Amyotrophic Lateral Sclerosis

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As new scientific information becomes available through basic and clinical research, recom-
mended treatments and drug therapies undergo changes. The authors and publisher have
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urged when using new or infrequently ordered drugs.
The authors dedicate this book to Joseph M. Foley, M.D., Professor Emeritus of Neurology, Case Western Reserve University. A teacher of teachers, Dr. Foley taught us how to dedicate ourselves in caring for the sick and desperately ill and continues to inspire us in our own personal growth and in the joy of practicing neurology.
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In 1967, when Dr. John Walton, now Lord Walton of Detchant, suggested that I start a research program into anterior horn cell and peripheral nerve disease, little did I realize that this would turn into a lifetime commitment to the neuromuscular diseases and, particularly, to what is known in Britain as motor neuron disease and in the United States as amyotrophic lateral sclerosis (ALS). At that time, I was a junior research registrar in the Muscular Dystrophy Group Research Laboratories of the University of Newcastle Upon Tyne in the northeast of England, where the research predominantly dealt with the muscular dystrophies. Very little was known about the causes of most of the peripheral neuropathies or ALS, though theories abounded. It was a very fertile time to launch into a research career.

The research I began in Newcastle has taken me to many parts of the world and into many fields of investigation that I never thought to explore. These have included studies of animal models, including the wobbler mouse, which has proved useful for investigating anterior horn cell degeneration. Investigation of axonal transport mechanisms and the use of neurotoxins proved valuable in those early days. I became involved in research into the etiology of all of the neuromuscular diseases, particularly ALS, and was soon involved not only in the care of ALS patients but also in therapeutic trials.

This work has brought me into contact with many of the most illustrious clinicians and research workers in neurology and has also given me the opportunity to share in the developing careers of many of the best and brightest of the younger generation, including the three authors of this book.

My early period of clinical training with Lord Walton and Dr. David Gardner-Medwin in Newcastle provided me with the skills and empathy needed to care for patients with chronic, progressive, disabling neuromuscular diseases. This has stood me in good stead when caring for what may be one of the most distressing of these diseases, ALS.

Thirty years ago, few knew much about ALS. Patients often confused it with multiple sclerosis or had never even heard of the condition. Now, as more and more prominent people have suffered from this disease, such as David Niven and Senator Jacob Javits, and as the medical knowledge of the population has increased, there are few who have not heard something about the disease. In the United States the disease is particularly known because of the very public development of the symptoms in the “Iron Man of Baseball,” Lou Gehrig. The touching film that was made about his life is shown around the time of each World Series.

Like many other neurologists, I find that my heart drops whenever I have to make the diagnosis of ALS. It always seems to be the nice people who are stricken with this disease. It is heartbreaking to give the diagnosis to someone who is quite young. How to face the patient and the family with this diagnosis is one of the most difficult tasks of the neurologist.

Nowadays, with the availability of the Internet and national associations such as the ALS Association and the Muscular Dystrophy Association, patients often know a great deal about their condition even before they come to a specialist. In describing the disease to a patient, one has to relate that the average survival is 3 to 5 years and that there is a progressive physical deterioration that affects all aspects of life, including walking, self-care, speech, swallowing, and breathing. One has to be honest
with patients, but one should not take away hope. I always point out that there are patients in whom ALS has remitted; I have seen three, and several others are described in the literature. There is an even greater number of patients in whom the ALS seems to burn itself out; these patients stabilize and remain in whatever state they have reached by this time. A significant proportion of ALS patients have a much slower progression than would be indicated by the average quoted figures for survival; 10% of patients with ALS live 10 years and 5% live 20 years. There are often clinical pointers at the outset that suggest that the patient is going to have a more benign prognosis than the average; these include the presence of pure lower motor neuron disease and involvement commencing in the lower limbs.

Neurologists have always been interested in the problem of reaching a diagnosis in patients with ALS, but few have been interested in providing ongoing care. I have heard too many times that a neurologist has told a patient that the disease is called ALS, that it is universally fatal, and that the patient should go home and put his or her affairs in order and prepare to die. These neurologists should remember that doctors are admonished “to cure rarely, to treat often, and to care always.” If no cure is available, then the physician must spend even more time with the patient and the family than would generally be needed if there were a cure.

The physician knowledgeable about ALS can provide many things in addition to empathy and information: physical aids so the patient can stay active as long as possible; access to assistance from other health care professionals; mechanisms to improve respiration; help with the problems of insurance and disability. Later, a physician comfortable with the primary goal of caring is needed to guide the patient with ALS in making decisions about parenteral feeding and ventilator support; and at the end of life, the physician can do much to alleviate distress.

