Copyright Statement

The digital copy of this thesis is protected by the Copyright Act 1994 (New Zealand).

This thesis may be consulted by you, provided you comply with the provisions of the Act and the following conditions of use:

- Any use you make of these documents or images must be for research or private study purposes only, and you may not make them available to any other person.
- Authors control the copyright of their thesis. You will recognise the author’s right to be identified as the author of this thesis, and due acknowledgement will be made to the author where appropriate.
- You will obtain the author's permission before publishing any material from their thesis.

To request permissions please use the Feedback form on our webpage.
http://researchspace.auckland.ac.nz/feedback

General copyright and disclaimer

In addition to the above conditions, authors give their consent for the digital copy of their work to be used subject to the conditions specified on the Library Thesis Consent Form.
THE EPIDEMIOLOGY OF MOTOR NEURON DISEASE IN SCOTLAND 1989-90.

A PROSPECTIVE STUDY OF INCIDENCE, CLINICAL FEATURES AND PROGNOSIS

AND INCORPORATING A CASE CONTROL STUDY OF ANTECEDENT

ENVIRONMENTAL FACTORS.

A thesis submitted to
The Faculty of Medicine, University of Auckland, New Zealand

for
The Degree of Doctor of Medicine, 1992.

by

Andrew Martin Chancellor BHB, MBChB, FRACP
To

Patricia and Elaine
"Somehow in the race for success in science, we are leaving behind the patient. There is no inherent competitiveness or reciprocity between the science and art of medicine. Without a knowledge of science, a compassionate wish to improve the health of mankind is meaningless...The increased complexity of technology and diagnostic and treatment options makes even more critical the physician's skill in managing illness and the art of communicating with patients and their loved ones. There but for the grace of God go we all, for all of us and our families are or will eventually become patients."

Louis R. Caplan¹
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Table of Contents</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>List of chapter contents</td>
<td>5</td>
</tr>
<tr>
<td>List of appendices</td>
<td>7</td>
</tr>
<tr>
<td>List of tables</td>
<td>8</td>
</tr>
<tr>
<td>List of figures</td>
<td>10</td>
</tr>
<tr>
<td>List of commonly used abbreviations</td>
<td>11</td>
</tr>
<tr>
<td>Thesis synopsis</td>
<td>12</td>
</tr>
<tr>
<td>List of publications arising from this thesis</td>
<td>18</td>
</tr>
<tr>
<td>Preface: Statement of the author's contribution to this thesis</td>
<td>19</td>
</tr>
<tr>
<td>Acknowledgments</td>
<td>21</td>
</tr>
<tr>
<td>Declaration</td>
<td>23</td>
</tr>
<tr>
<td>Body of thesis</td>
<td>24</td>
</tr>
<tr>
<td>Appendices</td>
<td>169</td>
</tr>
<tr>
<td>References</td>
<td>224</td>
</tr>
</tbody>
</table>
LIST OF CHAPTER CONTENTS

CHAPTER 1: INTRODUCTION TO THE THESIS. A HISTORY OF THE EARLY DESCRIPTIONS OF MOTOR NEURON DISEASE

The contributions by Edinburgh graduates to the first descriptions of MND
Formulation of the modern concept of MND
Terminology relating to MND
Why measure the incidence of MND?

CHAPTER 2: WORLDWIDE MORTALITY, INCIDENCE AND DISTRIBUTION OF ADULT ONSET MOTOR NEURON DISEASE SINCE 1950

Introduction
Methods of data retrieval for review
Analysis of existing studies
  Mortality studies
  Incidence studies
  Crude rates
  Age and sex specific incidence rates, standardised rates
  Clusters
  Western Pacific forms of MND
Summary and criteria for the ideal study of MND incidence


Introduction
Methods of the SMNDR
  Diagnostic criteria
  Clinically definite MND
  Clinically probable MND
Results
Discussion

CHAPTER 4: THE UTILITY OF HOSPITAL MORBIDITY DATA AND DEATH CERTIFICATES CODED AS MOTOR NEURON DISEASE (ICD 335) IN SCOTLAND 1989-90

Introduction
Methods
  Morbidity data retrieval
  Mortality data retrieval
Results
  Morbidity data
  Mortality data
Discussion
  Morbidity data
  Mortality data
CHAPTER 5: A CASE–CONTROL STUDY TO EXAMINE PRIOR HYPOTHESES CONCERNING THE POSSIBLE ROLE OF CERTAIN ENVIRONMENTAL FACTORS ANTECEDENT TO THE DEVELOPMENT OF MOTOR NEURON DISEASE

Introduction
Preceding trauma
Occupation, environmental toxins and xenobiotics
Social class and the environment in childhood

Methods
Patients
Controls
Data collection

Results
Patient characteristics
Trauma
Occupation, environmental toxins and xenobiotics
Social class and the environment in childhood

Discussion
Sources of bias
Risk factors
Trauma
Occupation, environmental toxins and xenobiotics
Social class and the environment in childhood

CHAPTER 6: THE PROGNOSIS OF MOTOR NEURON DISEASE

Introduction

Methods
Patients
Statistical methods

Results
Discussion

CHAPTER 7: CONCLUSIONS.

