DIABETIC NEUROPATHY: CLINICAL MANAGEMENT, SECOND EDITION

CONTEMPORARY DIABETES

ARISTIDIS VEVES, MD, DSc

SERIES EDITOR

Diabetic Neuropathy: Clinical Management, Second Edition, edited by Aristidis Veves, MD, DSC, and Rayaz A. Malik, MBChB, PhD, 2007

The Diabetic Foot, Second Edition, edited by Aristidis Veves, MD, DSC, John M. Giurini, DPM, and Frank W. LoGerfo, MD, 2006

The Diabetic Kidney, edited by PEDRO CORTES, MD, AND CARL ERIK MOGENSEN, MD, 2006 Obesity and Diabetes, edited by Christos S. Mantzoros, MD, 2006

DIABETIC NEUROPATHY

Clinical Management, Second Edition

Edited by

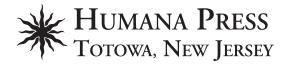
ARISTIDIS VEVES, MD, DSc

Beth Israel Deaconess Medical Center Harvard Medical School Boston, MA

and

RAYAZ A. MALIK, MBChB, PhD

Manchester Royal Infirmary and University of Manchester, Manchester, UK



© 2007 Humana Press Inc. 999 Riverview Drive, Suite 208 Totowa, New Jersey 07512

www.humanapress.com

All rights reserved. No part of this book may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, microfilming, recording, or otherwise without written permission from the Publisher.

The content and opinions expressed in this book are the sole work of the authors and editors, who have warranted due diligence in the creation and issuance of their work. The publisher, editors, and authors are not responsible for errors or omissions or for any consequences arising from the information or opinions presented in this book and make no warranty, express or implied, with respect to its contents.

Due diligence has been taken by the publishers, editors, and authors of this book to assure the accuracy of the information published and to describe generally accepted practices. The contributors herein have carefully checked to ensure that the drug selections and dosages set forth in this text are accurate and in accord with the standards accepted at the time of publication. Notwithstanding, as new research, changes in government regulations, and knowledge from clinical experience relating to drug therapy and drug reactions constantly occurs, the reader is advised to check the product information provided by the manufacturer of each drug for any change in dosages or for additional warnings and contraindications. This is of utmost importance when the recommended drug herein is a new or infrequently used drug. It is the responsibility of the treating physician to determine dosages and treatment strategies for individual patients. Further it is the responsibility of the health care provider to ascertain the Food and Drug Administration status of each drug or device used in their clinical practice. The publisher, editors, and authors are not responsible for errors or omissions or for any consequences from the application of the information presented in this book and make no warranty, express or implied, with respect to the contents in this publication.

Production Editor: Michele Seugling

Cover Illustration: Figure 3, Chapter 17, by Michael Polydefkis, "Punch Skin Biopsy in Diabetic Neuropathy."

Cover design by Karen Schulz

For additional copies, pricing for bulk purchases, and/or information about other Humana titles, contact Humana at the above address or at any of the following numbers: Tel.: 973-256-1699; Fax: 973-256-8341, E-mail: orders@humanapr.com; or visit our Website: www.humanapress.com

This publication is printed on acid-free paper.

ANSI Z39.48-1984 (American National Standards Institute) Permanence of Paper for Printed Library Materials.

Photocopy Authorization Policy:

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Humana Press Inc., provided that the base fee of US \$30.00 is paid directly to the Copyright Clearance Center at 222 Rosewood Drive, Danvers, MA 01923. For those organizations that have been granted a photocopy license from the CCC, a separate system of payment has been arranged and is acceptable to Humana Press Inc. The fee code for users of the Transactional Reporting Service is: [978-1-58829-626-9/07 \$30.00].

Printed in the United States of America. 10 9 8 7 6 5 4 3 2 1

e-ISBN 978-1-59745-311-0

Library of Congress Control Number: 2007932486

To my wife Maria and my son George.

— Aristidis Veves

To my wife Robina and beautiful daughters: Imaan, Hana and Ayesha.

— Rayaz A. Malik

PREFACE

It has been almost a decade since the first edition of *Clinical Management of Diabetic Neuropathy* was published. Since then, all societies have seen an explosion in obesity and diabetes. As a result, there is also an explosion in long-term diabetes complications, including diabetic neuropathy. Diabetic neuropathy therefore remains a major health problem that has not only serious consequences for the patient but also carries a significant financial burden for the health care-providing organizations of every society.

Another change that has taken place since the last edition is the accumulation of considerable data that has drastically expanded our knowledge regarding the pathophysiology and natural history of the disease. Unfortunately, this expansion in our knowledge has not been accompanied by success in treating diabetic neuropathy. Thus, considerable clinical research efforts that employed various therapeutic modalities, including aldose reductase inhibitors, nerve growth factor, and PKC beta inhibitors, failed to provide positive results and are currently not expected to gain approval for clinical use.

