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.

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by

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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.Caplan[1]

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LIST OF COMMONLY USED ABBREVIATIONS

MND	Motor neuron disease
ALS	Amyotrophic lateral sclerosis
PBP	Progressive bulbar palsy
PMA	Progressive muscular atrophy
PLS	Primary lateral sclerosis
NCS	Nerve condution studies
EMG	Electromyography
CT	Computed tomographic scan
MRI	Magnetic resonance imaging
OPCS	Office of Population Censuses and Surveys
SHIPS	Scottish hospital in patient survey
ISD	Information and statistics division of the Common Services Agency for the Scottish Health Service
SMNDA	Scottish Motor Neuron Disease Association
SMNDR	Scottish Motor Neuron Disease Register
RR	Relative risk
OR	Odds ratio
CI	Confidence interval

THESIS SYNOPSIS

Discussion of results is included at the end of each chapter. The following is an abstract of the contents and conclusions of this thesis.

Chapter 1

The part that 19th century Edinburgh medicine played in formulating the early concepts of motor neuron disease as a nosological entity is described, including some hitherto unrecognised descriptions by graduates of Edinburgh Medical School, including the first description of progressive bulbar palsy. Credit is given to the great European neurologists, especially Charcot's landmark contribution of the definitive clinico-pathological correlations.

Terminology relating to MND is discussed and the problems which have arisen over the nosology relating to diseases of motor neurons. The requirement for a clearly defined classification system and the importance of measuring incidence in this disease are outlined.

Chapter 2

A comprehensive review of previous studies of incidence, mortality and distribution is presented. It is suggested that the value of previous clinical descriptions and epidemiological studies of motor neuron disease (MND) have been limited by methodological problems.

There appears to have been a real increase in mortality from MND over recent decades. Comparison of incidence in different

places is complicated by non standardised methods of case-ascertainment and diagnosis but evidence is presented which challenges the traditional concept that the distribution of MND in developed countries is uniform and static. It remains uncertain, from the evidence available, if age specific incidence continues to rise into old age and the apparent "peak" in late-middle life is due to ascertainment bias. This is an important consideration on which to base aetiological hypotheses. In the northern hemisphere there is a weak positive correlation between standardised, age specific incidence and distance from the equator. There is a high prevalence focus of an atypical MND/ALS on Guam, and while an environmental factor is probably responsible, its nature is uncertain. The relevance of other reported clusters of MND is discussed and the requirements for the ideal study of MND incidence are outlined, which acted as the impetus for the Scottish Motor Neuron Disease Register (SMNDR).

Chapter 3

The methodology of the SMNDR is described. This is the first collaborative, population based, prospective, epidemiological study of MND and illustrates the feasibility of such a study and the way in which Scotland is suited (in terms of size and National Health Service structure) to such a project. Diagnostic criteria are outlined for application to this and other large scale studies.

Of 257 patients registered with the SMNDR as possible MND diagnosed in 1989 and 1990 in Scotland, 229 with proven (by autopsy), clinically definite or probable, sporadic or familial MND, form the basis of the description of incidence, distribu-

tion, clinical features and natural history contained in this chapter. The crude incidence was 2.24/100,000/year and age specific incidence continued to rise steeply with age into the very elderly age bands. No evidence for clustering on the basis of Scottish regions was found. 5% of patients had a family history of MND; the clinical pattern varied according to sex and age, with elderly women most likely to present with, or develop, progressive bulbar palsy.

Chapter 4

The utility of the 1989-90 Scottish Hospital In-Patient Statistics (SHIPS) and 1989-90 death certificate coding (Registrar General for Scotland) by International Classification of Diseases (ICD)-9, 335 (MND) are analysed as a tool for epidemiological studies and heath care planning. Coded hospital discharge data were an inaccurate record of a diagnosis of MND with a positive predictive value of a diagnosis of MND as determined by SHIPS of 70%. Such data cannot, in their present form, be used as a reliable measure of incidence in Scotland.

Greater care is required in the preparation of discharge summaries and coding if these data are to be useful for health care planning and epidemiological research. However, SHIPS acted as an important source of case notification for the SMNDR to achieve a complete sample of patients. There was also a problematic false positive rate (10%) for mortality data but this source more closely approximated true incidence.

