Clinical Applications of Anticholinesterases	79
Cholinesterase Inhibitors and Alzheimer's Disease	80

## 19. Amino Acid Neurotransmission

WILLIAM TALMAN

## 20. Peptidergic Neurotransmission

GRAHAM J. DOCKRAY

Families of Peptide Transmitters	83
Generic Features of Peptidergic Transmission	83
Biosynthesis	83
Storage and Release	83
Receptors	84
Degradation	84
Chemical Coding	84
Overview of Peptides in the Autonomic Nervous System	84

## 21. Leptin Signaling in the Central Nervous System

KAMAL RAHMOUNI, WILLIAM G. HAYNES, AND ALYN L. MARK

Central Neural Action of Leptin	86
Leptin Receptor	86
Intracellular Mechanisms of Leptin Signaling	86
Site of Leptin Action in the Brain	87
Interaction of Leptin and Neuropeptides in the Hypothalamus	87
Neuropeptide Y	87
Melanocortin System	88
Other Mediators	88
Conclusion	89

## 22. Nitrergic Neurotransmission

JILL LINCOLN

Synthesis of Nitric Oxide	90
Mechanisms of Nitrergic Neurotransmission	90
Nitrergic Neurotransmission in the Autonomic Nervous System and Pathologic Implications	91

## 23. Serotonin Receptors and Neurotransmission

ELAINE SANDERS-BUSH AND CHARLES D. NICHOLS

- Localization 93
- Synthesis and Metabolism 93
- Neurotransmission 93
- Receptors 94
- Pharmacology and Role in Disease 94

## 24. Antidepressant-Sensitive Norepinephrine Transporters: Structure and Regulation

RANDY D. BLAKELY

PART

III

## PHYSIOLOGY

### 25. Cardiac and Other Visceral Afferents

JOHN C. LONGHURST

- Anatomic Framework 103
- Afferent Stimuli 103
- Autonomic Reflex Responses to Visceral Afferent Activation 107
- Pathologic Alterations of Visceral Afferents 107

### 26. Skeletal Muscle Afferents

MARC P. KAUFMAN

### 27. Entrainment of Sympathetic Rhythms

MICHAEL P. GILBEY

- Sympathetic Rhythm 114
- Cardiac- and Respiratory-Related Rhythms 114
- Mechanisms Underlying Rhythms 114
  - Phasic Inputs Generate Rhythms 114
  - Entrainment of Rhythms 114
- How Many Central Oscillators? 115
- Functional Significance 115

### 28. Sexual Function

JOHN D. STEWART

- Peripheral Structures 116
- Central Nervous System 116
- Physiologic Events 116

## 29. Gastrointestinal Function

MICHAEL CAMILLERI

- Salivary Secretion 118
- Gastric Secretion 118
- Pancreaticobiliary Secretion 118
- Bile 118
- Intestinal Secretion and Absorption 119
- Control of Gut Motility 119
- Normal Gastrointestinal Motor Function 120

## 30. Regulation of Metabolism

ROBERT HOELDTKE

- Catecholamines and Glucose Metabolism 122
- Catecholamines and Fat Metabolism 122
- Catecholamines and Thermogenesis 122
- Insulin and Autonomic Function 123

## 31. The Sweat Gland

PHILLIP A. LOW

- Anatomy and Function of the Sweat Gland 124
  - Type 124
  - Density and Distribution 124
  - Physiology of Sweat Glands 124
  - Function 124
- Innervation of Sweat Gland 124
  - Denervation 126

## 32. Temperature Regulation

MIKIHIRO KIHARA, JUNICHI SUGENOYA, AND PHILLIP A. LOW

- Central Integration 127
- Effector Mechanisms 127
- Shivering 127
- Nonshivering Thermogenesis 128
- Vasomotor Response 128
- Sudomotor Response 129

## 33. Autonomic Control of Airways

PETER J. BARNES

- Overview of Airway Innervation 130
- Afferent Nerves 130
  - Slowly Adapting Receptors 130
  - Rapidly Adapting Receptors 130
  - C-Fibers 130
  - Cough 130
  - Neurogenic Inflammation 130
- Cholinergic Nerves 130
  - Cholinergic Efferents 131
  - Muscarinic Receptors 131

Cholinergic Reflexes	131
Anticholinergics in Airway Disease	131
Bronchodilator Nerves	131
Sympathetic Nerves	131
Inhibitory Nonadrenergic Noncholinergic Nerves	132
Neuropeptides	132
Neural Control of Airways in Disease	133
Asthma	133
Chronic Obstructive Pulmonary Disease	133

**34. Autonomic Control of Cardiac Function**

KLEBER G. FRANCHINI AND ALLEN W. COWLEY, JR.

