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Andrew G. Engel
Clara Franzini-Armstrong

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EDITORS

Andrew G. Engel, M.D.
William L. McKnight Professor of Neuroscience
Mayo Clinic College of Medicine
Director, Neuromuscular Disease Research Laboratory
Consultant, Department of Neurology
Mayo Clinic
Rochester, Minnesota

Clara Franzini-Armstrong, Laurea
Professor, Department of Cell
and Developmental Biology
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

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To Our Families, Students, and Coworkers

for their support, advice, and encouragement

CONTRIBUTORS

Joseph Alroy, D.V.M. [24]*
Associate Professor of Pathology
Tufts University Schools of Medicine
and Veterinary Medicine
Boston, Massachussetts

Zohar Argov, M.D. [48]
Professor of Neurology
Department of Neurology
Hadassah University Hospital and Hebrew
University–Hadassah Medical School
Jerusalem, Israel

Betty Q. Banker, M.D. [30, 31, 52, 53, 70]
Emeritus Professor of Pathology
Dartmouth Medical College
Hanover, New Hampshire

Robert W. Banks, B.Sc., Ph.D., D.Sc. [21]
Lecturer
School of Biological and Biomedical Sciences
University of Durham
Durham, United Kingdom

Brenda L. Banwell, M.D., F.R.C.P.C. [25, 41]
Assistant Professor of Pediatric (Neurology)
Hospital for Sick Children
Toronto, Canada

David Barker, M.A., D.Phil., D.Sci. [21]
Emeritus Professor of Zoology
Department of Biological Sciences
University of Durham
Durham, United Kingdom

Kimby N. Barton, M.Sc. [14]
Associate Editor
Geriatrics & Aging Marketed Pharmaceuticals
Division
Marketed Health Products Directorate
Ottawa, Canada

Kurt G. Beam, Ph.D. [12]
Professor of Anatomy and Neurobiology
Department of Anatomy/Neurobiology
Colorado State University
Fort Collins, Colorado

Richard Bischoff, Ph.D. [3]
Professor Emeritus
Department of Anatomy and Neurobiology
Washington University School of Medicine
St. Louis, Missouri

Eduardo Bonilla, M.D. [58]
Professor of Clinical Neurology
and Clinical Pathology
Departments of Neurology and Pathology
Columbia University College of Physicians
and Surgeons
New York, New York

Carsten G. Bönnemann, M.D. [37]
Assistant Professor of Neurology and Pediatrics
Departments of Neurology and Pediatrics
The Children's Hospital of Philadelphia
Pennsylvania Muscle Institute, University of
Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Bernard Brais, M.D., M.Phil., Ph.D. [40]
Associate Professor
Department of Medicine
Faculté de Médecine de l'Université de Montréal
Montreal, Canada

M. D. Brown, Ph.D. [22]
School of Sport and Exercise Sciences
University of Birmingham
Birmingham, United Kingdom

Robert H. Brown, Jr., D.Phil., M.D. [68]
Professor of Neurology
Harvard Medical School
Professor of Neurology
Massachusetts General Hospital
Boston, Massachusetts

*The number(s) in brackets following the contributor name refer to chapter(s) authored or co-authored by the contributor.

Robert E. Burke, M.D. [5]
Laboratory of Neural Control
National Institute of Neurological Disorders and Stroke
National Institutes of Health
Bethesda, Maryland

Kate Bushby, M.D., F.R.C.P. [37]
Professor of Neuromuscular Genetics
Institute of Human Genetics
School of Clinical Medical Sciences
University of Newcastle upon Tyne
Newcastle, United Kingdom

Lucia I. Comi, M.D. [45]
Associate Professor of Cardiology
Department of Clinical and Experimental Medicine and Surgery
2nd Naples University
Naples, Italy

Roger W. Craig, Ph.D. [7]
Professor of Biology
University of Massachusetts Medical School
Worcester, Massachusetts

Marinos C. Dalakas, M.D. [51]
Chief, Neuromuscular Diseases Section
National Institute of Neurological Disorders and Stroke
National Institutes of Health
Bethesda, Maryland

Jasper R. Daube, M.D. [26]
Professor of Neurology
Department of Neurology
Mayo Clinic College of Medicine
Rochester, Minnesota

Marianne de Visser, M.D., Ph.D. [27, 39, 67]
Professor of Neuromuscular Diseases
Department of Neurology
Academic Medical Center
Amsterdam, The Netherlands