Chapter 5

A review of previous case control studies of environmental risks for MND is presented. In order to test the hypothesis that certain environmental factors may play a role in the aetiology of MND, a case control study of 103 incident patients (diagnosis date May 1990-October 1991; 57 from the above cohort (as described in chapter 3) and 46 diagnosed in 1991, age and sex matched with community controls was conducted and is described. Measures were taken to minimise potential sources of bias and these are discussed.

Fractures were more common in patients than controls especially in the in the five years prior to symptom onset (odds ratio = 15 (95% CI, 2.3-654). Manual workers were over represented and a number of environmental exposures of potential toxicity including exposure to lead (OR = 5.3 ,95% CI,1.5-11) and solvents or chemicals (OR = 3.8, 95% CI 1.5-11) were found. The limited extent of these associations favours a multifactorial aetiology for MND. No relationship to social class, poliovirus infection or to factors which might increase the risk of enteroviral infection in childhood (home space and domestic amenities) was found.

Chapter 6

A comprehensive review of previous prognostic studies in MND is presented. An actuarial analysis of the survival of the cohort of 229 incident patients (57 seen in person) in Scotland in 1989-90, with complete follow up for a mean of two years from diagnosis, is calculated on the basis of the SMNDR clinical classification system.

The overall 50% survival from diagnosis was 1.2 years (95%

CI, 1.0-1.4) and from symptom onset, 2.5 years (95% CI, 2.2-3.0 years). There were significant differences in survival with a poorer prognosis for: progressive bulbar palsy (PBP), female sex and age > 65 years. The presence of PBP and old age were the strongest predictors of outcome, the difference in survival between the sexes was due to the higher frequency of PBP in females. The overall five year survival from symptom onset was 27.7% (95% CI, 19.9-36.0%) but for patients with PBP as the presenting feature was only 3.5% (95% CI, 0.0-15%). These results suggest that, in well defined cohorts, survival can be predicted with some confidence and are useful for the planning of treatment trials.

Chapter 7

In this concluding chapter I consider the applications of the work contained in this thesis.

Appendix A

This appendix describes the clinical details of 28 patients registered with the SMNDR and diagnosed in 1989-90 but excluded from the analysis of incidence because of failure to fulfil SMNDR diagnostic criteria (eg coexisting neurological disease or revision of diagnosis with follow up). This group represents part of the differential diagnosis of MND and highlights some of the difficulties in making the diagnosis when the disease is incompletely developed.

Appendix B

A summary of the pathological findings of those patients included in the incidence analysis who underwent autopsy is recorded. By definition, all patients had typical findings of MND, including some with the recently described ubiquinated inclusion bodies.

Appendix C

The results of pedigree searches of 11 families (5% of incident patients) with a probable genetic basis for MND are presented. These families demonstrate that autosomal dominant inheritance is usual and illustrate clinical heterogeneity of age and disease pattern.

Appendix D

Details of the questionnaire administered to subjects in the case-control study.

Appendix E

Sample letter of explanation to General Practitioners, sent after patient registration with the Scottish Motor Neuron Disease Register.

LIST OF PUBLICATIONS ARISING FROM WORK

ASSOCIATED WITH THIS THESIS

(Excludes publications in abstract form)

Chancellor AM, Carstairs V, Elton RA, Swingler RJ, Warlow CP. Affluence, age and motor neuron disease [letter]. *J Epidemiol Community Health* 1992;**46**:172-173.

Mitchell JD, Chancellor AM. *Amyotrophic lateral sclerosis-Aran's Edinburgh inspiration?* In:*Proceedings of the third European meeting for the history of the neurosciences* 1992.