Autonomic Nerves Innervating the Mammalian Heart	134
Myocardial Nerve Terminals	135
The Autonomic Nervous System and Cardiac Function	136
Interactions between Sympathetic and Parasympathetic Nerves	137

**35. Neurogenic Control of Blood Vessels**

KLEBER G. FRANCHINI AND ALLEN W. COWLEY, JR.

Sympathetic Component	139
Sympathetic Fibers	139
Neuroeffector Junction	140
Neurotransmitters of Sympathetic Component	140
Release of Transmitter and Effector Action	141
Parasympathetic Component	142
Neural Control of Veins	142
Differential Vasomotor Control	142

**36. Cerebral Circulation: Autonomic Influences**

PETER J. GOADSBY

Neural Innervation of Brain Circulation	144
Extrinsic Neural Influences	144
Sympathetic Nervous System	144
Parasympathetic Nervous System	145
Effect of Direct Parasympathetic Stimulation on Cerebral Blood Flow <i>In Vivo</i>	146

**37. High-Pressure and Low-Pressure Baroreflexes**

DWAIN L. ECKBERG

Anatomy	147
Transduction	147
Methods for Study of Human Baroreflexes	148
Integrated Baroreflex Responses	149
Baroreflex Resetting	150
Cardiopulmonary Baroreflexes	151
Summary	151

**38. Venoarteriolar Reflex**

PHILLIP A. LOW

Skin Blood Flow	152
Venoarteriolar Reflex	152

**39. The Cardioinhibitory Vasodepressor Reflex**

VALENTINA ACCURSO AND VIREND K. SOMERS

Physiology	154
Clinical Conditions Predisposing to Activation of the Reflex	154

**40. Autonomic Control of the Kidney**

EDWIN K. JACKSON

Innervation of the Kidney	157
Autonomic Receptors in the Kidney	157
Reflex Regulation of Blood Volume	159
The Renorenal Reflex	160
Autonomic Control of the Kidney in Pathophysiologic States	160

**41. Autonomic Control of the Pupil**

H. STANLEY THOMPSON

Parasympatholytic (Anticholinergic) Drugs	162
Parasympathomimetic (Cholinergic) Drugs	162
Sympathomimetic (Adrenergic) Drugs	164
Sympatholytic Drugs (Adrenergic Blockers)	164
Other Agents	164
Iris Pigment and Pupillary Response to Drugs	164

**42. Intraocular Pressure and Autonomic Dysfunction**

KAREN M. JOOS

Systemic Blood Pressure and Intraocular Pressure Relation	166
Ocular Blood Flow	166
Autonomic Dysfunction	166

**43. Angiotensin II/Autonomic Interactions**

DEBRA I. DIZ AND DAVID B. AVERILL

Sympathetic Nervous System	168
Angiotensin II Influence on the Sympathetic Nervous System	168
Sympathetic Nervous System Influence on the Renin-Angiotensin System	168

Parasympathetic Nervous System	168
Angiotensin II Influence on the Parasympathetic Nervous System	168
Physiologic Examples of Regulation/Interactions	169
Baroreceptor Reflex	169
Chemoreceptor Reflex	169
Other Sensory Modalities	169
Pathophysiology	170
Hypertension	170
Congestive Heart Failure	170
Consequences of Ang II-Mediated Enhancement of Sympathetic Nerve Activity to the Kidney	170
Receptor Pharmacology	170
Conclusions	171

#### 44. Autonomic Effects of Anesthesia

THOMAS J. EBERT

Direct Effects of Anesthetics on Sympathetic Outflow	172
Intravenous Anesthetics (Sedative/Hypnotics)	172
Human Baroreflex Function and Anesthetic Gases	173
Low-Pressure (Cardiopulmonary) Baroreflexes	173
High-Pressure Baroreflexes	173
Intravenous Anesthetics	173
Inhaled Agents	175

