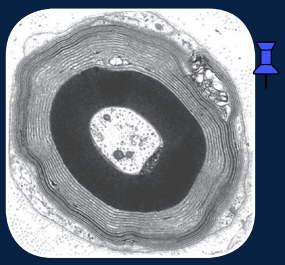

PERIPHERAL NERVE DISORDERS

Pathology and Genetics

Volume Editors
Jean-Michel Vallat and Joachim Weis

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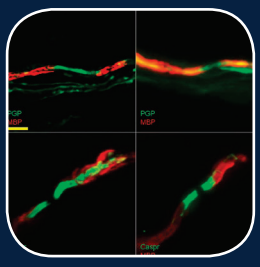
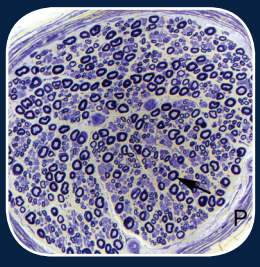
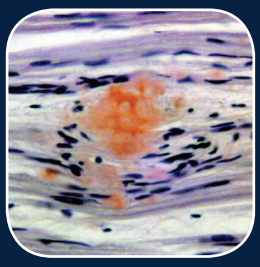
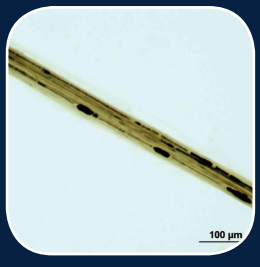
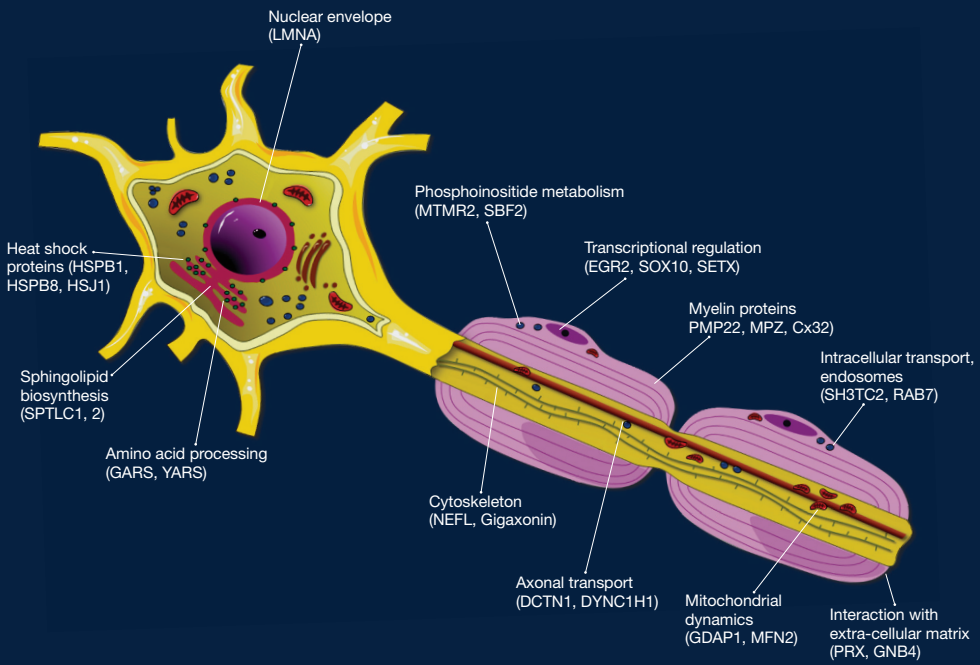
Françoise Gray and Katy Keohane











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Peripheral nerve disorders: pathology and genetics

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Foreword

It is exciting to welcome *Peripheral Nerve Disorders: Pathology and Genetics*. Like most future readers, I was not involved in the choice of authors and topics so it will be fun to explore the contents of this textbook. With you, I will enjoy seeing what topics are covered, new insights and mechanisms revealed, and adequacy of the illustrations. I hope and expect to be pleasantly surprised by the quality of the book, because I am familiar with many of the authors who are known for their contributions to the peripheral neuropathy field.

A quick look at the chapter headings indicates that the book will emphasize pathologic alterations and molecular genetics. To give these subjects context there will also be extensive descriptions of clinical disorders. This restricted approach probably makes sense because as we found (I and P. K. Thomas) it is increasingly difficult to review the whole subject of the neurobiology and diseases of the peripheral nervous system in a two-volume set of books as we attempted to do in our four editions of *Peripheral Neuropathy* (W. B. Saunders and Elsevier, Inc. 1975, 1984, 1993, and 2005). In confronting the issue of the breadth and complexity of knowledge about the peripheral nervous system, Co-editors of *Companion to Peripheral Neuropathy* (Elsevier, Inc., 2010) focused on new topics of interest to neuromuscular physicians (e.g., MRI targeted fascicular nerve biopsy, pathologic alterations, especially of focal nerve lesions and genetic topics). The present textbook edited by Vallat, Weis, Gray, and Keohane made the sensible decision to focus on pathology and genetics on the background of clinical disorders.