Chancellor AM, Mitchell JD, Swingler RJ. The first description of idiopathic progressive bulbar palsy. *J Neurol Neurosurg Psych* 1992;**In press.**

Chancellor AM, Warlow CP. Adult onset motor neuron disease: Worldwide mortality, incidence and distribution since 1950. *J Neurol Neurosurg Psychiatry* 1992;**In press.**

Chancellor AM, Swingler RJ, Fraser H, Warlow CP. The Scottish motor neuron disease register: A prospective study of adult onset motor neuron disease in Scotland. Methodology, demography and clinical features of incident cases in 1989. *J Neurol Neurosurg Psychiatry* 1992;**In press.**

Chancellor AM, Fraser H, Swingler RJ, Clarke JA, Warlow CP. The utility of Scottish morbidity and mortality data for epidemiological studies of motor neuron disease. *Submitted to J Epidemiol Community Health* 1992.

de Belleroche J, Chancellor AM, King A, Hardy J, Lane R, Houlden H. Absence of linkage between chromosome 21 loci and familial amyotrophic lateral sclerosis [letter]. *Submitted to The New England Journal of Medicine* 1992.

Chancellor AM, Fraser H, Slattery J, Swingler RJ, Warlow CP. The clinical features and prognosis of motor neuron disease: A prospective population based study. *In preparation* 1992.

Chancellor AM, Swingler RJ, Fraser H, Slattery J, Warlow CP. Motor neuron disease and the environment: A case-control study *In preparation* 1992.

Willison HJ, Chancellor AM, Whitelaw JW, Warlow CP. The frequency of anti-GM1 antibodies and paraproteins in motor neuron disease: A population based case-control study. *In preparation* 1992.

PREFACE: STATEMENT OF THE AUTHOR'S CONTRIBUTION TO THIS THESIS

My work for this thesis spanned two years and began on a part time basis in June 1990, when working as Clinical Neurology Registrar for the Lothian Health Board. In November 1990 I began a full time Research Fellowship in the University of Edinburgh based in the Department of Clinical Neurosciences, Western General Hospital. The thesis was completed in May 1992.

The observations concerning the early descriptions of Motor Neuron Disease by Edinburgh graduates were my own, based on reading in the Royal College of Physicians' of Edinburgh library and information from the British Library, London. The identification and compilation of the references to previous work essential for background reading including the review of the worldwide epidemiology of MND and the entry and organisation of all references within a medical reference database (Research Information Systems "Reference Manager") was my own work. All references quoted in this thesis have been viewed in the original except for parts of foreign language references, some of which were not translated in their entirety.

I was responsible for: the supervision and organisation of patient information compiled by the Scottish Motor Neuron Register; ongoing adaptation of the patient database to the needs of the project; keeping collaborators with the project informed of developments by monthly newsletter; devising diagnostic criteria suitable for use by the project; classification of patients according to these criteria; negotiating retrieval of Scottish hospital morbidity and mortality data for International Classification of diseases code 335 (Motor Neuron Disease) for 1989-90

and the inspection of all medical records (hospital, general practice and autopsy records) relating to the patients described including the details of pedigrees for familial MND.

I approached the specialists and GP's for permission to see all (n=103) patients in the case control study and interviewed these patients with 103 control subjects at their homes in all regions of Scotland as necessary. The questionnaire for the case control study was devised personally and all data entered into a computerised database (dbase IV-registered trade mark) myself. I saw and examined six patients from four of the pedigrees with familial MND and undertook correspondence to establish features of family members in other pedigrees. I collected and arranged for the storage and transportation of all blood samples including those for linkage analysis (not reported here).

The statistical analysis of demographic variables, incidence, distribution, and descriptive statistics relating to the clinical features of all patients described herein was my own work.

ACKNOWLEDGMENTS

Many people have contributed to this thesis without whose help it would never have reached fruition. The Scottish Motor Neuron Disease Register (SMNDR), funded by The Scottish Motor Neurone Disease Association (SMNDA) was established in January 1989, largely through the work of Dr.R.J.Swingler and I was most fortunate to have the opportunity to build upon his work. The SMNDR is a collaborative project and I am grateful to the neurologists, neurophysiologists and others in Scotland for their registrations and the permission to see their patients without whose help this thesis would not have been possible. They included:

Dr J.E.C. Hern, Dr. R. Knight (Aberdeen); Dr. D. Davidson, Dr. A. Forster, Dr. R. Roberts (Dundee); Dr. B. Ashworth, Dr. R.E. Cull, Dr. E.H. Jellinek, Dr. A. McInnes, Dr. B. Pentland, Dr. P.A.G. Sandercock, Professor C.P. Warlow, Dr. R. Will (Edinburgh); Dr. J.P. Ballantyne, Professor P.O. Behan, Dr. I. Bone, Professor F.I.Caird, Dr. I. Draper, Dr. W.F. Durward, Dr. G. Jamal, Professor P. Kennedy, Dr. R. Metcalfe, Dr. M. Thomas, Dr. A.I. Weir (Glasgow); Dr. L.R. Fisher (Inverness).