#### 45. Peripheral Dopamine Systems

GRAEME EISENHOFER AND DAVID S. GOLDSTEIN

Dopamine in the Kidneys	176
Dopamine in the Gastrointestinal Tract	176
Diet and Dopamine Sulfate	177
Perspectives	177

#### 46. Dopamine Mechanisms in the Kidney

ROBERT M. CAREY

Renal Dopamine Formation and Excretion	178
Renal Dopamine Receptor Expression	178
Dopaminergic Regulation of Renal Sodium Excretion	178
D <sub>1</sub> -Like Receptors	178
D <sub>2</sub> -Like Receptors	179
Physiologic Interactions of the Renal Dopaminergic System and the Renin-Angiotensin System	179
Renal Dopamine and Hypertension	180

#### STRESS

##### 47. Exercise and the Autonomic Nervous System

VERNON S. BISHOP

##### 48. Effects of High Altitude

LUCIANO BERNARDI

Effects of Acute Hypoxia	185
Effects of Chronic Hypoxia	186
Autonomic Nervous System and High-Altitude Illness	186

##### 49. Hypothermia

BRUCE C. PATON

Etiologic Factors	187
General Response to Heat Loss	187
Specific Systematic Changes	187
Diagnosis	188

##### 50. Psychological Stress and the Autonomic Nervous System

MICHAEL G. ZIEGLER

Normal Psychological Stresses and Autonomic Activity	189
Patterns of Autonomic Response to Stress	189
Gastrointestinal Control	190
Psychosomatic Disorders and the Autonomic Nervous System	190
Posttraumatic Stress Disorder, Panic, and Anxiety	190

##### 51. Aging and the Autonomic Nervous System

VERA NOVAK AND LEWIS A. LIPSITZ

Baroreflex Function	191
Sympathetic Activity	191
Parasympathetic Activity	191
Variability of Cardiovascular Signals	192
Neurotransmitters and Receptors	192
Cardiac β-Adrenergic Receptors	192
Vascular Reactivity	192
Volume Regulation	193
Cerebral Vasoregulation	193

---

**52. Mind-Body Interactions**

DANIEL TRANEL

Nonconscious Memory 194

Nonconscious Face Recognition in Prosopagnosia 194

Nonconscious Recognition in the Auditory Modality 194

Nonconscious Learning 195

Nonconscious Face Learning in Prosopagnosia 195

Nonconscious Learning of Affective Valence 195

Conditioning Without Awareness 196

Emotion 196

Impaired Skin Conductance Responses to Emotionally Charged Stimuli 196

Impaired Skin Conductance Responses to Familiar Faces 197

The Somatic Marker Hypothesis 197

---

PART**V****NEUROPATHOLOGY****53. Oxidative Processes**

JING ZHANG AND THOMAS J. MONTINE

Oxidative Stress 201

Mechanisms to Limit Reactive Oxygen Species and Reactive Nitrogen Species Accumulation 201

Oxidative Damage to Cellular Macromolecules 201

Lipid Peroxidation 201

Nucleic Acid 202

Protein 202

Cellular Repair and Detoxification Mechanisms for Oxidative Damage 203

Glutathione-S-transferases 203

Aldo-keto Oxidoreductases 203

DNA Repair 203

Summary 203

**54.  $\alpha$ -Synuclein and Neurodegeneration**

MICHEL GOEDERT

The Synuclein Family 204

The  $\alpha$ -Synuclein Diseases 204Models of  $\alpha$ -Synucleinopathies 205**55. Experimental Autoimmune Autonomic Neuropathy**

STEVEN VERNINO

Autoimmune Autonomic Neuropathy 208

Experimental Autoimmune Autonomic Neuropathy 208

---

PART**VI****EVALUATION OF AUTONOMIC FAILURE****56. Clinical Assessment of Autonomic Failure**