Stefano Di Donato, M.D. [57]
Director, Department of Research and Diagnostic
Director, Division of Biochemistry and Genetics
Istituto Nazionale Neurologico C. Besta
Milan, Italy

Salvatore DiMauro, M.D. [55, 58]
Lucy G. Moses Professor of Neurology
Department of Neurology
Columbia University College of Physicians and Surgeons
New York, New York

Peter James Dyck, M.D. [69]
Professor of Neurology and Roy E. and Merle Meyer Professor of Neuroscience
Peripheral Neuropathy Research Laboratory
Mayo Clinic College of Medicine
Rochester, Minnesota

S. Egginton, Ph.D. [22]
Department of Physiology
University of Birmingham Medical School
Birmingham, United Kingdom

Charles P. Emerson, Jr., Ph.D. [1]
Director, Boston Biomedical Research Institute
Watertown, Massachusetts

Andrew G. Engel, M.D. [15, 29, 30, 31, 34, 43, 49, 50, 53, 56, 64, 66]
William L. McKnight Professor of Neuroscience
Mayo Clinic College of Medicine
Director, Neuromuscular Disease Research Laboratory
Mayo Clinic
Rochester, Minnesota

Kevin M. Flanigan, M.D. [38]
Associate Professor
Departments of Neurology, Human Genetics, Pathology, and Pediatrics
University of Utah School of Medicine
Salt Lake City, Utah

Clara Franzini-Armstrong, Laurea, member N.A.S., F.R.S. [2, 3, 11, 19a]
Professor of Cell and Developmental Biology
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Alfred L. Goldberg, Ph.D. [23]
Professor of Cell Biology
Harvard Medical School
Boston, Massachussetts

Yale E. Goldman, M.D., Ph.D. [9]
Professor of Physiology and Director Pennsylvania Muscle Institute
Department of Physiology
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Manuel R. Gomez, M.D. [25]
Emeritus Professor of Pediatric Neurology
Department of Neurology
Mayo Clinic College of Medicine
Rochester, Minnesota

Robert C. Griggs, M.D. [42]
Professor and Chair of Neurology
University of Rochester School of Medicine and Dentistry
Rochester, New York

Ronald G. Haller, M.D. [28]
Professor of Neurology
Neuromuscular Center
Institute for Exercise and Environmental Medicine of Presbyterian Hospital
Departments of Neurology and Internal Medicine
University of Texas Southwestern Medical School and Veterans Affairs Medical Center
Dallas, Texas

C. Michel Harper, M.D. [63]
Professor of Neurology
Department of Neurology
Mayo Clinic College of Medicine
Rochester, Minnesota

Peter S. Harper M.D. [36]
Professor
Institute of Medical Genetics
University of Wales College of Medicine
Cardiff, Wales, United Kingdom

Ian K. Hart, Ph.D., F.R.C.P. [47]
Senior Lecturer in Neurology
University Department of Neurological Science
Walton Center for Neurology and Neurosurgery
Liverpool, United Kingdom

Stephen D. Hauschka, Ph.D. [1]
Professor
Department of Biochemistry
University of Washington School of Medicine
Seattle, Washington

Arthur P. Hays, M.D. [55]
Associate Professor of Clinical Neuropathology
Department of Pathology
Columbia University College of Physicians and Surgeons
New York, New York

Rochelle Hirschhorn M.D., F.A.C.M.G. [56]
Professor of Medicine, Cell Biology and Pediatrics
New York University School of Medicine
Department of Medicine/Division of Medical Genetics
New York, New York

Reinhard Hohlfeld, M.D. [32, 49, 64]
Professor of Neurology
Institute for Clinical Neuroimmunology
Ludwig Maximilians University of Munich
Munich, Germany

Earl Homsher, Ph.D. [8]
Professor of Physiology
Center for Health Science
University of California at Los Angeles
Los Angeles, California

Paul Horowicz, Ph.D.† [12]
Former Professor of Physiology and Chair
Department of Physiology
University of Rochester School of Medicine
Rochester, New York

Alan R. Horwitz, Ph.D. [19a]
Department of Cell Biology
University of Virginia
Health Sciences Center
Charlottesville Virginia

Anne Houdusse, Ph.D. [8]
Équipe Motilité Structurale
Centre National de la Recherche Scientifique
Institute Curie
Paris, France

†Deceased.