Europeans have contributed in a major way to the contents of this text. This is entirely reasonable considering the historic role Europeans have played in the history of peripheral nerve discovery (e.g., Remak; Virchow; Waller; Ranvier; Gombault and Mallet; Charcot, Marie, and Tooth; Friedreich; Aran and Duchenne; Cajal and Krücke – to name only a few).

From reading the Contents list, I judge that molecular genetic abnormalities are described by known clinical patterns of involvement. For the clinician it is helpful to classify neuropathies by which classes of neurons (fibers) are affected, by clinical and physiologic characterization of the pathologic abnormalities, and by the temporal pattern of involvement. With increasingly detailed information about molecular genetic abnormalities, it will be necessary to relate these genetic derangements to known clinical patterns of involvement. It is likely that, in a short period of time, chips with diverse multiple probes representing different genetic disorders will be available to decrease confusion.

Finally, I thank the authors and John Wiley & Sons, Ltd for their willingness to produce a textbook at this time, knowing that the writing of medical textbooks no longer provides high financial rewards. Hopefully, many readers will express their thanks by buying the book in print or online.

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Preface

With this book, the International Society of Neuropathology is devoting a volume of the established series of "Pathology and Genetics" textbooks to the pathology of peripheral nerve diseases. It is regrettable but true that nerve biopsy has become less frequent in recent years, so neuropathologists have less experience than before in this technique. The knowledge accrued is diminishing, with long term implications for its sustainability. This also applies to electron microscopic (EM) examination. EM requires a dedicated team and elaborate instrumentation, and is thus nowadays often regarded as too expensive.

These views are held even though nerve biopsy (with electron microscopy) can provide a diagnosis, can point to a disease mechanism that will guide treatment, and can redirect investigation toward a hereditary neuropathy with implications for genetic counseling. For example, when neuropathy develops in patients undergoing chemotherapy for a hematological disorder, the differential diagnosis includes a neurotoxic effect of treatment or spread of the underlying process such as immunoglobulin or amyloid deposition or infiltration of malignant cells to directly involve nerves. Defining the exact pathological process leads to specific therapeutic intervention such as reduction of toxic therapy, or conversely, modification of immune therapy, a requirement for bone marrow transplant. As another example, even though clinical and electrophysiological criteria are useful for the diagnosis of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or peripheral nerve vasculitis, in practice these criteria are often not sufficient; nerve biopsy will lead to diagnosis and treatment of patients with atypical clinical and neurophysiological features.

Regarding the hereditary neuropathies, correlation of histological and genetic findings is essential for a number of reasons. It is accepted that mutations of more than 60 genes are likely to be responsible for hereditary neuropathies. Nowadays the diagnosis is achieved in many cases by molecular genetic analysis; however, nerve biopsy can be helpful in identifying the decisive pathomechanisms especially in the growing number of cases where next generation sequencing techniques are employed and often reveal several candidate gene defects. Nerve biopsy will also uncover concomitant (e.g., inflammatory) pathology. Moreover, it is expected to provide clues for eventual therapeutic interventions, for example, by defining subgroups of patients. Finally, nerve biopsy analysis has contributed greatly to the understanding of the pathophysiology of neuropathies including hereditary neuropathies. Nerve biopsy studies will even increase in importance with the ever growing number of animal models that need to be correlated with and adjusted to the human pathology. Thus, contrary to earlier oversimplified views, at this point in time, it is not true that molecular biology will replace pathology. For a certain number of patients, all these techniques are very useful and complement each other, it being understood that nerve biopsy is an invasive process, so the decision to undertake it must be discussed on a case-by-case basis.

For the purpose of this volume, we felt it was important to devote a special chapter to skin biopsy in the investigation of small fiber or painful sensory neuropathies, given that this technique essentially studies unmyelinated intra-epidermal nerve fibers and that skin biopsies for this purpose are rapidly increasing in number.

We also included some clinical, electrophysiological, and other ancillary investigative data, depending on the context of the entities discussed. In practice integrating these combined variables together with the nerve biopsy results is key to a correct diagnosis. In fact this monograph is hoped to be of interest to all those involved in the study of peripheral nerve disorders: clinicians, neurophysiologists, neuropathologists, and molecular biologists.

Of course we have been able to benefit from the efforts of numerous international authors who wrote about their own area of expertise in human peripheral neuropathies, often also summarizing studies in animal models. Each chapter is accompanied by quality

illustrations of the lesions described in the text. The interactions with the authors have been most productive, interesting, and constructive, and we sincerely thank them all.