MAKING USE OF THE WORK FROM THIS THESIS
LIST OF APPENDICES

APPENDIX A:

SUMMARY OF THE CLINICAL FEATURES OF
28 PATIENTS EXCLUDED FROM THE MAIN ANALYSES 169

APPENDIX B:

DETAILS OF FAMILY MEMBERS IN 11 PEDIGREES WHERE A
GENETIC BASIS FOR MOTOR NEURON DISEASE
SEEMS LIKELY 190

APPENDIX C:

SUMMARY OF THE PATHOLOGICAL FEATURES OF
15 PATIENTS INCLUDED IN THE MAIN ANALYSES WHO
UNDERWENT AUTOPSY 203

APPENDIX D:

QUESTIONNAIRE USED IN THE CASE-CONTROL
STUDY 210

APPENDIX E:

INFORMATION FOR MEDICAL PRACTITIONERS CONCERNING
THE SCOTTISH MOTOR NEURON DISEASE REGISTER 218

REFERENCES: 224
LIST OF TABLES

2-1: Syndromes which may mimic or resemble idiopathic MND 56
2-2a: Studies of adult onset MND based only on mortality (death certificate) data 57
2-2b: A comparison of age specific mortality rates per 100,000 between countries 58
2-3a: Retrospective incidence studies of adult onset MND most likely to have complete or near complete case ascertainment 59
2-3b: Retrospective incidence studies of adult onset MND where case ascertainment is likely to be incomplete 60
2-3c: Retrospective incidence studies of adult onset MND which rely exclusively or principally on tertiary referral centres for case ascertainment 61
2-3d: A comparison of age and sex specific incidence and age standardised incidence, 45-74 years, by country 62

3-1: SMNDR Registration form details 82
3-2: Physical signs by region used in the classification of patients with MND 83
3-3: Summary of diagnostic categories used by the SMNDR 83
3-4: Alternatives for the distribution of clinical signs in the limbs and trunk for diagnosis of different categories of MND by the SMNDR 84
3-5: Summary of patients registered with the SMNDR but excluded from the main analyses 85
3-6: Descriptive statistics comparing the differences between the means for selected variables 86
3-7: First source of referral to the SMNDR in 1989-90 87
3-8: Clinical classification of MND subtypes at disease onset and by January 1st. 1992 88
3-9: Anatomical site of onset of muscle weakness 89
3-10: Relative risks (RR) and 95% confidence limits for clinical subtypes of MND according to sex 90
3-11: Age-sex specific incidence rates for MND in Scotland (1989-90) 91
3-12: Standardised incidence ratios for the nine Scottish regions and three island areas 1989-90 92
Outline

List of tables (cont)

4-1: International classification of diseases-9 (1979); 335, anterior horn cell disorders 107
4-2: Summary of SHIPS in relation to the SMNDR 108
4-3: Sensitivity and positive predictive value of a diagnosis of MND as determined by SHIPS 109
4-4: Classification of 112 patients miscoded as MND by SHIPS 110
4-5: Summary statistics relating to 1989-90 death certificates coded as ICD 335 111
4-6: Errors in mortality data with respect to MND 112

5-1: Published case control studies of MND 133
5-2: Patients included in the case control study 135
5-3a: Fractures by case, control, sex and number 136
5-3b: Matched case-control analysis, all subjects lifetime history of fractures 137
5-3c: Matched case-control analysis of fractures within five years of symptom onset 137
5-3d: Details of patients with MND who sustained a fracture within five years of symptom onset 138
5-4: Distribution of injuries by case, control and number of injuries 139
5-5: Distribution of operations by case, control and number of operations 139
5-6: Electric shocks 139
5-7: Blood transfusion 139
5-8: Matched case control analysis of occupation (manual vs non-manual) 140
5-9a: Matched case-control analysis of environmental/occupational toxins 140
5-9b: Details of 19 patients with MND in whom lead exposure was reported over a period of more than 12 months 141
5-10: Matched case-control analysis of domestic amenities in the first 10 years of life 142

6-1: Studies of prognosis in MND 154
LIST OF FIGURES

2-1: Mean annual death rates per 100,000 population for MND in Norway 63
2-1: Age specific incidence of adult onset MND in three countries 64
2-2: Correlation of age standardised incidence of MND with degrees north latitude 65

3-1: Diagram to illustrate the organisation of the SMNDR 93
3-2: Age specific incidence (95% CI) for 229 patients with MND in Scotland 1989-90 94
3-3: Age and sex specific incidence for 132 males, 97 females with MND in Scotland 1989-90 95
3-4: Age adjusted standardised incidence ratios of MND by region in Scotland 1989-90 96

5-1a-5-1d: Age standardised mortality ratios for lung cancer and MND in Scotland by deprivation category 143
5-2: Distribution of fracture frequency by interval before onset of symptoms due to motor neuron disease 144
5-3: Odds ratio for a fracture occurring at various intervals before the onset of MND symptoms 145

6-1
6-8: Actuarial analysis of survival for 229 patients with MND in Scotland 1989-90 156-163

Appendix B:
Pedigrees of familial cases 192-202
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MND</td>
<td>Motor neuron disease</td>
</tr>
<tr>
<td>ALS</td>
<td>Amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td>PBP</td>
<td>Progressive bulbar palsy</td>
</tr>
<tr>
<td>PMA</td>
<td>Progressive muscular atrophy</td>
</tr>
<tr>
<td>PLS</td>
<td>Primary lateral sclerosis</td>
</tr>
<tr>
<td>NCS</td>
<td>Nerve conduction studies</td>
</tr>
<tr>
<td>EMG</td>
<td>Electromyography</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomographic scan</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>OPCS</td>
<td>Office of Population Censuses and Surveys</td>
</tr>
<tr>
<td>SHIPS</td>
<td>Scottish hospital in patient survey</td>
</tr>
<tr>
<td>ISD</td>
<td>Information and statistics division of the Common Services Agency for the Scottish Health Service</td>
</tr>
<tr>
<td>SMNDA</td>
<td>Scottish Motor Neuron Disease Association</td>
</tr>
<tr>
<td>SMNDR</td>
<td>Scottish Motor Neuron Disease Register</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
</tbody>
</table>