DAVID ROBERTSON

Orthostatic Test 213

Tilt-Table Testing 216

Pharmacologic Tests 216

**57. Evaluation of the Patient with Syncope**

HORACIO KAUFMANN

Mechanisms of Syncope 217

Orthostatic Hypotension 217

Acute Decrease in Cardiac Output 218

Acute Increase in Cerebrovascular Resistance 218

Diagnosis 219

Tilt Testing 220

Prognosis 220

**58. Evaluation of the Patient with Orthostatic Intolerance**

RONALD SCHONDORF

Overview 221

Clinical Features 221

Pathophysiology of Orthostatic Intolerance 221

Laboratory Evaluation of Orthostatic Intolerance 221

Symptoms of Orthostatic Intolerance 223

**59. Sympathetic Microneurography**

B. GUNNAR WALLIN

Methodology 224

Equipment 224

Procedure 224

Analysis 225

Potential Difficulties 226

Mixed Sites 226

Changes of Electrode Site 226

**60. Assessment of the Autonomic Control  
of the Cardiovascular System by Frequency  
Domain Approach**

RAFFAELLO FURLAN AND ALBERTO MALLIANI

Methodology	228
Functional Significance of Cardiovascular Rhythms	228
Relation between Cardiovascular and Neural Rhythms	229
Physiology and Pathophysiology	229

**61. Assessment of Sudomotor Function**

PHILLIP A. LOW AND RONALD SCHONDORF

Tests of Sudomotor Function	231
Quantitative Sudomotor Axon Reflex Test	231
Skin Imprint Recordings	231
Skin Potential Recordings	231
Thermoregulatory Sweat Test	233
Integrated Evaluation of Sweating	233

**62. Biochemical Assessment of  
Sympathoadrenal Activity**

JOSEPH L. IZZO, JR., AND STANLEY F. FERNANDEZ

Catecholamine Metabolism	234
Urinary Excretion of Catecholamines and Metabolites	234
Urinary Vanillylmandelic Acid Excretion	234
Urinary-Free Catecholamines	234
Urinary Metanephrines	234
Urinary Methoxyhydroxyphenyl Glycol	234
Plasma Catecholamines and Metabolites	235
Plasma Norepinephrine	235
Plasma Epinephrine	236
Plasma Dopamine	236
Plasma Dihydroxyphenyl Glycol	236
Plasma Metanephrines	236
Sulfocoujugates	236
Other Proteins and Peptides in Plasma	236
Dopamine $\beta$ -hydroxylase	236
Chromogranin A	236
Neuropeptide Y	236
Tissue Catecholamine Concentrations	237
Tissue Catecholamines	237
Platelet Catecholamine	237
Cerebrospinal Fluid Catecholamines and Metabolites	237
Kinetic (Turnover) Studies	237
General Methodology	237
Radiotracer Infusions	237
Analytic Methods for Catecholamines	238
Sample Preservation	238
Analytic Techniques	238

PART

**VII**

**CARDIOVASCULAR DISORDERS**

**63. Hypertension and Sympathetic  
Nervous System Activity**

DAVID A. CALHOUN AND SUZANNE OPARIL

Renal Sympathetic Stimulation in Experimental and Human Hypertension	241
Cardiac Sympathetic Stimulation in Human Hypertension	241
Sympathetic Nervous System Activity and Vascular Remodeling	242
Plasma Norepinephrine Levels	242
Regional Norepinephrine Spillover	243
Microneurography	243
Sympathetic and Vascular Reactivity	244

**64. The Autonomic Nervous System  
and Sudden Cardiac Death**

DAN M. RODEN

Clinical Links between Autonomic Dysfunction and Sudden Cardiac Death	245
Basic Mechanisms	245
Conclusion	246

**65. Congestive Heart Failure**

MAZHAR H. KHAN AND LAWRENCE I. SINOWAY

Sympathetic Nervous System	247
Regulation of Sympathetic Nervous System Activity in Congestive Heart Failure	247
Implication of Sympathetic Nervous System Activation in Congestive Heart Failure	247
Implications for Therapy	248

**66. Neurally Mediated Syncope**

SATISH R. RAJ AND ROSE MARIE ROBERTSON

Pathophysiology of Neurally Mediated Syncope	249
Diagnosis of Neurally Mediated Syncope	249
Tilt-Table Testing	250
Natural History of Neurally Mediated Syncope	250
Neurally Mediated Syncope Treatment	250