I am especially grateful to Mrs. Hazel Fraser, with whom I worked closely, and who managed the large amount of secretarial work associated with running the SMNDR database and helped in the retrieval of patient records. I would like to thank Miss Shona Henderson and Mrs. Rita Walker, SMNDA family care officers, for

informing patients about the SMNDR and for their helpful liaison when approaching patients. Dr. Susan Holloway, Clinical Geneticist, helped with the description of pedigrees of familial MND (Appendix B) by tracing the death certificates of affected and unaffected relatives in Register House, Edinburgh; I have applied measures of deprivation (Chapter 5) to a cohort of deaths from MND based on work by Dr. Vera Carstairs (Edinburgh Health Services Research Network). Much of the statistical computation relating to the case control study and to the prognosis of MND was done by Mr.J.Slattery, Medical Statistician. Dr. Jan Bell, neuropathologist at the Western General Hospital, Edinburgh, performed most of the autopsies described in Appendix C. Susan McHugh, medical artist, was responsible for some of the graphical illustrations; Huub Williams, Dutch Medical student, helped in translation of papers in German and Rosemarie Bland, those in French. Dr. J.D.Mitchell introduced me to the writings of Charles Bell. I would like to thank The David Cummings Trust, based in Blenheim, New Zealand for monetary assistance with the purchase of items of computer hardware.

Finally, I am immensely grateful to Professor Charles P. Warlow for allowing me to join his Department to undertake this work, for his tireless instruction in the science of clinical medicine and his continuing guidance, support and encouragement both in personal and professional matters.

DECLARATION

No work contained in this thesis has ever been presented for a degree or diploma at the University of Auckland or any other University, neither is it presently being submitted for a degree or diploma, except to the University of Auckland.

CHAPTER 1

INTRODUCTION TO THE THESIS.

A HISTORY OF THE EARLY DESCRIPTIONS OF MOTOR NEURON DISEASE

"...life itself is a whole process of rediscovery of what our forebears have known-pain and pleasure, ecstasy and despair, beauty and ugliness. And for even the most modest of those who have had the privilege of working in biomedical science there has been the rediscovery of something that we can share even with Galileo-the excitement of making a discovery.

Sir C.C.Booth[2].

" Now and again there is a man whose life and work make an enduring impression and who, escaping the thralls of nationalism becomes a teacher and a leader."

From Sir William Osler's obituary on Jean-Martin Charcot[3].

THE CONTRIBUTIONS BY EDINBURGH GRADUATES TO THE FIRST DESCRIPTIONS OF MOTOR NEURON DISEASE

It difficult to disentangle the precise sequence of events in the mid 19th century surrounding the early descriptions of idiopathic motor neuron disease (MND) and its principal clinical presentations: amyotrophic lateral sclerosis (ALS), progressive bulbar palsy (PBP), progressive muscular atrophy (PMA) and primary lateral sclerosis (PLS). Virtually no disease subsequently eponymously endowed has been described by only one person and the process of rediscovery is a particular feature of the clinical practice of medicine[2]. Nowhere is this more true than for MND, for while there is no doubt that the definitive synthesis of the clinical and pathological features was crystallised in the writings of Charcot[4], whose name is associated with "classical" MND, many other physicians contributed to the earliest descriptions. Of these there are four who, to a greater or lesser extent, were associated with the "Golden Age" of Edinburgh medicine.