For Diabetic Neuropathy: Clinical Management, Second Edition, we have made every effort to reflect the above changes. We have included new chapters that focus more detail on the pathophysiology of the disease, and we have also expanded the sections regarding the diagnosis and the management of the various presentations of diabetic neuropathy. We feel very fortunate that we were able to recruit all leading authorities in their respective fields, and we believe that this has tremendously increased the quality of this edition. We therefore hope that this edition will be helpful not only to the practicing clinicians but also to researchers who would like to examine this condition in more detail.

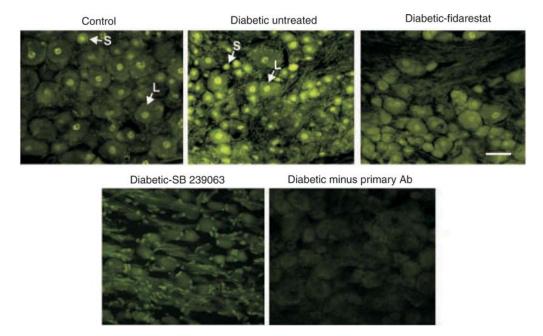
We would like to sincerely thank all of the contributors to *Diabetic Neuropathy: Clinical Management, Second Edition*, as it is their hard work that has resulted in this successful textbook. We would like also to thank Humana Press for their trust in our abilities and all of their help in accomplishing this project.

Aristidis Veves, MD, DSc Rayaz A. Malik, MBChB, PhD

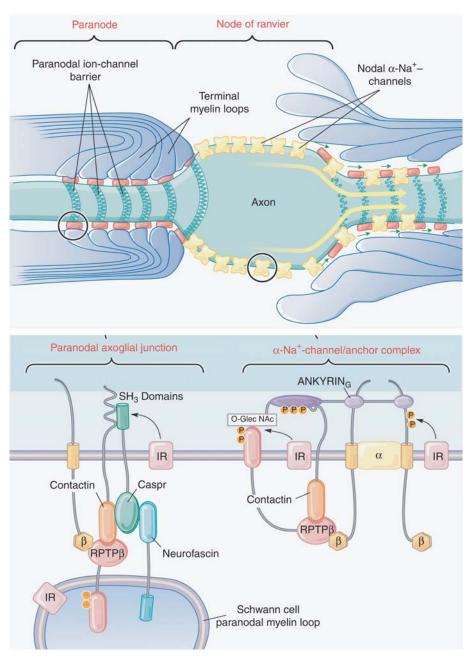
LIST OF COLOR IMAGES

The images listed below appear in the color insert within the text.

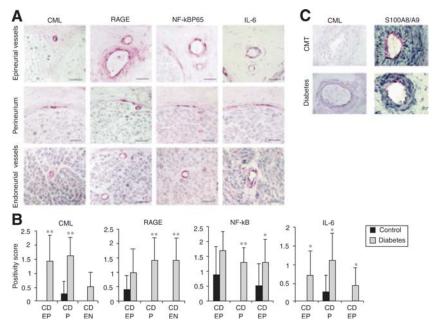
- **Color Plate 1.** Fig. 5, Chapter 6: Bar charts and Western blots showing the effects of insulin, fidarestat and the p38 mitogen-activated protein kinases inhibitor, SB239063. (See complete caption on p. 103.)
- Color Plate 2. Fig. 5, Chapter 8: Axoglial dysjunction is a characteristic degenerative change of type 1 DPN. (See complete caption on p. 142.)
- Color Plate 3. Fig. 2, Chapter 13: (A) Localization of CML. (B) Quantification of staining intensities of epineurial vessels, perineurium, and endoneurial vessels. (C) Comparison of the staining intensity for CML and the receptor for advanced glycation end products. (See complete caption on p. 234.)
- **Color Plate 4.** Fig. 3, Chapter 17: Normal human epidermal and dermal innervation visualized with confocal microscopy. (See complete caption on p. 297.)
- **Color Plate 5.** Fig. 5, Chapter 17: (A) Method to measure collateral sprouting of human epidermal nerve fibers. (B) Example of collateral sprouting. (See complete caption on p. 302.)
- **Color Plate 6.** Fig. 7, Chapter 17: For each subject, a regression line from postcapsaicin time-points is generated and the slope of this line is used as the rate of regeneration. (See complete caption on p. 304.)