**67. Syncope in the Athlete**

VICTOR A. CONVERTINO

Treatment 273

 $\text{BH}_4$  Deficiencies 273

Tyrosine Hydroxylase Deficiency 273

Aromatic L-Amino Acid Decarboxylase Deficiency 273

PART

**VIII****CATECHOLAMINE DISORDERS****68. The Autonomic Storm**

ALEJANDRO A. RABINSTEIN AND EELCO F. M. WIJDICKS

Definition 257

Causes and Pathophysiology 257

Incidence 257

Clinical Manifestations 257

Differential Diagnosis and Diagnostic Evaluation 258

Treatment 258

Prognosis 258

**69. Pheochromocytoma**

WILLIAM M. MANGER, RAY W. GIFFORD, JR., AND GRAEME EISENHOFER

**70. Chemodectoma and the Familial Paraganglioma Syndrome**

TERRY KETCH AND JAMES L. NETTERVILLE

**71. Baroreflex Failure**

JENS JORDAN

Causes of Baroreflex Failure 267

Clinical Presentation 267

Diagnosing Baroreflex Failure 269

Treatment 270

**72. Deficiencies of Tetrahydrobiopterin, Tyrosin Hydroxylase, and Aromatic L-Amino Acid Decarboxylase**

KEITH HYLAND AND LAUREN A. ARNOLD

Biochemistry 271

Presentation and Neurologic Symptoms 271

Diagnosis 272

Tetrahydrobiopterin Deficiencies 272

Tyrosine Hydroxylase Deficiency 273

Aromatic L-Amino Acid Decarboxylase Deficiency 273

**73. Dopamine  $\beta$ -Hydroxylase Deficiency**

ANTON H. VAN DER MEIRACKER, FRANS BOOMSMA, AND JAAP DEINUM

Clinical Presentation 274

Diagnosis 274

Differential Diagnosis 275

Genetics 275

Therapy 275

**74. Menkes Disease**

STEPHEN G. KALER

Epidemiology 277

Clinical Phenotype 277

Biochemical Phenotype 277

Autonomic Manifestations 277

Clinical Signs of Pysautonomia in Menkes Disease 277

Neurochemical Abnormalities 277

Molecular Diagnosis 278

Treatment 278

**75. Norepinephrine Transporter Dysfunction**

MAUREEN K. HAHN

Role of the Norepinephrine Transporter 280

The Human Norepinephrine Transporter Gene 280

Human Norepinephrine Transporter Single-

Nucleotide Polymorphisms 280

A457P and Orthostatic Intolerance 280

Conclusions 281

**76. Monoamine Oxidase Deficiency**

JACQUES W. M. LENDERS AND GRAEME EISENHOFER

PART

**IX****CENTRAL AUTONOMIC DISORDERS****77. Parkinson's Disease**

THOMAS L. DAVIS

Cardiac Sympathetic Denervation 287

Tests of Sympathetic Function 287

Tests of Parasympathetic Function	287
Orthostatic Hypotension	287
Constipation	288
Dysphagia	288
Drooling	288
Sexual Function	288
Bladder Dysfunction	288

## 78. Multiple System Atrophy

NIALL QUINN

History, Nosology, Epidemiology, Demographics, and Prognosis	290
History and Nosology	290
Epidemiology	290
Demographics and Prognosis	290
Clinical Features	290
Clinical Diagnostic Criteria	291
Differential Diagnosis	291
Paraclinical Investigations	291
Management	291

## 79. Dementia with Lewy Bodies

GREGOR K. WENNING AND MICHAELA STAMPFER

Clinical Aspects and Differential Diagnosis	293
Practical Management	293
Dementia	293
Hallucinations and Psychosis	293
Parkinsonism	294
Dysautonomia	294

## 80. Central Disorders of Autonomic Function

EDUARDO E. BENARROCH

Disorders of Telencephalic Autonomic Regions	295
Stroke	295
Seizures	295
Disorders of the Diencephalon	295
Hypothalamic Disorders	295
Paroxysmal Sympathetic Storms ("Diencephalic Seizures")	296
Fatal Familial Insomnia	296
Disorders of the Brainstem	296
Vertebrobasilar Disease	296
Posterior Fossa Tumors	296
Degenerative and Developmental Disorders	296
Inflammatory, Toxic, and Metabolic Disorders	297
Disorders of the Spinal Cord	297

