

## Foreword

We are pleased and proud to present this volume on disorders of the neuromuscular junction in the *Handbook of Clinical Neurology* series, and congratulate the editor, Professor Andrew Engel, and the outstanding group of authors whom he brought together as contributors to the book.

In an excellent chapter on historic aspects of neuromuscular junction disorders, John Keesey reviews how knowledge of the neuromuscular junction developed from the 1743 illustration by Herman Boerhaave, the founder of Dutch medicine, who showed the nerve as flowing directly into the substance of the muscle, leading eventually to recognition of the molecular defects of presynaptic, synaptic, and postsynaptic proteins in congenital myasthenic syndromes, to which Dr. Engel has himself contributed so much. A varied assortment of people has contributed to our current insights, including Emperor Napoleon III, who donated the South American arrow poison, curare, to Claude Bernard. Important insights came also from clinical descriptions, such as the first one in 1672, by Thomas Willis in *De Anima Brutorum*, of a “prudent and honest woman” with fluctuating muscle weakness “not only in the members but also in her tongue” and epidemics such as the sausage poisoning (*Wurstvergiftung*) in Germany, now known to have been due to botulism. The road from curare to immunotherapy, via muscle antibodies, took 330 years.

Recent progress has been at higher speed. Volumes 40 and 41 of the *Handbook*, which appeared in 1979, contained a chapter by Andrew Engel on myasthenia gravis. The rapid advances in our understanding of the neurobiology of neuromuscular transmission, and of the molecular background of the various forms of neuromuscular junction disorders that have been made since then, make publication of the present volume very timely. New insights have been obtained into the immunopathogenesis of myasthenia gravis, not only in relation to anti-acetylcholine receptor antibodies but also to different antibodies, such as those against the voltage-gated calcium channels on the presynaptic membrane. Considerable knowledge has also been gained recently into the molecular mechanisms underlying the links between activity and patterns of gene expression, particularly in muscle, and we have a much better idea of the factors regulating the adaptive plasticity of the neuromuscular junction, which may in turn lead to new therapeutic strategies for enhancing the restoration of normal function in neuromuscular disorders. The clinical features and electrodiagnosis of neuromuscular junction disorders, and the optimal treatment of myasthenia gravis, receive exquisite attention in this volume. Novel and important information is also provided to enhance understanding of the pathophysiology of the heterogeneous group of peripheral nerve hyperexcitability syndromes, and the toxicity of pesticides such as the acetylcholinesterase-inhibiting organophosphates and carbamates.

We are greatly indebted to the volume editor and to the authors who have put together this outstanding volume, which will be of great interest to both practising neurologists and scientists working in this field. As always, we are also very grateful to the team at Elsevier for their expert assistance in the development and production of this book.

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## Preface

In 1992, when the second series of the *Handbook of Clinical Neurology* was published, a single 65-page chapter summarized the then current knowledge of diseases of the neuromuscular junction. Commensurate with advances in the field, the third series of the *Handbook* devotes an entire volume comprised of 14 chapters to these disorders.

The book begins with an account by John Keesey on the historic aspects of diseases that commonly involve neuromuscular transmission. Chapters 2–4 acquaint the reader with the structure and function of the neuromuscular junction and with the relevant clinical electrodiagnostic methods. Thus, Chapter 2 by Clarke Slater reviews the safety margin of neuromuscular transmission. Chapter 3 by Andrew Engel describes the basic anatomy and the functional significance of each structural component of the neuromuscular junction. Chapter 4 by C. Michel Harper explains how electrophysiologic techniques identify defects of neuromuscular transmission and provide information related to the mechanism and severity of the disorder.

Chapters 5–8 focus on autoimmune myasthenia gravis. In Chapter 5, Norbert Sommer, Björn Tackenberg and Reinhard Hohlfeld review the immunological principles relevant to myasthenia gravis, survey the autoantibodies and their target antigens, discuss the associated cellular immune responses, and consider the contribution of genetic factors and the thymus gland to the pathogenesis of the disease. In Chapter 6, Angela Vincent describes different antibodies directed against the acetylcholine receptor (AChR) and how these antibodies can be assayed. She also explains how antibodies against the fetal form of AChR in maternal sera can cause multiple joint contractures at birth and compromise the survival of the offspring. She also relates the intriguing discovery that autoantibodies directed against the muscle specific tyrosine kinase (MuSK) underlie the pathogenesis of autoimmune myasthenia in a proportion of patients who harbor no anti-AChR antibodies. Chapter 7 by Donald Sanders and Janice Massey details the semiology of myasthenia gravis, and discusses different subtypes of the disease and their diagnosis. Chapter 8 by Dan Drachman is an elegant and authoritative exposition of the principles of therapy based on many decades of personal experience. This chapter will serve as a valuable guide to therapy of myasthenic patients whose disease ranges from mild ocular symptoms to recurrent life-threatening crises.