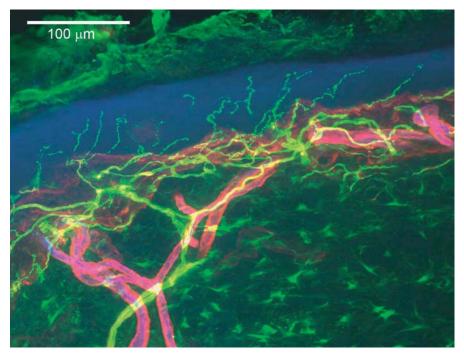
Color Plate 1. Bar charts and Western blots showing the effects of insulin, fidarestat and the p38 mitogen-activated protein kinases inhibitor, SB239063. (Fig. 5, Chapter 6; *see* complete caption on p. 103.)



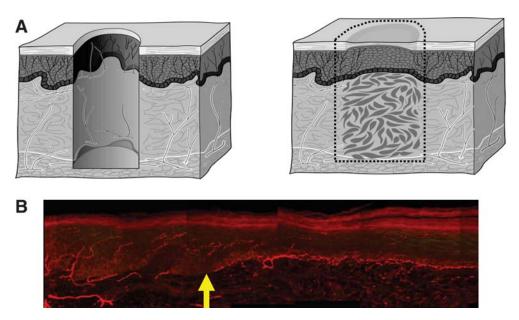
Color Plate 2. Axoglial dysjunction is a characteristic degenerative change of type 1 DPN. (Fig. 5, Chapter 8; *see* complete caption on p. 142.)



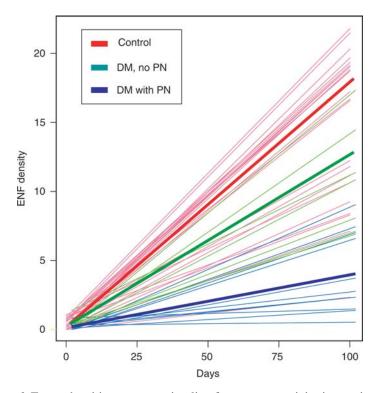
Color Plate 3. (A) Localization of CML. (B) Quantification of staining intensities of epineurial vessels, perineurium, and endoneurial vessels. (C) Comparison of the staining intensity for CML and the receptor for advanced glycation end products. (Fig. 2, Chapter 13; *see* complete caption on p. 234.)



Color Plate 4. Normal human epidermal and dermal innervation visualized with confocal microscopy. (Fig. 3, Chapter 17; *see* complete caption on p. 297.)



Color Plate 5. (A) Method to measure collateral sprouting of human epidermal nerve fibers. **(B)** Example of collateral sprouting. (Fig. 5, Chapter 17; *see* complete caption on p. 302.)



Color Plate 6. For each subject, a regression line from postcapsaicin time-points is generated and the slope of this line is used as the rate of regeneration. (Fig. 7, Chapter 17; *see* complete caption on p. 304.)

Contents

Preface	vii
	ages viii
	xi
1	Historical Aspects of Diabetic Neuropathies
2	The Epidemiology of Diabetic Neuropathy
3	Genomics of Diabetic Neuropathy
4	Transgenic and Gene Knockout Analysis of Diabetic Neuropathy
5	Hyperglycemia-Initiated Mechanisms in Diabetic Neuropathy 69 <i>Irina G. Obrosova</i>
6	Effectors—Sonic Hedgehog and p38 Mitogen-Activated Protein Kinase
7	Neuronal and Schwann Cell Death in Diabetic Neuropathy 113 James W. Russell, Rita M. Cowell, and Eva L. Feldman
8	Metabolic-Functional-Structural Correlations in Somatic Neuropathies in the Spontaneously Type 1 and Type 2 Diabetic BB-Rats
9	Experimental Diabetic Autonomic Neuropathy
10	Spinal Cord: Structure and Function in Diabetes
11	Diabetic Encephalopathy
12	Microangiopathy, Diabetes, and the Peripheral Nervous System
13	Pathogenesis of Human Diabetic Neuropathy
14	Clinical Features of Diabetic Polyneuropathy

Contents x

Aristidis Veves and Antonella Caselli

Micro- and Macrovascular Disease in Diabetic Neuropathy 259

15

16	Clinical Diagnosis of Diabetic Neuropathy
17	Punch Skin Biopsy in Diabetic Neuropathy
18	Aldose Reductase Inhibitors for the Treatment of Diabetic Neuropathy
19	Other Therapeutic Agents for the Treatment of Diabetic Neuropathy
20	Pathophysiology of Neuropathic Pain
21	Treatment of Painful Diabetic Neuropathy
22	Focal and Multifocal Diabetic Neuropathy
23	Hypoglycemia and the Autonomic Nervous System
24	Cardiovascular Autonomic Neuropathy
25	Postural Hypotension and Anhidrosis
26	Gastrointestinal Syndromes Due to Diabetes Mellitus
27	Genitourinary Complications
28	Management of Diabetic Foot Complications
Index	