## 81. Autonomic Disturbances in Spinal Cord Injuries

CHRISTOPHER J. MATHIAS

Cardiovascular System	298
Cutaneous Circulation	300
Thermoregulation and Sudomotor Function	300
Gastrointestinal System	301
Urinary System	301
Reproductive System	301

## 82. Neuroleptic Malignant Syndrome

P. DAVID CHARLES AND THOMAS L. DAVIS

Clinical Features	302
Medications and Risk Factors	302
Differential Diagnosis	303
Pathogenesis	304
Treatment	304

PART

## X

## PERIPHERAL AUTONOMIC FAILURE

### 83. Pure Autonomic Failure

HORACIO KAUFMANN AND IRWIN J. SCHATZ

Differential Diagnosis	309
Catecholamine Studies	310
Neuroendocrine Studies	310
Diagnostic Imaging Techniques	310
Neuropathology	310
Management	310

### 84. Familial Dysautonomia

FELICIA B. AXELROD AND MAX J. HILZ

Genetics and Diagnosis	312
Pathology	312
Sural Nerve	312
Spinal Cord	312
Sympathetic Nervous System	312
Parasympathetic Nervous System	313
Biochemical Data	313
Clinical Symptoms and Treatments	313
Prognosis	314

**85. Hereditary Autonomic Neuropathies**

YADOLLAH HARATI AND OPAS NAWASIRIPONG

Fabry's Disease 316

Clinical Manifestations of Fabry's Disease 316

Autonomic Involvement 316

Porphyria 317

Clinical Manifestation of Porphyria 317

Autonomic Involvement in Porphyria 318

Treatment of Porphyria 318

Multiple Endocrine Neoplasia Type 2B 318

Hereditary Motor and Sensory Neuropathies Type I and II (Charcot-Marie Tooth 1 and 2) 319

Types I, II, IV, and V Hereditary Sensory and Autonomic Neuropathy 319

**86. Amyloidotic Autonomic Failure**

HAZEM MACHKHAS, OPAS NAWASIRIPONG, AND YADOLLAH HARATI

Immunoglobulin Amyloidosis 320

Pathogenesis 320

Diagnosis 321

Treatment 321

Prognosis 322

Reactive Amyloidosis 322

Hereditary Amyloidosis 322

Pathogenesis 323

Laboratory Data and Diagnosis 323

Treatment and Prognosis 323

**87. Autoimmune Autonomic Neuropathy**

STEVEN VERNINO, PHILLIP A. LOW, AND VANDA A. LENNON

Autoimmune Autonomic Neuropathy 324

Description 324

Diagnosis 325

Clinical Course 325

Treatment 326

Paraneoplastic Autoimmune Autonomic Neuropathy 326

**88. Diabetic Autonomic Dysfunction**

ANDREW C. ERTL, MICHAEL PFEIFER, AND STEPHEN N. DAVIS

Iris 328

Esophagus 328

Stomach 328

Gallbladder 329

Colon 329

Bladder 329

Penis 329

Vagina 330

Adrenal Medulla 330

Sudomotor 330

Cardiovascular 330

**89. Guillain-Barré Syndrome**

PHILLIP A. LOW AND JAMES G. MCLEOD

Clinical Features 332

Investigations 332

Etiology or Mechanisms 332

Course and Prognosis 333

Management 333

**90. Chagas' Disease**

DANIEL BULLA, ALBA LARRE BORGES, RAQUEL PONCE DE LEON, AND MARIO MEDICI

**91. Drug-Induced Autonomic Dysfunction**

NEAL L. BENOWITZ

Importance of Aging 336

Drug Interactions 336

Autonomic Neuropathy Produced by Specific

Chemicals and Drugs 337

---

PART**XI****ORTHOSTATIC INTOLERANCE****92. Neuropathic Postural Tachycardia Syndrome**

PHILLIP A. LOW

Clinical Features 341

Quality of Life 341

Evidence of Peripheral Denervation 341

Other Pathophysiologic Studies 341

Follow-up 342

Management 342

**93. Hyperadrenergic Postural Tachycardia Syndrome**

SIMI VINCENT AND DAVID ROBERTSON

**94. Hypovolemia Syndrome**

FETNAT FOUD-TARAZI

Blood Volume and Syncope 346

Relation between Chronic Global Blood Volume

Depletion and Neurocardiogenic Response to

Upright Posture 347

Dynamics of Postural Blood Volume Shifts	347
Clinical Features of Chronic Idiopathic Hypovolemia	
Hypovolemia	347
Hemodynamic Profile of Chronic Idiopathic Hypovolemia	348
Neurohumoral Indexes of Chronic Idiopathic Hypovolemia	348
Possible Mechanisms of Chronic Idiopathic Hypovolemia	348
Response to Therapy	349
Future Considerations	349