Chapters 9 and 10 deal with myasthenic syndromes. In Chapter 9, Donald Sanders and Vern Juel provide a full account of the clinical presentation, pathophysiology, immunopathology, diagnosis, association with malignancy, and therapy of the Lambert–Eaton syndrome. Unlike in myasthenia gravis, where antibodies directed against AChR or MuSK attenuate the synaptic response to acetylcholine, in the Lambert–Eaton syndrome antibodies directed against the presynaptic voltage-gated calcium channel decrease the number of transmitter quanta released by nerve impulse. In Chapter 10, Andrew Engel describes the clinical and basic science features and therapy of the congenital myasthenic syndromes and discusses how defects in different components of the neuromuscular junction, namely choline acetyltransferase, the collagenic tail of acetylcholinesterase, the acetylcholine receptor, rapsyn, the voltage-gated sodium channel, MuSK, and Dok-7, the recently identified muscle-intrinsic activator of MuSK, impair the safety margin of neuromuscular transmission. The commonest congenital syndromes are caused by defects in AChR that either reduce the expression or profoundly alter the kinetic properties of the receptor.

Chapters 11–13 survey neuromuscular transmission disorders caused by the exogenous agents that include bacterial and marine toxins, numerous drugs, and organophosphates. Perhaps the commonest of the intoxications worldwide is botulism, and Chapter 11 by Eric Johnson and Cesare Montecucco provides a scholarly and definitive account of the various types of botulinus toxins, and the diagnosis and therapy of the various forms of human botulism.

The final chapter by Steven Vernino discusses the clinical features and pathophysiology of genetic, toxic, and immune-mediated diseases that cause neuromyotonia. The majority of these disorders stem from hyperexcitability of the distal motor nerve, or motor nerve terminal, so they are appropriately considered neuromuscular junction disorders.

## PREFACE

Diseases of the neuromuscular junction are, and are likely to remain, of keen interest to clinicians and basic scientists alike. Although many are highly disabling, most are treatable; and understanding their basis has yielded sharp insights into basic immunology, neurotoxicology, and the neurobiology of synaptic transmission.

I wish to thank Michael J. Aminoff for reading and critiquing each chapter and the production staff of Elsevier for their expert assistance in bringing this volume of the *Handbook of Clinical Neurology* to fruition.

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## Chapter 1

# The most vulnerable synapse: historic aspects of neuromuscular junction disorders

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### 1.1. Introduction

The site where a motor nerve meets a skeletal muscle fiber, termed either the “neuromuscular” or the “myoneural” junction, was a very poorly understood structure until the 20th century. Herman Boerhaave, the 18th century founder of Dutch medicine, illustrated the nerve as flowing directly into the substance of the muscle (Boerhaave, 1743) and these structures were still pictured as fused 100 years later (Doyère, 1840). Willy Kühne, one of the finest light microscopists of the 19th century, although able to visualize the “motor endplate” of skeletal muscle *en face* (Kühne, 1863), was unable to resolve whether it was a part of the terminal innervation or a part of the skeletal muscle fiber (Keeseey, 2002).

Despite this uncertainty, in 1850 the great French physiologist Claude Bernard reasoned from ingenious experiments on frogs that the South American arrow poison, curare (a gift from Emperor Napoleon III), acted only at the terminal fibers of motor nerves (Bernard, 1857). Emil Du Bois-Reymond, the pre-eminent electrophysiologist of his time, speculated in 1877 that transmission between the nerve and the muscle was either electrical or else occurred by liberation from the motor nerve of a substance, such as ammonia or lactic acid, capable of exciting the muscle (Du Bois-Reymond, 1877). During the first half of the 20th century, pharmacological evidence for acetylcholine in that latter role became compelling (Brown, 1937). When electron microscopes became commercially available, the nerve terminal and the specialized region of muscle where the nerve terminated were shown to be separate, highly organized structures with a space in between (Robertson,

1956). At about the same time biophysicists, using saline-filled glass microelectrodes in muscle fibers near nerve terminals, were able to describe in detail the electrical events occurring during normal neuromuscular transmission (Fatt and Katz, 1952).

It was only by using these new tools in the second half of the 20th century that the pathophysiology of an assortment of previously unrelated conditions could be localized to the neuromuscular junction. These include the most common neuromuscular disorders worldwide—those caused by particular snake and spider venoms—as well as illnesses caused by some bacterial and marine toxins and by numerous drugs, all of which may be regarded as “exogenous” neuromuscular disorders (Swift and Greenberg, 1984). This chapter will focus on one of these, botulism. It will also describe the history of myasthenia gravis and its relatives, major representatives of what Swift and Greenberg (1984) termed “endogenous” neuromuscular disorders. The eventful histories of botulism and myasthenia gravis began long before it was realized that the neuromuscular junction, “the most vulnerable synapse known” (Estable, 1959), was involved.

### 1.2. History of human botulism

The word “botulism” is derived from *botulus*, the Latin word for “sausage,” suggested by the German physician Müller in 1870 (Erbguth and Naumann, 1999) to describe a peculiar type of food poisoning, the only known cause of which at that time was the ingestion of spoiled sausages. Others preferred to describe it by the term “allantiasis,” derived from the Greek word for sausage, *allantiko*.

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