**Amyotrophic Lateral Sclerosis**

A synthesis of research and clinical practice

Amyotrophic lateral sclerosis (ALS), otherwise known as Lou Gehrig's disease or motoneuron disease, is one of several degenerative diseases of the ageing nervous system. Commonly affecting those in their mid-50s and beyond, it is a progressive illness resulting in death within a few years. The decade of the brain has seen an explosion in research into this particular condition, which this text neatly synthesizes to construct a detailed and comprehensive overview. From its epidemiology, molecular biology and pathophysiology right through to clinical assessment and care, Professor Eisen and Doctor Krieger use their research expertise and extensive clinical experience to provide this practical and thought-provoking account.

> The range of subjects covered is astonishing ... their reviews are comprehensive and sophisticated. Their writing is clear and the several controversies are given balanced reviews. The ample illustrations have been selected thoughtfully ... This book ought to appeal to practising neurologists, medical students and residents and other health care workers involved with people who have ALS. Anyone interested in ALS will find material for thought and for practice.
>
> From the Foreword by Professor L. P. Rowland.

**Andrew Eisen** is Professor of Neurology at the University of British Columbia and Head of the Neuromuscular Diseases Unit, Vancouver General Hospital, Canada. He has a particular interest in electromyography, spinal cord disease and ALS. Past President of both the Canadian Society of Clinical Neurophysiologists and the American Association of Electrodiagnostic Medicine, he has published 120 articles in prestigious medical journals, including 29 papers devoted to ALS. In addition to authorship of this book, he is an editor of two earlier publications on spinal cord disease: *Diseases of the Spinal Cord* (1992) and *Spinal Cord Disease: Basic Science, Diagnosis and Management* (1997).

**Charles Krieger** is Associate Professor of Neurology at the University of British Columbia, Vancouver, Canada, and has been involved in the care of ALS patients for more than 15 years. During this time his extensive research studies into the cause of ALS have resulted in the publication of more than 35 important original articles.

# AMYOTROPHIC LATERAL SCLEROSIS

## A synthesis of research and clinical practice

ANDREW EISEN

and

CHARLES KRIEGER

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To our wives, Kathleen and Alisa, and to the 700 patients with ALS who we have seen and whose plight has given us continual inspiration

# Contents

# Foreword

The past five years have seen the publication of several books on amyotrophic lateral sclerosis (ALS). Why another one now? Several answers are evident. Some of the previous books were focused on clinical management, or diagnosis, or pathology. None has been as comprehensive as this volume of Professor Eisen and his colleague Dr Krieger. The writing here is seamless, in contrast to multi-authored books. The range of subjects covered is astonishing, especially for a veteran like me. I can remember when there was almost no research on ALS, because there was not much to do except for clinico-pathological correlations. This book, however, considers the whole range in depth from epidemiology to clinical features. Why the predominance in men? How does age at onset or family history affect prognosis? What accounts for clusters? What is the current interpretation of the high incidence on Guam? The differential diagnosis is discussed in detail, including a judicious presentation of motoneuropathy. The authors also provide a full description of cellular pathology and theories of pathogenesis, including inherited human and mouse diseases, and transgenic murine models. Questions are raised and answered about the significance of ubiquitination, Bunina bodies, Lewy bodies, and neurofilaments. Apoptosis is explained. In a detailed discussion of pathogenesis, the authors consider the excitotoxic theory of pathogenesis, which they favour, and the autoimmune theory, which they find wanting. Naturally, electrophysiology gets full treatment, including the authors' theory that the disease begins in the upper motoneuron rather than in both upper and lower motoneurons simultaneously. In addition to the details of electromyography and nerve conduction studies, they also explain the use of transcranial magnetic stimulation. Modern imaging is advancing even in ALS, and includes magnetic resonance spectroscopy, which is also presented clearly. The authors are judicious in describing symptomatic

therapy and they are optimistic about prospects for truly effective therapy in the near future.

In all of this, their reviews are comprehensive and sophisticated. Their writing is clear and the several controversies are given balanced reviews. The ample illustrations have been selected thoughtfully; the references are complete and up-to-date. This book ought to appeal to practising neurologists, medical students and residents and other health care workers involved with people who have ALS. Anyone interested in ALS will find material for thought and for practice.

Lewis P. Rowland, MD

# Preface

In my dreams I climb the mountains high,
In my dreams I face the samurai.
In my dreams I stroke my lover's hair,
In my dreams I travel everywhere.
In my dreams I kiss and never tell,
In my dreams I'm not a languid shell.
In my dreams I never convalesce,
In my dreams I don't have ALS.