**PART****XII****OTHER CLINICAL CONDITIONS****95. Disorders of Sweating**

ROBERT D. FEALEY

Hypohidrosis and Anhidrosis	354
Distal Anhidrosis	356
Global Anhidrosis	356
Dermatomal, Focal, or Multifocal Anhidrosis	356
Segmental Anhidrosis	356
Hemianhidrosis	356

**96. Male Erectile Dysfunction**

DOUGLAS F. MILAM

Mechanism of Erection	359
Etiologic Factors of Erectile Dysfunction	359
Neuromuscular Junction Disorders	359
Neurogenic Erectile Dysfunction	360
Endocrine Disorders	360
Medical and Surgical Treatment	360

**97. Sleep-Disordered Breathing and Autonomic Failure**

SUDHANSU CHOKROVERTY

Sleep-Disordered Breathing in Autonomic Failure	362
Diagnosis	364
Treatment	364
General Measures and Medical Treatment	364
Mechanical Treatment	364
Surgical Treatment	365

**98. Hypoadrenocorticism**

DAVID H. P. STREETEN

Effects of Autonomic Activity on Adrenocortical Secretion	366
Effects of Hypoadrenocorticism on Autonomic Failure	366

**99. Mastocytosis**

L. JACKSON ROBERTS, II

Mastocytosis and Allied Activation Disorders of the Mast Cell	368
Symptoms and Signs	368
Mast Cell Mediators Responsible for the Symptoms and Signs	368
Diagnosis	369
Summary	369

**100. Cocaine Overdose**

WANPEN VONGPATANASIN AND RONALD G. VICTOR

Effects of Cocaine on the Peripheral Circulation	370
Autonomic Effects of Cocaine on the Heart	370
Effects of Cocaine on Thermoregulation	371
Treatment of Cocaine Overdose	371

**101. Sympathetic Nervous System and Pain**

WILFRID JÄNIG

Sympathetic-Afferent Coupling Depending on Activity in Sympathetic Neurons: Hypotheses Driven by Clinical Observations	374
Role of Sympathetic Nervous System in Generation of Pain and Hyperalgesia During Inflammation: Hypotheses Developed on the Basis of Experiments in Behavioral Animal Models	374
Cutaneous Mechanical Hyperalgesia Elicited by the Inflammatory Mediator Bradykinin	375
Cutaneous Hyperalgesia Generated by Nerve Growth Factor	375
Mechanical Hyperalgesic Behavior Generated by Activation of the Sympathoadrenal System (Adrenal Medulla)	375

**102. Baroreflex Functioning in Monogenic Hypertension**

FRIEDRICH C. LUFT

Autosomal-Dominant Hypertension with Brachydactyly	377
--	-----

Neurovascular Contact	378
Baroreflex Testing	378
Invasive Baroreflex Testing	378
Comparisons with Patients Who have Essential Hypertension	379
Lessons from Monogenic Hypertension	380

**103. Carcinoid Tumors**

KENNETH R. HANDE

**104. Chronic Fatigue and the Autonomic Nervous System**

ROY FREEMAN

Chronic Fatigue Syndrome, Orthostatic Intolerance, and Neurally Mediated Syncope	385
Chronic Fatigue Syndrome, Postural Tachycardia, and Orthostatic Intolerance	386
Pathophysiology of Postural Tachycardia	386
Conclusion	386

**105. Paraneoplastic Autonomic Dysfunction**

RAMESH K. KHURANA

Brainstem Dysfunction Syndrome	388
Morvan Syndrome	388
Subacute Sensory Neuronopathy	388
Enteric Neuronopathy	388
Autonomic Neuropathy	388
Lambert-Eaton Myasthenic Syndrome	389
Diagnosis	389
Treatment	390