A letter by R.W.R.Robinson (1777-1866), of Preston, England dated July 21st. 1825, is quoted by the Edinburgh neuroanatomist and surgeon Sir Charles Bell (1774-1842), in his book on the nervous system[5] and is probably the first documented case of MND. This contribution by Robinson and Bell to the early descriptions of MND has not previously been recognised. Robinson was born in Lancashire and graduated doctor of medicine at Edinburgh on 12th September, 1800. He was president of Edinburgh's Royal Medical Society, founded in 1734 by a group of medical students after the acquisition of a fresh body for dissection and meeting initially in taverns

> *"...with the intention that a dissertation in English or Latin on some medical subject...should be composed and read"*[6].

Robinson's doctorate was not, however, on a neurological subject (*Disputatio medica inauguralis de vesicea, urethraeque morbis*); he became a Licentiate of the College of Physicians (London) in 1807 and practised in Lancashire where he was an important influence in the board of management of the Preston Dispensary, founded in 1809[7]. He wrote to Charles Bell for advice about a previously well woman of nearly 70 years.

> *" From the first of her complaint to the present moment she has been free from headach (sic) and from pain, numbness, or debility of the limbs. The vision and hearing are natural; the appetite good; the bowels regular, and the sleep natural ....Some few months ago she had some difficulty in using the tongue and in expressing particular words. This difficulty has gradually increased, and now she cannot protrude the tongue, or even move it. She has lost her speech altogether. The tongue itself is soft and pulpy; but it retains its sense of taste and feeling. The deglutination is impaired and occasionally she is distressed with a sense of suffocation, in attempting to swallow food, which she is now obliged to do with great care.*

She cannot hack up any thing from the throat, nor draw any thing from the posterior nares by a back draught. The features of the face are quite natural, and the skin retains its feeling. The saliva occasionally flows from the mouth."

No follow up is available to tell if the disease became more widespread, neither is information available about the examination of deep tendon reflexes which was not introduced into clinical practice until 1875[8]. Bell noticed the similarity between this patient's condition and the syndrome observed in a dog after section of the lower cranial nerves and concluded that the patient was suffering from

"...a paralytic affection of the ninth nerve."

and noted that the

"...function of the fifth nerve was entire."

He recommended nauseating medicines and leeches under the mastoid amongst other remedies. This syndrome combining anarthria, impaired deglutition, ptyalism and impaired tongue movement, probably with mixed upper (slow clumsy tongue) and lower (soft, possibly wasted tongue) motor neuron signs, is undoubtedly due to PBP and was published 30 years before that usually quoted[9,10] as the first descriptions of PBP by Duchenne de Boulongne in 1860[11] and Leyden[12] in 1870.

The Edinburgh contribution to early descriptions of MND is also evident in the writings of Bell himself[5]. Charles Bell was born in Edinburgh where he trained in anatomy and surgery. His contributions to neurology are numerous[13], including the formulation of the concept of a different function for the posterior and anterior spinal roots; he is remembered by every

medical student for Bell's palsy and for the long thoracic nerve of Bell but he also made other, less well known, original clinical descriptions in neurology[14,15]. He was a surgeon in the Napoleonic wars; an author of beautifully illustrated books on neuroanatomy and a medical artist (his paintings of opisthotonus in tetanus and gun shot wounds adorn the Edinburgh College of Surgeon's museum). In the book which contains Robertson's letter[5] he described a woman of 41,

> *"...apparently in good health with weakness of the left foot, and five weeks afterwards, with weakness of the right foot.....gradually she was altogether deprived of motion in her legs...it was remarkable that she experienced no diminution of the sensibility of the skin of the affected parts...a flea bite distressed her, yet she could not move to scratch herself...A year after the commencement of the complaint, the weakness extended to the arms, and she began to experience difficulty in her breathing. The accessory muscles of respiration in the neck and chest were then seen to act with remarkable force...and died in six weeks".*

John Abercrombie (1780-1844) was born in Aberdeen and graduated MD from Edinburgh in 1803. He became physician to the King in Scotland in 1828 but failed in his bid to become professor of medicine; Oxford awarded him the degree of Doctor of Medicine and it was remarked of him by Dr. James Gregory,

> *"...that wee fellow will some day be Edinburgh's most sought after consultant".*

His portrait can be seen today in the Royal College of Physician's, Edinburgh, as can the copy of his book on the brain and spinal cord which he donated to the library[16] and which was translated into French and quoted by Aran. He describes a patient who had a scapulo-humeral syndrome, probably a spinal muscular atrophy:

"...a young man, aged 14, who had nearly lost the muscular power of the upper part of both his arms, accompanied by a most remarkable diminution of substance of the principal muscles. The deltoid and biceps are reduced to the appearance of mere membranes and the same affection extends in rather a less degree to the muscles upon the scapula; the muscles upon the forearm, however are full and vigorous....in other respects he is in perfect health. The affection has come on gradually.