*Laugh, I Thought I'd Die – My Life With ALS*

Dennis Kay, 1993

Amyotrophic lateral sclerosis (ALS) research has escalated considerably during this, 'the decade of the brain'. Frequently read neurological–neuroscience journals contain at least one article related to ALS in virtually each issue. A current Medline search reveals more than 1000 titles relevant to ALS or motoneuron disease (MND). The latter term is still commonly used synonymously with ALS in much of Europe. The Internet too has a growing number of WEB sites devoted to ALS, but one in particular (http://http1.brunel.ac.uk8080/~hssrsdn/alsig/alsig.htm) has a weekly digest that maintains much current information of interest to patients, their care-givers and professionals. The subcommittee on ALS and Motoneuron Diseases of the World Federation on Neuromuscular Diseases, a standing committee of the World Federation of Neurology, has substantially expanded its activities. In the last four years, the committee has developed the first formal classification of ALS, criteria and valid end-points for therapeutic trials and a worldwide consortium directed towards the collaborative performance of therapeutic trials. An annual meeting, devoted to ALS research, which originated in England just a few years ago, has become international and sizeable, with several

countries bidding each year to host subsequent meetings. The associated International Alliances of ALS/MND now represent almost every country in the world.

Several excellent, edited, multi-author texts on ALS have been published within the last five years, but books written by a single or, as in this case, two authors are uncommon. Their slant is different, more focused and obviously biased by personal perspective. This monograph is derived from our examination of 664 patients with ALS seen since 1982. We have tried to review those aspects of ALS that presently occupy the forefront. Many people have made major contributions to these topics. Some we know personally and some are good friends. We have enjoyed reviewing their work, but the references at the end of the book aim to be current rather than complete. The experience of studying many patients with a single disease gives one the opportunity to think about the particular disorder in depth. This provokes speculation and commentary that is not always shared by conventional dictum. For this we make no apology and hope that our thoughts will encourage debate and further research.

The book has eight chapters, each emphasizing a particular aspect of the disease. The chapters have a summarizing paragraph or two and are written so that each is largely 'stand-alone' which has necessitated some replication. The eight chapters deal with epidemiology, clinical aspects, pathology, aetiopathogenesis, physiology, imaging, overlap syndromes and therapy. New information in ALS is surfacing so rapidly that even as we were preparing the manuscript, aspects that were current when we started have become outdated. For example, the hope for brain-derived neurotrophic factor (BDNF) as a therapy for ALS was not to be, and the first attempts at using intracranial delivery of another trophic factor glial cell-derived neurotrophic factor (GDNF) are underway.

Andrew Eisen
Charles Krieger

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We are very grateful for the material supplied to us by Drs Samuel Chou, San Francisco; Stirling Carpenter, Toronto; Jean-Pierre Julien and Heather Durham, Montreal; Shoichi Sasaki, Tokyo; and Drs Kenneth Berry, Gillian Gibson and Tom Beach in Vancouver.

# Abbreviations

| | |
|---|---|
| AA | amino acid |
| AALS | Appel rating scale for amyotrophic lateral sclerosis |
| AD | Alzheimer's disease |
| ALS | amyotrophic lateral sclerosis |
| AMPA | α-amino-3-hydroxy-5-methyl-1,4-isoxazole-proprionic acid |
| ASP | [$^3$H]-D-aspartate |
| BCAA | branched chain amino acid |
| BDNF | brain-derived neurotrophic factor |
| BIPAP | bimodal passive airway pressure |
| BMAA | β-N-methylamino-L-alanine |
| BOAA | β-N-oxalylamino-L-alanine |
| CaBP | calbindin-$D_{28K}$ |
| CAG | repeating trinucleotide sequence |
| CaMKII | $Ca^{2+}$ calmodulin-dependent kinase II |
| CB | calbindin |
| CDF | cholinergic differentiation factor |
| CGRP | calcitonin gene-related peptide |
| Cho | choline |
| CIDP | chronic idiopathic demyelinating polyneuropathy |
| CJD | Creutzfeldt–Jakob (Jakob–Creutzfeldt) disease |
| C–M | corticomotoneuronal |
| CMAP | compound muscle action potential |
| CNS | central nervous system |
| CNTF | ciliary neurotrophic factor |
| COPD | chronic obstructive pulmonary disease |
| Cr | creatine |
| CR | calretinin |
| CSF | cerebrospinal fluid |
| CT | computerized tomography |
| Cu | copper |
| Cu/Zn–SOD | copper/zinc–superoxide dismutase |
| CUSM | cumulative sum analysis |
| DAP | 3,4-diaminopyridine |
| DDPAC | disinhibition–dementia–Parkinson–amyotrophy complex |