O. Hudlicka, M.D., Ph.D. [22]
Professor
Department of Physiology
University of Birmingham Medical School
Birmingham, United Kingdom

Maryann L. Huie, Ph.D. [56]
Research Associate Scientist
Department of Medicine
Division of Medical Genetics
New York University School of Medicine
New York, New York

R. Thomas Jagoe, M.B., B.S., Ph.D., M.R.C.P. [23]
Senior Lecturer
Department of Medicine
University of Liverpool
Liverpool, United Kingdom

G. Joost Jöbsis, M.D., Ph.D. [39]
Department of Neurology
Slotervaart Hospital
Amsterdam, The Netherlands

Karin Jurkat-Rott, M.D., Ph.D. [10, 46]
Assistant Professor
Department of Applied Physiology
Ulm University
Ulm, Germany

Henry J. Kaminski, M.D. [62]
Professor of Neurology and Neurosciences
Case Western Reserve University and Cleveland
Veterans Administration Center
Cleveland, Ohio

Alan M. Kelly, Ph.D., B.V.S.c, M.R.V.V.S. [4]
Dean Veterinary School
Professor of Pathology and Pathobiology
Member Pennsylvania Muscle Institute
University of Pennsylvania Veterinary School
Philadelphia, Pennsylvania

Christopher J. Klein, M.D. [69]
Assistant Professor of Neurology
Department of Neurology
Mayo Clinic College of Medicine
Rochester, Minnesota

Edwin H. Kolodny, M.D. [24]
Bernard A. and Charlotte Marden
Professor and Chair
Department of Neurology
New York University School of Medicine
New York, New York

Frank Lehmann-Horn, M.D., Ph.D. [10, 46]
Professor and Chair
Department of Applied Physiology
Ulm University
Ulm, Germany

Jon M. Lindstrom, Ph.D. [17]
Trustee Professor of Neuroscience and Professor
of Pharmacology
Medical School of the University of Pennsylvania
Philadelphia, Pennsylvania

David H. MacLennan, Ph.D., D.Sc., F.R.S.C., F.R.S. [14, 59]
J. W. Billes Professor of Medical Research
and University
Charles H. Best Institute
University of Toronto,
Toronto, Canada

Karl L. Magleby, Ph.D. [16]
Professor and Chair
Department of Physiology and Biophysics
University of Miami School of Medicine,
Miami, Florida

Nadir M. Maraldi, Ph.D. [35]
Professor of Histology and Chair, Department
of Anatomical Science
University of Bologna
Director of Research
Laboratory of Cell Biology
National Research Council and Institute
for Organ Transplants and Immunocytology
Rizzoli Orthopedic Institute
Bologna, Italy

Luciano Merlini, M.D. [35]
Neuromuscular Unit
Rizzoli Orthopedic Institute
Bologna, Italy

Jacqueline Mikol, M.D. [50]
Professor of Pathology
Denis Diderot University
Neuropathologist
Hopital Lariboisiere
Paris, France

Darren G. Monckton, Ph.D. [36]
Reader in Genetics
Institute of Biomedical and Life Sciences
University of Glasgow
Glasgow, United Kingdom

John Newsom-Davis, M.D. [47, 65]
Professor Emeritus
Department of Clinical Neurology
University of Oxford
Oxford, United Kingdom

Gerardo Nigro, M.D. [45]
Assistant Professor
Department of Cardiology
2nd Naples University
Naples, Italy

Giovanni Nigro, M.D. [45]
Professor and Chair of Internal Medicine
Gaetano Conte Academy
Naples, Italy

Kathryn North M.D., M.B.B.S., B.Sc (Med), F.R.A.C.P. [54]
Professor of Paediatrics and Child Health
Faculty of Medicine
University of Sydney
Head, Neurogenetics Research Unit
The Children's Hospital at Westmead
Sydney, Australia

Kinji Ohno, M.D., Ph.D. [66]
Assistant Professor
Department of Neurology
Mayo Clinic College of Medicine
Rochester, Minnesota

Eijiro Ozawa, M.D., Ph.D. [19b, 34]
Emeritus Director General National Institute of Neuroscience
National Center of Neurology and Psychiatry
Kodaira, Tokyo, Japan

Raúl Padrón, Ph.D. [7]
Senior Investigator
Department of Structural Biology
Venezuelan Institute for Scientific Research
Caracas, Venezuela

Audrey S. Penn, M.D. [60]
Emeritus Professor of Neurology
Department of Neurology
Columbia University College of Physicians and Surgeons
New York, New York
Deputy Director
National Institute of Neurological Disorders and Stroke
National Institute of Health
Bethesda, Maryland

Samuel Victor Perry, Ph.D. [13]
Professor Emeritus
University of Birmingham School of Medicine
Department of Physiology
Birmingham, United Kingdom