From my vantage point, it seems that now is a more exciting period in ALS research than we have seen at any time in the last 30 years. We now are witnessing real advances in our understanding of the disease and its treatment. For the patients and their families, these research advances are the hope to which they inevitably cling. I have always felt it important that the physician make every effort to share research advances with patients. Such foundations as the ALS Association and the Muscular Dystrophy Association provide significant help in this area, both by supporting research and by disseminating information about research. It is particularly helpful when the physician caring for an ALS patient is involved in research; this keeps up the spirits not only of the patient but also of the doctor.

There have been many theories of the cause of ALS, but in the last few years we have begun to feel confident that we are getting closer to a true understanding. This particularly relates to the hypotheses of oxidative damage and glutamate excess. The strongest support for the oxidative hypothesis comes from the discovery of the mutations of the superoxide dismutase-1 gene in familial ALS. The glutamate hypothesis sprang from basic neuroscience research into excitotoxic damage and the finding that in ALS there is a decreased ability to handle the excitatory neurotransmitter, glutamate. In the end, ALS may turn out to be due to many other causes in addition to these two. The disease in some patients may be due to abnormalities of neurofilaments, other specific gene defects, and deficiencies of neurotrophins or neurotrophin receptors. From the patient’s point of view, although this plethora of hypotheses may be confusing, any new information raises the spirits.

Even more hope for patients comes from the advances in treatment. Over the last two decades, many of us have undertaken therapeutic trials in ALS that were based mainly on whatever drugs were available that might work or whatever treatment was suggested by a new hypothesis. The first small trial of a drug in ALS is often reported to be positive, but until recently, further studies have failed to repeat any positive benefit. With the new development of the science of clinical therapeutic trials, we have come to realize that power calculations are essential to determine whether a
study can prove or disprove the efficacy of a drug. In ALS, it appears that between 100 and 300 patients per treatment arm are required for a study to have the power to detect about a 15% slowing in the rate of progression of the disease over a 9-month period of patient follow-up. Hence, at present, therapeutic trials in ALS are very large and extremely costly. What is still needed is a biological marker of the disease process in ALS. Although we have several animal models of ALS, in the final analysis they are no substitute for proof of efficacy of a therapy in humans with the disease.

As we stand here at the end of 1996, we now have the first drug that has been proven to slow the rate of progression of ALS, namely, the antiglutamate agent riluzole. Several other agents are undergoing therapeutic trials, including gabapentin, another antiglutamate agent, as well as various growth factors. The latter include insulin-like growth factor-1, brain-derived neurotrophic factor, and other similar agents that are moving rapidly from the basic research laboratories into the clinical arena. These include small-molecular-weight compounds that can stimulate neurotrophin receptors and pass the blood-brain barrier as well as new growth factors such as glial-derived neurotrophic factor.

An indication of the enormous recent increase in our ability to deal with ALS is provided by the very large audiences that now come to hear about ALS at our neurological meetings and the many national and international meetings currently devoted to research into ALS. Another indication is the appearance of several books on ALS that have been published over the past few years. All are excellent in their own ways, illustrating the multifaceted aspects of ALS and the many approaches to its investigation and management. This book comes at a particularly opportune time, for it presents an excellent and comprehensive review of current information on the clinical features of the disease, its pathology and pathophysiology, and its treatment and management. Now, when we are beginning to see the product of decades of research manifesting as clear insights into the cause of the disease and ways to treat it, the information learned over the decades continues to be crucial in the fight to finally cure and prevent the creeping paralysis, ALS. Even if the cause of ALS were discovered tomorrow and the way to arrest the disease were discovered the day after, the information in this book would still continue to be of importance to all who care for patients with ALS.

Walter G. Bradley, D.M., F.R.C.P.
Miami, Florida
August, 1996
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When we began writing this book in the spring of 1994, there were no approved drugs for ALS. A few clinical trials were underway, but their results were still uncertain. In the last 3 years, the neurological community has progressed on a number of fronts, including understanding the basic biology of this disorder; developing novel, effective therapies; and renewing emphasis on patient care. Those of us who look after patients with ALS are now in the midst of some very important developments. Plausible hypotheses of ALS pathogenesis have been proposed, and the process of motor neuron death is now better understood. The first drug for ALS, although modest in its effects, was approved in 1995 by the United States Food and Drug Administration, and several additional medications are now on the horizon. The many aspects of patient care have drawn increasing attention from a diverse array of disciplines, among them physical and occupational therapy, nutritional science, speech-language pathology, psychosocial-spiritual counseling, and hospice care; therefore, in these times of exciting scientific insights, promising therapeutic advances, and multidisciplinary comprehensive patient care, we welcomed the opportunity to write this book. For us, the process of researching, reflecting, and writing has been a richly rewarding educational experience.