He speculates as to the lesion involved:

"It is impossible, I think, to explain such cases as these, except upon the principle of local affections of the nerves, which are at present involved in much obscurity".

Six *"cases of a peculiar species of paralysis"*[17] are outlined by the fourth Edinburgh graduate, John Darwall (1796-1833). Darwall graduated MD from Edinburgh in 1821 with his thesis entitled *"Diseases of Artisans with particular reference to the inhabitants of Birmingham"* - where he was born and spent much of his life[18]. His cases are heterogeneous and some may have had brachial neuritis as the disease responsible for the patchy limb weakness beginning in proximal arm muscles and sparing the bulbar region, however, some may have had MND. Darwall died of septicaemia following a post mortem room accident[19].

Unfortunately it is unlikely that these four Edinburgh graduates ever exchanged ideas in person because a review of the chronology shows that they were never all residing simultaneously in Edinburgh[20].

FORMULATION OF THE MODERN CONCEPT OF MOTOR NEURON DISEASE

F.M. Aran (1817-1861), and his teacher G.M.A. Duchenne de Boulogne (1806-1895) were responsible for the more definitive descriptions of PMA, particularly the juvenile, inherited forms[21,22] although, to begin with, there was confusion over the difference between the amyotrophies and muscular dystrophies[23]. A patient with amyotrophy and colic, thought to be due to lead poisoning, prompted Aran to wonder if lead might be responsible for other, apparently idiopathic cases of MND[21]. Duchenne noted the palatal weakness in PBP[11].

> *" The patient could not produce a large enough breath, not even to extinguish a candle. But if we pinched the patient's nose the breath emanating from the mouth was sufficient...Pronunciation of the letters p and b was much clearer when the nose was pinched shut."*

In Goldblatt's account of the history of motor neuron disease[24] the descriptions of PMA by Aran and Duchenne in 1848-50 were said to predate those of ALS. However, a review by Veltema[25] of the case of Prosper Lecompte, a French Circus owner and patient of J. Cruveilheir (1791-1874), who was admitted in 1850 and died in 1853, shows that descriptions of ALS were documented about the same time as discussions of PMA. The description of Lecompte's illness leaves no doubt that he had a combination of lower motor neuron (LMN) and upper motor neuron (UMN) signs, although there is no information on deep tendon reflexes. Intellect, sensation and sphincter function were unaffected and the anterior roots were shrunken at autopsy.

Duchenne was a close and trusted friend of the great J-M Charcot (1825-1893). In 1869 Charcot described, in detail, both the clinical and pathological features of ALS in two cases at the

Salpêtrière[26]. It is to Charcot that most of the credit is due for setting down the definitive descriptions of ALS in lectures given in 1874 and subsequently, based on 20 clinical cases and 5 autopsies[4,27]. Charcot recognised medullary involvement and the UMN signs described as *"spasmodic"* and *"contracture"* as well as the previously emphasised atrophy of muscles. His preponderance of females is an early example of selection bias, given the Salpêtrière's use for

> *"...the confinement of beggars, unwanted womanhood and the infirm"*[3].