Luisa Politano, M.D. [45]
Associate Professor of Medical Genetics
Department of Clinical and Experimental Medicine and Surgery
2nd Naples University
Naples, Italy

Carl D. Reimers, M.D. [27]
Department of Neurology
Saechsisches Krankenhaus
Arnsdorf, Germany

Richard L. Rotundo, Ph.D. [18]
Professor of Cell Biology and Anatomy
Department of Cell Biology and Anatomy
University of Miami School of Medicine
Miami, Florida

Devon I. Rubin, M.D. [26]
Assistant Professor
Department of Neurology
Mayo Clinic College of Medicine
Mayo Clinic
Jacksonville, Florida

Neil A. Rubinstein, M.D., Ph.D. [4]
Associate Professor of Cell
and Developmental Biology
Department of Cell and Developmental Biology
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Reinhardt Rüdel, M.D. [46]
Professor and Chair
Department of General Physiology
University of Ulm
Ulm, Germany

Sabine Rudnik-Schöneborn, M.D. [67]
Consultant Clinical Geneticist
Institute of Human Genetics
Aachen University of Technology
Aachen, Germany

Robert L. Ruff, M.D., Ph.D. [62]
Professor and Vice Chair
Department of Neurology and Neurosciences
Case Western Reserve University
Veterans Administration Medical Center
Cleveland, Ohio

Menachem Sadeh, M.D. [6]
Associate Professor of Clinical Neurology
Department of Neurology
Wolfson Medical Center
Holon, Israel
Sackler School of Medicine
Tel Aviv University
Tel Aviv, Israel

Joshua R. Sanes, Ph.D. [20]
Alumni Endowed Professor of Neurobiology
Department of Anatomy and Neurobiology
Washington University School of Medicine
St. Louis, Missouri

Jean M. Sanger, Ph.D. [2]
Research Professor of Cell
and Developmental Biology
Department of Cell and Developmental Biology
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Joseph W. Sanger, Ph.D. [2]
Professor and Interim Chair of Cell
and Developmental Biology
Department of Cell and Developmental Biology
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Eric A. Schon, Ph.D. [33]
Professor of Genetics and Development
(in Neurology)
Department of Neurology
Columbia University College of Physicians
and Surgeons
New York, New York

Duygu Selcen, M.D. [43]
Assistant Professor of Neurology
Department of Neurology
Mayo Clinic College of Medicine
Rochester, Minnesota

Joern P. Sieb, M.D. [60, 61]
Privat Dozent
Department of Neurology
University of Bonn, Bonn, Germany
Chair, Department of Neurology
Stralsund General Hospital
Stralsund, Germany

Steven M. Sine, Ph.D. [66]
Professor of Physiology and Biophysics
Department of Physiology
and Biomedical Engineering
Mayo Clinic College of Medicine
Rochester, Minnesota

H. Lee Sweeney, Ph.D. [8]
William Maul Measy Professor
and Chair of Physiology
Department of Physiology
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Franco Taroni, M.D. [57]
Associate Neurologist and Senior Research Scientist
Division of Biochemistry and Genetics
Istituto Nazionale Neurologico C. Besta
Milan, Italy

Nicholas E. Tawa, Jr. M.D., Ph.D. [23]
Assistant Professor of Surgery (Cell Biology)
Department of Surgery
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Massachusetts

Fernando M.S. Tomé, M.D., Ph.D. [40, 44,]
Professor "Agregado" (Neurology)
University of Lisbon
Former Director of Research
INSERM
Paris, France

Seiichi Tsujino, M.D. [55]
Section Chief, Department of Inherited Metabolic Disease, National Institute of Neuroscience
National Center of Neurology and Psychiatry
Tokyo, Japan

Eroboghene E. Ubogu, M.D. [62]
Instructor
Department of Neurology
Case Western Reserve University
Cleveland Veterans Administration Center
Cleveland, Ohio

Bjarne Udd, M.D., Ph.D. [42]
Associate Professor
Folkhalsan Genetic Institute, Biomedicum
University of Helsinki
Department of Neurology
University Hospital of Tampere
Neuromuscular Unit
Vasa Central Hospital
Finland

Anneke J. van der Kooi, M.D., Ph.D. [39]
Department of Neurology
Academic Medical Center
University of Amsterdam
Amsterdam, The Netherlands

John Vissing, M.D., Ph.D. [28]
Associate Professor
Department of Neurology
University of Copenhagen
Director
Neuromuscular Clinic
Rigshospitalit
Copenhagen, Denmark