We must also express our huge gratitude to Professors Francoise Gray and Katy Keohane for their editorial skills and patience and for their input into every chapter, to improve the overall style and English, and for ensuring that a quality volume was produced.

Jean-Michel Vallat and Joachim Weis
Limoges and Aachen

Abbreviations

(genes are written in italics)

α-Gal	Alpha-Galactosidase
α -NAGA	α -N-Acetylgalactosaminidase
AARS	Alanyl-tRNA-synthetase
AAV	ANCA-Associated Vasculitides
ABCA1	ATP-Binding Cassette Transporter A1
ACA	Acrodermatitis chronica atrophicans
ACE	Angiotensin-Converting Enzyme
ACR	American College of Rheumatology
AD	Autosomal Dominant
ADCA	Autosomal dominant spinocerebellar atrophies
AFB	Acid Fast Bacilli
AFLP	Amplified Fragment Length Polymorphism
AIDP	Acute Inflammatory Demyelinating Polyneuropathy
ALN	Alcohol Related Neuropathy
ALS	Amyotrophic Lateral Sclerosis
ALS11	Amyotrophic Lateral Sclerosis of Type 11
AMAN	Acute Motor Axonal Neuropathy
AMP	Adenosine Monophosphate
AMSAN	Acute Motor and Sensory Axonal Neuropathy
ANA	Antinuclear Antibody
ANCA	Anti-Neutrophil Cytoplasmic Antibody
ANS	Ataxia Neuropathy Spectrum
APBD	Adult Polyglucosan Body Disease
APC	antigen-Presenting Cell
Apo	Apolipoproteins
ApoA-I	Apolipoprotein A-I
ApoB	Apolipoprotein B
AR	Autosomal Recessive
AR CMT	Autosomal Recessive Charcot–Marie–Tooth Neuropathy
AR CMT1	Autosomal Recessive Charcot–Marie–Tooth Neuropathy, of Demyelinating Type
AR CMT2	Autosomal Recessive Charcot–Marie–Tooth Neuropathy, of Axonal Type
ARHGEF10	Rho Guanine-Nucleotide Exchange [GEF] Factor 10
ARSA	Arylsulfatase A
ATL1	Atlastin 1
B.b	Borrelia burgdorferi
BBW rats	Biobreeding Wor rats
BDNF	Brain Derived Neurotrophic Factor
BEAR	Brain Stem Evoked Auditory Responses
CAN	Congenital Amyelinating Neuropathy
CANOMAD	Chronic Ataxic Neuropathy, Ophthalmoplegia, IgM paraprotein, cold Agglutinins and Disialosyl antibodies
CCT	Cytosolic Chaparonin-Containing T-complex peptide
CD4	Cluster of Differentiation 4
CES	Cholesterol Emboli Syndrome
CETP	Cholesteryl Ester Transfer Protein
CG	Cryoglobulinemia
CHCC	Chapel Hill Consensus Conference
CHIKV	Chikungunya Virus
CHN	Congenital Hypomyelination Neuropathy
CHS	Chediak–Higashi Syndrome
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy/Polyradiculoneuropathy
CIM	Critical Illness Myopathy
CIP	Critical Illness Polyneuropathy
CIPA	Congenital Insensitivity to Pain with Anhydrosis
CIPN	Chemotherapy-Induced Toxic Peripheral Neuropathies
CMAP	Compound Muscle Action Potential(s)
CMT	Charcot–Marie–Tooth
CMT DI	Charcot–Marie–Tooth Neuropathy, Autosomal Dominant, of Intermediate type
CMT RIA	Charcot–Marie–Tooth Neuropathy, Autosomal Recessive, of Intermediate type A
CMT X	X-linked Charcot–Marie–Tooth Neuropathy
CMT	Charcot–Marie–Tooth disease/neuropathy
CMT1	Charcot–Marie–Tooth neuropathy, autosomal dominant, of demyelinating type
CMT2	Charcot–Marie–Tooth neuropathy, autosomal dominant, of axonal type/type 2
CMT4	Charcot–Marie–Tooth neuropathy, autosomal recessive, of demyelinating type
CMTID	Intermediate Charcot–Marie–Tooth
CMTX	X-linked Charcot–Marie–Tooth
CMV	Cytomegalovirus
CNM	Centronuclear Myopathy
CNS	Central Nervous System
CNTF	Ciliary Neuron Trophic Factor
COPD	Chronic Obstructive Pulmonary Disease
COX	Cytochrome c OXidase
CRMP5	Collapsin Response Mediator Protein 5
CSAP	Compound Sensory Action Potential
CSF	Cerebrospinal Fluid