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978-0-521-03426-5 - Amyotrophic Lateral Sclerosis: A Synthesis of Research and Clinical Practice

Andrew Eisen and Charles Krieger

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## 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.

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CAMBRIDGE UNIVERSITY PRESS

Cambridge, New York, Melbourne, Madrid, Cape Town, Singapore, São Paulo

Cambridge University Press

The Edinburgh Building, Cambridge CB2 2RU, UK

Published in the United States of America by Cambridge University Press, New York

[www.cambridge.org](http://www.cambridge.org)

Information on this title: [www.cambridge.org/9780521581035](http://www.cambridge.org/9780521581035)

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First published 1998

This digitally printed first paperback version 2006

*A catalogue record for this publication is available from the British Library*

*Library of Congress Cataloguing in Publication data*

Eisen, Andrew, 1936–

Amyotrophic lateral sclerosis: synthesis of research and clinical practice/by Andrew Eisen and Charles Krieger.

p. cm.

ISBN 0 521 58103 6 (hb)

1. Amyotrophic lateral sclerosis. I. Krieger, Charles, 1954–.

II. Title.

[DNLM: 1. Amyotrophic Lateral Sclerosis.]

RC406.A24E37 1998

616.8'3–dc21 97-42597 CIP

ISBN-13 978-0-521-58103-5 hardback

ISBN-10 0-521-58103-6 hardback

ISBN-13 978-0-521-03426-5 paperback

ISBN-10 0-521-03426-4 paperback

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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

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## 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



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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

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## 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.uk/08080/~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

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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.

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## Acknowledgements

Professor Lewis P. Rowland has reviewed the manuscript. We appreciate his most thoughtful comments and his generous Foreword.

Our sincere thanks to Heather Stewart and Ellen Higgins for their editorial expertise and support, and thanks to the neurologists of British Columbia who over many years have entrusted their patients with ALS to us.

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	$\alpha$ -amino-3-hydroxy-5-methyl-1,4-isoxazole-propionic acid
ASP	[ <sup>3</sup> H]-D-aspartate
BCAA	branched chain amino acid
BDNF	brain-derived neurotrophic factor
BIPAP	bimodal passive airway pressure
BMAA	$\beta$ -N-methylamino-L-alanine
BOAA	$\beta$ -N-oxalylamino-L-alanine
CaBP	calbindin-D <sub>28k</sub>
CAG	repeating trinucleotide sequence
CaMKII	Ca <sup>2+</sup> 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

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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	[ <sup>18</sup> F]-2-fluoro-2-deoxy-D-glucose
FDI	first dorsal interosseus
F <sup>1</sup> H-MRS	functional H-magnetic resonance spectroscopy
FMRI	functional magnetic resonance imaging
FTD	frontotemporal dementia
FVC	forced vital capacity
GABA	γ-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 <sub>2</sub> O <sub>2</sub>	hydrogen peroxide
HLA-DR	human leucocyte antigen-DR
<sup>1</sup> 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
<sup>123</sup> I-IMP	N-isopropyl-p- <sup>123</sup> 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

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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 <sup>2-</sup>	superoxide ion
ONOO <sup>-</sup>	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

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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