Thomas Voit, M.D. [44]
Professor and Chair of Pediatrics and Pediatric Neurology
Managing Director
Center of Pediatric and Adolescent Medicine
University Hospital and University of Essen
Essen, Germany

Denise J. Wedel, M.D. [59]
Professor
Department of Anesthesiology
Mayo Clinic College of Medicine
Rochester, Minnesota

Klaus Zerres, M.D. [67]
Professor and Department Chair
Institute of Human Genetics
Aachen University of Technology
Aachen, Germany

PREFACE

A swell of enormous advances swept across the field of myology since the second edition of *Myology* was published in 1994. In the basic sciences, the molecular aspects of the development, organization, and function of muscle have been greatly extended. Myriad components have been added to the list of proteins that constitute the contractile, metabolic, and regulatory machinery of skeletal muscle. At the same time, the clinical significance of some of the heretofore unknown molecules was revealed by pathologic effects of their mutant alleles in both previously identified and newly recognized diseases.

Building on the pioneer discoveries of the past, recent research on muscle differentiation has painted a complete picture of the regulatory genes, signaling networks, and cellular mechanisms that control the embryonic origins of muscle progenitors and their subsequent differentiation to form mature muscle fibers (Chapter 1). That precise coordination and appropriate timing of developmental events are essential for the normal development of muscle and other tissues is now well recognized (Chapter 2). A disruption or inappropriate activation of this stereotyped developmental program in muscle and other tissues is a recurrent theme in the congenital muscular dystrophies and in the myofibrillar and congenital myopathies (Chapters 42, 43, and 54). The recent discovery of stem cells (other than satellite cells) in muscle and other tissues has raised hopes that stem cells derived from muscle or bone marrow could be used for therapeutic intervention; however, the therapeutic potential of stem cells remains unrealized (Chapters 3 and 34).

Intrinsic and environmental (including hormonal) factors shape the destiny of the muscle fibers, so that they become tuned to their varied roles in motor activity. Awareness of these developmental strategies provides a framework for understanding the reactions and adaptations of muscle in disease (Chapters 4 and 5).

The extraocular muscles harbor subcategories of muscle fibers highly specialized for extremely fast as well as slow, tonic movements. These muscles are either preferentially involved or spared in a variety of neuromuscular diseases. Their vulnerability in neuromuscular junction diseases and mitochondrial myopathies, and in oculopharyngeal dystrophy is well known, yet they are spared in most other muscle diseases (Chapter 6).

The building blocks of the muscle fiber—myofibrils, the accompanying membrane systems, and the cytoskeletal network that binds them together—have revealed unexpected complexities of composition and structure. The recent additions to the muscle protein catalogue reveal that appropriate muscle function depends directly on functional integration of all major and minor components of the muscle fiber (Chapter 7). For example, 12 mutations of major structural and regulatory myofibrillar components result in hypertrophic cardiomyopathy; and myosin heavy-chain isoforms are implicated in a form of inclusion body myopathy and hyaline body myopathy (Chapters 8, 48, and 54). A variety of myopathies stem from mutations of structural proteins less directly involved in the contractile functions: limb-girdle muscular dystrophy type 2G (telethonin), limb-girdle muscular dystrophy type 1A (myotilin), desminopathy, and nemaline myopathy (see below) (Chapters 37, 43, and 54).

Knowledge of the number, functional properties, and molecular aspects of plasmalemmal ion channels and pumps has greatly expanded in recent times. Chapter 10 reviews the classical channels responsible for excitatory activity and the equally important channels that contribute to the resting membrane potential, volume regulation, and signal transduction. Understanding the functional role of these channels sets the stage for grasping the complexities of the myotonias, periodic paralyses, and neuromyotonias (Chapters 36, 46, and 47). Muscle activation and the control of muscle fiber activity require a complex machinery based on specialized membrane systems that may occupy a third or more of the fiber volume (Chapters 11–14). Advances in this area have revealed how calcium channels in plasmalemma (the dihydropyridine receptors) and in the sarcoplasmic reticulum (the ryanodine receptors) cross talk and thus influence each other's ctivity. This close functional interaction may well explain that mutations in either channel can cause malignant hyperthermia (Chapter 59). Phospholamban (PLN) is an accessory protein that regulates the activity of the sarcoplasmic reticulum (SR) Ca^{2+} pump (SERCA) in slow skeletal and cardiac muscle. By decreasing the affinity of SERCA 2a for Ca^{2+}, PLN has dramatic beneficial

effects on cardiac function. Thus modifying PLN/SERCA 2a interaction sites may be a promising therapeutic approach to heart failure (Chapter 14).