**106. Panic Disorder**

MURRAY ESLER, MARLIES ALVARENGA, DAVID KAYE,  
 GAVIN LAMBERT, JANE THOMPSON, JACQUI HASTINGS,  
 ROSEMARY SCHWARZ, MARGARET MORRIS, AND  
 JEFF RICHARDS

Resting Sympathetic Nervous System Function in Panic Disorder	391
Sympathetic Nervous Activity and Epinephrine Secretion Rates	391
Epinephrine Cotransmission in Sympathetic Nerves	391
Reduction in Neuronal Norepinephrine Reuptake by Sympathetic Nerves	392
Autonomic Nervous Changes During a Panic Attack	392
Sympathetic Nerve Firing and Secretion of Epinephrine	392
Release of Neuropeptide Y	393
Mediating Autonomic Mechanisms of Cardiac Risk During a Panic Attack	393

---

**PART**  
**XIII**  
**MANAGEMENT OF AUTONOMIC DISORDERS**

**107. Hypoglycemic Associated Autonomic Dysfunction**

DARLEEN A. SANDOVAL AND STEPHEN N. DAVIS

**108. Surgical Sympathectomy**

EMILY M. GARLAND

**109. Physical Measures**

WOUTER WIELING

Physical Counter Maneuvers	403
Leg-Crossing	403
Squatting	403
External Support	404
Conclusion	406

**110. Treatment of Orthostatic Hypotension: Nutritional Measures**

JENS JORDAN

Water: A Pressor Agent	407
Caffeine	408
Tyramine	409
Sodium	409
Licorice	409
Nutritional Treatment of Supine Hypertension	409

**111. Fludrocortisone**

ROSE MARIE ROBERTSON

**112. Midodrine and Other Sympathomimetics**

JANICE L. GILDEN

Midodrine	413
Mechanism of Action	413
Pharmacology	413
Efficacy	413
Adverse Effects and Disadvantages	414
Dosing	414
Ephedrine/Other $\alpha$ Agonists	414
Mechanism of Action	414

Adverse Events and Disadvantages 414  
Dosing 415

Clinical Role of Acupuncture 427  
Outstanding Issues in Acupuncture Research 427

### 113. Dihydroxyphenylserine

ROY FREEMAN

Precursor Therapy for Orthostatic Hypotension 416

### 114. Adrenergic Agonists and Antagonists in Autonomic Failure

ROY FREEMAN

Sympathomimetic Agents 419  
Clonidine 420  
Yohimbine 420

### 115. Erythropoietin in Autonomic Failure

ITALO BIAGGIONI

Modulation of Erythropoietin Production by the  
Autonomic Nervous System 421  
The Anemia of Autonomic Failure 421  
Recombinant Human Erythropoietin in the  
Treatment of Orthostatic Hypotension 421

### 116. Bionic Baroreflex

TAKAYUKI SATO, ANDRÉ DIEDRICH, AND KENJI SUNAGAWA

Bionic Baroreflex System 423  
Theoretic Background 423  
Implementation of Algorithm of Artificial Vasomotor  
Center in Bionic Baroreflex System 423  
Efficacy of Bionic Baroreflex System 423  
Epidural Catheter Approach for Human Bionic  
Baroreflex System 424  
Clinical Implications 425

### 117. Acupuncture

JOHN C. LONGHURST

Western Understanding of Acupuncture 426  
Neurologic Substrate 426

PART

## XIV

### EXPERIMENTAL AUTONOMIC NEUROSCIENCE

#### 118. Autonomic Disorders in Animals

MATTHEW J. PICKLO, SR.

Sympathectomy 433  
Surgical Sympathectomy 433  
Anti-Nerve Growth Factor Immunosympathectomy 433  
Immune-Mediated Sympathectomy 433  
Chemical Sympathectomy 433  
Immunotoxin Sympathectomy 434  
Pathologic Autonomic Failure in Animals 434

#### 119. Transgenic Strategies in Autonomic Research

KAZUTO KOBAYASHI AND TOSHIHARU NAGATSU

Transgenic Animal Model 435  
Experimental Strategy of Immunotoxin-Mediated Cell  
Targeting Technique 435  
Model for Autonomic Neuropathy 435  
Future Aspects 436

#### 120. Mouse Homologous Recombination Models

NANCY R. KELLER

Index 449