| | |
|---|---|
| DHEA | dehydroepiandrosterone |
| DHEAS | dehydroepiandrosterone sulphate |
| DNA | deoxyribonucleic acid |
| DOPAC | 3,4-dihydroxyphenylacetic acid |
| DRG | dorsal root ganglion |
| DTR | deep tendon reflex |
| EAA | excitatory amino acid |
| EAAC1 | glutamate transporter |
| EDC | extensor digitorum communis |
| EEG | electroencephalogram |
| EMG | electromyography |
| EPSP | excitatory postsynaptic potential |
| FALS | familial amyotrophic lateral sclerosis |
| FGF | fibroblast growth factor |
| FD | fluorodopa |
| FDA | Food and Drug Administration |
| FDG | [$^{18}$F]-2-fluoro-2-deoxy-D-glucose |
| FDI | first dorsal interosseus |
| F$^{1}$ H-MRS | functional H-magnetic resonance spectroscopy |
| FMRI | functional magnetic resonance imaging |
| FTD | frontotemporal dementia |
| FVC | forced vital capacity |
| GABA | $\gamma$-aminobutyric acid |
| G-ALS | Guamanian amyotrophic lateral sclerosis |
| GD1b | ganglioside GD1b |
| GDH | glutamate dehydrogenase |
| GDNF | glial cell-derived neurotrophic factor |
| GFAP | glial fibrillary acidic protein |
| GLAST | glial glutamate transporter |
| GLT-1 | glutamate transporter-1 |
| GLU | glutamate |
| GM1 | ganglioside GM1 |
| $H_2O_2$ | hydrogen peroxide |
| HLA-DR | human leucocyte antigen-DR |
| $^{1}$H-MRS | proton magnetic resonance spectroscopy |
| IBM | inclusion body myositis |
| ICD | International Classification of Diseases |
| ICU | intensive care unit |
| IGF | insulin-like growth factor |
| IgG | immunoglobulin G |
| IL-6 | interleukin-6 |
| $^{123}$I-IMP | N-isopropyl-p-$^{123}$I-amphetamine |
| IVIg | intravenous immunoglobulin |
| KSP repeats | lysine–serine–proline repeats |
| LIF | leukaemia inhibitory factor |
| LMN | lower motoneuron |
| MAPK | mitogen-activated protein kinase |
| MEP | motor evoked potential |
| MHC | major histocompatibility complex |
| MMN | multifocal motor neuropathy |
| MMNCB | multifocal motor neuropathy with conduction block |
| mnd 1 | motoneuron degeneration 1 |

| | |
|---|---|
| MND | motoneuron disease |
| MOA-B | mono-oxidase-$\beta$ inhibitor |
| MPTP | 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine |
| MRC | Medical Research Council |
| MRI | magnetic resonance imaging |
| MRS | magnetic resonance spectroscopy |
| MS | multiple sclerosis |
| MSV | murine sarcoma virus |
| MUAP | motor unit action potential |
| MUP | motor unit potential |
| MUNE | motor unit numerical estimate |
| NA | N-acetyl acetate |
| NAA | N-acetyl aspartate |
| NAAG | N-acetyl aspartyl-glutamate |
| NAC | n-acetyl cysteine |
| NADH | nicotinamide adenine dinucleotide |
| NAIP | neuronal apoptosis inhibitory protein |
| NDA | new drug application |
| NGF | nerve growth factor |
| NF | neurofilament |
| NF-H | high molecular weight neurofilament |
| NF-L | low molecular weight neurofilament |
| NF-M | medium molecular weight neurofilament |
| NMDA | N-methyl-D-aspartate |
| NO | nitric oxide |
| NOS | nitric oxide synthase |
| NSAID | non-steroidal anti-inflammatory drug |
| NT-3 | neurotrophin-3 |
| NT-4 | neurotrophin-4 |
| $O^{2-}$ | superoxide ion |
| $ONOO^{-}$ | peroxynitrite anion |
| PCr | phosphocreatine |
| PD | Parkinson's disease |
| PEG | percutaneous endoscopically placed gastrostomy |
| PET | positron emission tomography |
| PKA | protein kinase A |
| PKC | protein kinase C |
| PKM | protein kinase M |
| PLS | primary lateral sclerosis |
| PMA | progressive muscular atrophy |
| PMP | peripheral myelin protein |
| PNS | peripheral nervous system |
| PP | protein phosphatase |
| PP1 | protein phosphatase 1 |
| PP2A | protein phosphatase 2A |
| PPMA | post-polio progressive muscular atrophy |
| PSMA | progressive spinal muscular atrophy |
| PSTH | peristimulus time histogram |
| PUMNS | possible upper motoneuron signs |
| PV | parvalbumin |
| rCBF | regional cerebral blood flow |
| rhCNTF | recombinant ciliary neurotrophic factor |

| | |
|---|---|
| rhIGF-1 | myotrophin |
| SIP | sickness impact profile |
| SFEMG | single fibre electromyography |
| SMA | spinal muscular atrophy |
| SMN | survival motoneuron gene |
| SNAP | sensory nerve action potential |
| SOD1 | superoxide dismutase |
| SPECT | single photon emission computed tomography |
| T | Tesla |
| 99m Tc-Hm PAO | technetium-99m hexamethylpropylene amine |
| TGF-$\beta$ | transforming growth factor-$\beta$ |
| TMS | transcranial magnetic stimulation |
| TQNE | Tufts Quantitative Neuromuscular Exam |
| Trk | tyrosine kinase receptor |
| TrkC | receptor for NT-3 |
| UMN | upper motoneuron |
| WFN | World Federation of Neurology |