The mechanism of a protein's action is best understood after its architecture is deciphered at the atomic level. This is dramatically illustrated in Color Plates 1–5. In 1994, understanding of mechanochemical transduction by myosin cross-bridge action had just been revolutionized by the first crystal structures of the myosin molecule. Since then, the structure of other sarcomeric proteins in various functional states has been resolved (Chapters 7–9 and 13, and Color Plates 1–3). The first atomic models of large intramembrane proteins—the SR Ca^{2+} pump, voltage gated ion channels, and the extracellular part of the acetylcholine receptor—are now also available (Chapters 10, 14, 17, and 66, and Color Plates 4–6). The selectivity filter of the potassium channel, seen in its fine detail (Color Plate 5), is a marvel worthy of the 2003 Nobel prize; and the conformational changes in the SR Ca^{2+} pump that accompany the active transport of two Ca^{2+} ions involve impressively large to-and-fro movements in cytoplasmic domains of an innately flexible molecule (Color Plate 4).

Understanding the cytoskeletal network of muscle has been revolutionized by the realization that several macromolecular complexes initially thought to act independently are closely intertwined. Thus, the internal desmin scaffolding and its association with the plasmalemma are intimately linked to dystrophin- utrophin- and spectrin-based networks as these connect through the plasmalemma to the extracellular matrix (Chapters 19a and 19b). This has reinforced the notion that maintenance of sarcolemmal integrity is not limited to dystrophin and dystrophin-associated proteins but involves other components of the subplasmalemmal cytoskeleton and associated integral membrane proteins (Chapters 34 and 37).

The extracellular matrix plays a complex role as an "insoluble" network of proteins that traps bioactive molecules, contributes to fiber differentiation, and dictates specializations at the neuromuscular and myotendinous junction (Chapter 20). An exciting development of the past decade has been that defects in the extracellular matrix have pathogenic effects. Thus, mutations in laminin $\alpha 2$ (Chapter 44) and collagen VI (Chapters 39 and 44) cause muscular dystrophies; perlecan defects underlie the Schwartz-Jampel syndrome (Chapter 63); and mutations in ColQ result in a congenital myasthenic syndrome (Chapter 66).

An increased understanding of the structure and function of the neuromuscular junction (Chapters 15–18) proved to be a stepping stone to unraveling the complexities of the autoimmune and genetic disorders of neuromuscular transmission (Chapters 64–66).

The immense advances in the basic sciences were paralleled by a corresponding expansion of the horizons of clinical myology. The identification of disease genes and mutations has become increasingly important for accurate diagnosis, genetic counseling, and disease prevention. In the *dystrophinopathies*, better understanding of the structure and functional domains of dystrophin has provided new insights into pathogenic effects of dystrophin mutations and clues for designing constructs for possible gene therapy. Improved methods for detecting small DNA rearrangement of the dystrophin gene and for identifying carriers have been devised. The potentials of gene therapy with viral vectors has been explored in animal models but targeting the entire striated musculature, efficient delivery to the host's myofiber nuclei, and long-term expression of the transduced gene are yet to be realized. However, at least some frameshifting dystrophin mutations may be amenable to antisense-induced skipping of the mutant exon, aminoglycosides may suppress some stop codon mutations, and myostatin blockade may mitigate the course of the disease (Chapter 34).

The *classic form of myotonic dystrophy* (DM1) caused by a CTG_n expansion in the 3′ untranslated region of the *DMPK* gene is now matched by *myotonic dystrophy type 2* [DM2, or proximal myotonic myopathy (PROMM)] caused by a $CCTG_n$ expansion in the *ZNF9* gene. The multisystem effects of both disorders have been traced to repressed expression of other genes by the expanded mRNAs. In DM1, this effect has now been attributed to sequestration of nuclear transcription factors of selected genes by the abnormal DM1 mRNAs (Chapter 36).

The mechanism by which deletion of an integral number of repeats in the telomeric region of chromosome 4 causes *facioscapulohumeral dystrophy* (FSHD) has been debated over the past decade. Current evidence, based on detailed microarray studies, indicates FSHD-specific alterations in at least 27 genes. Several of these genes are targets of MyoD, suggesting a defect of myogenic differentiation; others are involved in response to oxidative stress (Chapter 38).