CONTRIBUTORS

MD

- MISHA-MIROSLAV BACKONJA Department of Neurology, School of Medicine and Public Health, University of Wisconsin—Madison, Madison, WI
- Geert Jan Biessels Department of Neurology of the Rudolf Magnus Institute for Neuroscience, University Medical Centre, Utrecht, The Netherlands
- Andrew J. M. Boulton Department of Medicine, Manchester Royal Infirmary, Manchester, UK
- EDWARD J. BOYKO VA Puget Sound Healthcare System, Seattle, WA
- Rebecca C. Burnand Faculty of Life Sciences, University of Manchester, Manchester, UK
- Nigel A. Calcutt Department of Pathology, University of California San Diego, La Jolla, CA
- Antonella Caselli Microcirculation Lab, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA
- Sookja K. Chung Department of Anatomy, The University of Hong Kong, Hong Kong, SAR China
- Stephen S. Chung Department of Physiology, The University of Hong Kong, Hong Kong, SAR China
- RITA M. COWELL Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham, Birmingham, AL
- Andrew G. Demaine Molecular Medicine Research Group, Peninsula Medical School, Plymouth, UK
- Eva L. Feldman Department of Neurology, University of Michigan, Ann Arbor, MI Roy Freeman Autonomic Lab, Beth Israel Deaconess Medical Center, Boston MA John W. Griffin Department of Neurology, The Johns Hopkins Hospital, Baltimore,
- Corinne G. Jolivalt Department of Pathology, University of California San Diego, La Jolla. CA
- Hideki Kamiya Department of Pathology, Wayne State University, Detroit, MI
- PHILLIP A. Low Department of Neurology, Mayo Clinic, Rochester, MN
- Thomas E. Lyons Division of Podiatric Medicine and Surgery, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA
- Juan-R. Malagelada Digestive System Research Unit, Hospital General Vall d'Hebron, Autonomous University of Barcelona, Barcelona, Spain
- RAYAZ A. Malik Division of Cardiovascular Medicine, University of Manchester, Manchester, UK
- Justin McArthur Department of Neurology, The Johns Hopkins Hospital, Baltimore, MD
- Andrew P. Mizisin Department of Pathology, University of California San Diego, La Jolla, CA
- Irina G. Obrosova Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA

xii Contributors

Henri Pharson • Department of Internal Medicine, Strelitz Diabetes Institutes, Eastern Virginia Medical School, Norfolk, VA

- Gary L. Pittenger Department of Internal Medicine, Strelitz Diabetes Institutes, Eastern Virginia Medical School, Norfolk, VA
- MICHAEL POLYDEFKIS Department of Neurology, The Johns Hopkins Hospital, Baltimore, MD
- Sally A. Price Faculty of Life Sciences, University of Manchester, Manchester, UK James W. Russell Department of Neurology, University of Maryland, Baltimore, MD
- GÉRARD SAID Service de Neurologie and Laboratoire Louis Ranvier, Hopital de Bicetre, Assistance Publique-Hopitaux de Paris and Universite Paris-sud, Paris, France
- Anders A. F. Sima Departments of Pathology and Neurology and The Morris Hood Comprehensive Diabetes Centre, Wayne State University, Detroit, MI
- Nalini Singh VA Puget Sound Health Care System, Seattle, WA
- VLADIMIR SKLJAREVSKI Lilly Research Laboratories, Indianapolis, IN
- Martin J. Stevens Division of Medical Sciences, University of Birmingham, Birmingham, UK
- Christian Stief LMU University of Munich Hospital, Clinic for Urology, Munich, Germany
- Goran Sundkvist Department of Endocrinology, University of Lund, Malmo University Hospital, Sweden
- Solomon Tesfaye \bullet Diabetes Research Unit, Royal Hallamshire Hospital, Sheffield, UK
- David R. Tomlinson Faculty of Life Sciences, University of Manchester, Manchester, UK
- Jagdeesh Ullal Department of Internal Medicine, Strelitz Diabetes Institutes, Eastern Virginia Medical School, Norfolk, VA
- Aristidis Veves Microcirculation Lab, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA
- AARON I. VINIK Department of Internal Medicine, Strelitz Diabetes Institutes, Eastern Virginia Medical School, Norfolk, VA
- Stephanie Wheeler VA Puget Sound Health Care System, Seattle, WA
- Bingmei Yang Molecular Medicine Research Group, Peninsula Medical School, Plymouth, UK
- Weixian Zhang Department of Pathology, Wayne State University, Detroit, MI
- Dan Ziegler German Diabetes Center, Leibniz Center at the Heinrich Heine University, Institute for Clinical Diabetes, Düsseldorf, Germany
- Douglas W. Zochodne Department of Clinical Neurosciences, Foothills Medical Center, University of Calgary, Alberta, Canada