Although several excellent books on ALS have already been published, this book is the first written by only a few authors. Taking advantage of the small authorship, we strove to present cohesive and balanced information for every student of ALS. The more we discussed the disease and our approach to writing the book, the more we came to realize the remarkably complex and multifaceted nature of ALS. In an effort to increase our knowledge of the disease and write about it as comprehensively as possible, we carefully considered a host of individual disciplines that we believe are relevant to an understanding of ALS, among them motor system anatomy and physiology, neuropathology, neuroimaging and neurodiagnostic methods, mechanisms of neuronal degeneration and death, epidemiology, biostatistics, and clinical trials. In the final analysis, we wrote the book with the belief that to understand ALS is to understand clinical neurology as well as many of the neurosciences.

Although we brought diverse experience in clinical care, teaching, and research to the task of writing this book, the major emphasis for each of us in our own work is the diagnosis and management of patients with ALS; therefore, we crafted the book mainly for the neurologist who looks after patients with ALS and shares our desire to learn more about its mysterious biology. Although the primary audience for this book is the practicing neurologist, neurology trainees and other health care professionals will also find it useful. The book consists of four major sections: Introduction to ALS, Clinical Features of ALS, Pathology and Pathogenesis, and Treatment and Management. To clarify the material presented, we frequently use summary tables and figures (line drawings and photomicrographs). To help readers recall the main ideas discussed, each chapter has a detailed summary.

We are grateful to many people for their support and assistance during the course of our writing this book. First of all, we are most indebted to Dr. Sid Gilman, Editor-in-Chief of the Contemporary Neurology Series, who encouraged us to start this project, promptly read a series of draft chapters, gave us invaluable suggestions, and
set the tone for the entire book. Initial drafts of our chapters were all carefully reviewed by our expert medical editors, Cassandra Talerico, M.A., and Tom Lang, M.A., of the Scientific Publications Department, the Cleveland Clinic Foundation (CCF). We admire their meticulous editing and their helpful comments and suggestions. Ms. Bernice Wisler at the F. A. Davis Company provided additional editorial assistance and encouragement, helping us to craft the final version of the text. We are particularly privileged and honored that our mentor (of H.M. and D.A.C.), Walter G. Bradley, D.M., F.R.C.P., has written the Foreword. He is a consummate clinician, an inspired teacher, and a tireless investigator of ALS, who introduced us to the care of the patient with ALS and to research in the field. We are delighted that Lisa S. Krivickas, M.D., a former neuromuscular and electromyography fellow at CCF, with a special interest in chronic respiratory rehabilitation, contributed Chapter 22, Pulmonary Function and Respiratory Failure.

We are fortunate that many of our colleagues with expertise in the varied aspects of ALS critically reviewed one or more chapters and provided suggestions that we believe strengthened our book. We, however, are solely responsible for the contents and for the accuracy of the material. Those who shared their expertise with us were Neil Aronin, M.D., University of Massachusetts Medical Center (UMMC); Carolyn Benson, M.S., R.N., UMMC; Carolyn Berger, O.T.R./L., CCF; Jesse M. Cedarbaum, M.D., Regeneron Pharmaceuticals; Michelle Secic, M.S., CCF; Vanina DelBello-Haas, M.S., P.T., CCF; Nancy Fontneau, M.D., UMMC; Tom Greene, Ph.D., CCF; Asao Hirano, M.D., Montefiore Medical Center; John Kelemen, M.D., Long Island Neurological Associates; Ann Kloos, P.T., M.S., CCF; David Lacomis, M.D., University of Pittsburgh; Ronald M. Lindsay, Ph.D., Regeneron Pharmaceuticals; Errol Malta, Ph.D., Amgen Inc; Michael T. Modic, M.D., CCF; Dominic Nompelleghi, M.D., UMMC; Robert J. O’Hara, M.D., Hines VA Medical Center; Carrie Proch, P.T., CCF; Douglas Seidner, M.D., CCF; Lauren Shockley, R.N., CCF; Teepu Siddique, M.D., Northwestern University; and Asa J. Wilbourn, M.D., CCF.

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Most of all, we wish to thank the patients with ALS and their families with whom
we have had the opportunity to develop a therapeutic partnership. Not only have they taught us volumes about the many clinical aspects of the disease, but they have also shown us that life with ALS can be lived productively, creatively, and with dignity.

Last, we would like to thank our wives, Chizuko, Rita, and Mattie, and our families for their unlimited support and forbearance, which made our work possible.

HM
DAC
EPP
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