Oculopharyngeal muscular dystrophy is now known to be caused by short (GCG_{8-13}) expansions of alanine codons in the first exon of the *PABP1* that encodes the nuclear polyadenylate-binding protein. Polymerization of the polyalanine domains results in formation of characteristic intranuclear filaments that may trap mRNA (Chapter 40).

The number of genetically defined *limb-girdle dystrophies* has increased from one dominant and three recessive forms in 1994 to six dominant and 10 recessive forms in 2004 (Chapter 37).

During the same period, the number of genetically distinct *congenital muscular dystrophies* grew from three to 10 and, with the exception of integrin α7-deficient muscular dystrophy, they all involve the muscle fiber basement membrane. Aberrant *O*-glycosylation of α-dystroglycan has been identified in five congenital muscular dystrophies, highlighting the crucial role of α-dystroglycan in maintaining basement membrane function in different organs, and especially in muscle and brain (Chapter 44). Both the autosomal dominant *Bethlem myopathy* and the autosomal recessive *Ulrich's congenital muscular dystrophy* were traced to mutations in collagen type VI (Chapters 39 and 44).

Different types of *X-linked vacuolar myopathies*, one with excessive autophagy and one with cardiomyopathy and mental retardation (Danon disease), are now recognized. Danon disease results from defects in the lysosome-associated membrane protein 2 (LAMP2), and is reproduced in mice by targeted disruption of *lamp2* (Chapter 41).

Among the *distal myopathies*, the genetic basis of tibial muscular dystrophy has been traced to mutations in titin. The chromosomal loci of the distal myopathies named after Welander and after Laing have been identified but the disease genes and their mutations are not yet known (Chapter 42).

The term *myofibrillar myopathy* (MFM) has been applied to disorders associated with characteristic changes in trichromatically stained frozen sections, ectopic accumulation of multiple proteins in abnormal fiber regions, disintegration of myofibrils that begins at the Z-disk and, frequently, distal as well as proximal weakness, cardiomyopathy, and peripheral neuropathy. A small proportion of MFM patients carry disease-associated mutations in desmin, αB-crystallin, or myotilin. In most patients, however, the molecular basis of the disease awaits discovery (Chapter 43).

In the *congenital myopathies* the genetic basis of nemaline myopathy has been traced to mutations in thin-filament associated proteins (nebulin, α-actin, α- and β-tropomyosin, and slow-troponin-T). The typical form of multiminicore disease is caused by mutations in selenoprotein N, which is also implicated in a form of the rigid spine syndrome; and the cause of hyaline body disease resides in the slow β cardiac myosin heavy-chain (Chapter 54).

Two eloquent messages emerge from these chapters: First, a decade ago only defects in dystrophin, α-sarcoglycan, and laminin α2 were recognized as proteins associated with muscular dystrophy. Today, an array of other proteins—in the plasmalemma, the internal and external cytoskeleton, the sarcomere as well as a chaperone protein, enzymes, and defects in RNA metabolism—are implicated. Second, the molecular and the phenotypic distinctions between congenital dystrophies, limb-girdle dystrophies, and some congenital myopathies are becoming blurred.

At least two genetically distinct forms of *hereditary inclusion body myopathies* have emerged: A dominant form caused by mutations in heavy myosin chain IIA is associated with early contractures, ophthalmoplegia and proximal weakness; and a recessive form caused by mutations in UDP-*N*-acetylglucosamine 2-epimerase/*N*-acetylmannosamine kinase, encoded by *GNE*, a bifunctional key enzyme in sialic acid synthesis. Interestingly, *GNE* mutations spare the quadriceps muscle in middle-eastern Jews but not in Japanese patients (Chapter 48).

The immunopathogenesis of T-cell-mediated *inflammatory myopathies* is now investigated by laser-assisted dissection of single inflammatory cells combined with single-cell PCR amplification of the sequences of the T-cell receptor. However, the antigen(s) recognized by the autoaggressive T cells remain unidentified (Chapter 49). The etiology of sporadic *inclusion body myositis* remains elusive despite numerous tantalizing clues that relate it to Alzheimer disease, and the observation that expression of the small-heat shock protein, αB-crystallin, is upregulated in numerous nonvacuolated fibers.

Novel *glycogenoses* caused by defects in aldolase A and in β-enolase were discovered, branching enzyme deficiency is turning out to be more heterogeneous than was thought, and the pathogenesis of Lafora disease (polyglucosan storage disease) is becoming clarified (Chapter 55). In acid maltase deficiency, no fewer than 70 mutations have been identified over the past decade, and enzyme replacement therapy of infantile patients is off to a promising start (Chapter 56). The concept of *mitochondrial encephalomyopathies* has also expanded. Mitochondrial DNA (mtDNA) is now known to harbor more than 150 mutations (compared to about 30 in 1994), and a number of nuclear mutations instigating defects in the respiratory chain or in intergenomic communication have been identified. The basis of mtDNA depletion and of multiple mtDNA deletions has been related to alterations of the nucleotide pool (Chapter 58).

In *myasthenia gravis* (MG), the muscle specific protein kinase (MUSK) has emerged as a novel autoantigen, but an animal model based on immunization with MUSK or detailed

analysis of end plate pathology and physiology in a series of MUSK-antibody-positive MG patients is unavailable (Chapter 65). The *congenital myasthenic syndromes* (CMSs) are now known to arise from defects in five end-plate-associated proteins (choline acetyltransferase, the acetylcholine receptor, acetylcholinesterase, rapsyn, and the skeletal muscle sodium channel $Na_v1.4$) that harbor no fewer than 144 mutations. Clinical, morphologic, and electrophysiology clues now allow rational therapy for most CMSs (Chapter 66).

Among the *motor neuron diseases*, it is now realized that mutations in the telomeric form of the *SMN1* gene underlie all three forms of spinal muscular atrophy, and that the number of centromeric *SMN2* copies modulate disease severity (Chapter 67). And now, the serendipitous observation that SMN2 protein level is upregulated by valproic acid has raised hopes that juvenile and adult cases of spinal muscular atrophy may become therapeutically accessible. Mutations in three proteins—superoxide dismutase 1, alsin, and dynactin—have been implicated in familial forms of amyotrophic lateral sclerosis (ALS). Analysis of the deleterious effects of the mutant alleles may eventually provide clues to the cause, pathogenesis, and treatment of sporadic ALS. Of further interest, one-half of ALS patients have detectable reverse transcriptase in serum, pointing to a possible retroviral instigator (Chapter 68).

The clinical spectrum and molecular diversity of hereditary motor and sensory as well autonomic neuropathies have also expanded over the past decade. New methods have been devised to assess sensory and autonomic dysfunction and loss, and specific prevention and therapy have become available for a number of metabolic and immune neuropathies.

But the miraculous progress of the past decade has also challenged the traditional classification and categorization of neuromuscular diseases. Mutations in diverse genes can have converging functional and pathologic effects and, conversely, different mutations in a given gene can produce divergent clinical phenotypes. As examples, consider mutations in dysferlin, myotilin, or caveolin causing limb-girdle dystrophy or distal myopathy; mutations in lamin A/C resulting in Emery-Dreifuss dystrophy, cardiac conduction defect, lipodystrophy, axonal neuropathy, mandibuloacral dysplasia, or progeria; mutations in $Na_v1.4$ causing different forms of periodic paralysis, myotonia, or a CMS; and mutations in either $Na_v1.4$ or $Ca_v1.1$ causing hypokalemic periodic paralysis. Thus neither the traditional classification of diseases by their clinical or morphologic phenotype, nor their categorization by the mutated gene, the altered protein and, still less, by an ever increasing number of alphanumeric labels, is entirely satisfactory.

The third edition of *Myology* is organized in two volumes, comprising three parts. Part 1 (Chapters 1–24) deals with the development, differentiation and diversity of skeletal muscles, muscle contraction, the control of muscle fiber activity, neuromuscular transmission, and muscle as a tissue. Part 2 (Chapters 25–33) focuses on the general approaches to neuromuscular diseases. Part 3 (Chapters 34–70) presents the various disorders of muscle. Here the traditional phenotype-based classification of muscle diseases is retained, because phenotypic features of a given patient are the starting point for further studies and the subsequent molecular diagnosis. The biochemical aspects of glycogen, lipid, and mitochondrial metabolism, presented as separate chapters in Part 1 in the second edition, are now presented in the context of the corresponding clinical chapters in Part 3. Most chapters were thoroughly revised or written de novo, and eight new chapters were added. The new titles are: Extraocular Muscles (Part 1), Immune Mechanisms in Muscle Diseases (Part 2), Bethlem Myopathy, X-Linked Vacuolar Myopathies, Myofibrillar Myopathies, Cardiomyopathies Associated with Muscular Dystrophies, Generalized Peripheral Nerve Hyperexcitability, and Hereditary Inclusion Body Myopathies (Part 3).

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Andrew G. Engel, M.D.

Clara Franzini-Armstrong, Laurea