Charcot also described a patient with isolated spastic quadraparesis due to degenerative disease of the pyramidal tract[28] and W.H.Erb (1840-1921) was also one of the earliest to draw attention to a chronic form of spastic spinal paralysis[29] in 1875, the year of the account of the tendon reflexes. In his account of 16 cases, translated by Saundby, Erb acknowledged Charcot's case report but felt that

> *"...not a single example of the real primary lateral sclerosis existed in the literature'*

and

> *"...the disease approached the 'sclérose latérale amyotrophic', excellently described by Charcot, but the absence of muscular atrophy, of which no trace was ever present, distinguishes it from that...the anterior grey matter cannot be materially implicated...the disease must be distinguished from the following: chronic transverse myelitis, tabes dorsalis...multiple sclerosis and paralysis of the cauda equina, also the hemiplegic form from cerebral hemiplegia..."*

In nine of Erb's patients the spasticity was isolated but nearly half had disturbances of sensation (but not anaesthesia),

two had *"bladder feebleness as a temporary condition"*. One had bulbar involvement but non had sexual dysfunction, cognitive disturbances, pain or bedsores.

Sir W.R. Gowers (1845-1915) also entertained the possibility of a *"pure"* primary lateral sclerosis. Spillane refers to Gower's *"Manual of diseases of the nervous system* as the *"neurological bible"*[10]. In this authoritative text (viewed in the National Hospital library, Queen's Square, London) Gowers expanded the concept of PLS as a disease due to *"sclerosis"* of pyramidal tracts manifesting only UMN signs while sparing sensation and sphincter function. He separated this from multiple sclerosis and the ataxias although some of his patients may have had hereditary spastic paraparesis[30]. The debate about whether PLS represents a discrete entity has continued but recent clinical[31,32] and pathological[33,34] evidence supports the concept of an isolated UMN (corticospinal) degeneration as one of the subgroups of motor neuron disease. Gowers entertained the possible relationship of trauma to MND and also coined the term "abiotrophy" to describe the selective premature decay of a functionally related population of neurons[35].

By the end of the nineteenth century, as the anatomy of upper and lower motor neurons as separate anatomical structures became acknowledged, the clinical descriptions of MND in its various forms were well documented in standard textbooks of the day, although the relationship of pathology to clinical signs remained a matter of debate[36].

TERMINOLOGY RELATING TO MOTOR NEURON DISEASE

Charcot coined the term *"sclérose latérale amyotrophique"*[37] to emphasise the pronounced degeneration of lateral corticospinal tracts principally in the cervical cord and noted the atrophy of hypoglossal nuclei and the anterior but not dorsal roots. *"Charcot's Disease"* is sometimes applied to *"classical"* ALS as well as to other diseases for which the founder of modern neurology is now remembered. However, motor information is conveyed from higher centres to the brainstem in the cerebral peduncles and pyramids, not by lateral columns, so that the term ALS, if literally applied, implies disease confined to the spinal cord (although this was not as originally intended by Charcot). In addition, gliosis is the major histological finding in MND not *"sclerosis"*, derived from a Greek word for hard[38], usually applied to overgrowth of fibrous tissue.

From the start there was a confusion over when to use the terms ALS, PMA and PBP. Charcot had included cases of PBP with his list of earlier descriptions of ALS. Leyden[12] allotted the syndrome of ALS to the category of either PMA or PBP dispensing with the former. Gowers' pathological illustrations in his Manual of Diseases of the Nervous System[30] show the similarity of lesions in cases with clinically defined PLS, PMA and ALS he stated:

> *" I have not met with a single case of progressive muscular atrophy in which the pyramidal tracts were unaffected"* (p373).

He did not think Charcot's introduction of the term ALS very helpful, with its implication that the primary lesion was the

degeneration of the pyramidal tracts, and that the atrophy of the anterior horn cells was secondary or *"deuteropathic"*.

> *" Charcot's distinction is in effect giving a new name to an old disease....a division into two classes* [meaning PMA and ALS] *(into which the same case may fall at different periods) is less in harmony with the facts of the disease than is a recognition of the varying extent of the lesion and the corresponding variation of clinical character and course"*[30].

A unifying concept of diseases of the motor system was evolved by Brain and the term *"motor neurone disease"* introduced to apply to a spectrum of clinical subtypes[39], leaving authors to describe more precisely to which clinical pattern they refer. This approach has influenced much British writing when discussing this group of disorders and is a useful generic term which has withstood the ephemeral fashions of classification systems.

Today, the terms used today by authors under the rubric of MND often vary in their meaning[40]. ALS in the North American literature is *usually* applied to mean MND, with both UMN and LMN involvement, either confined to spinal levels or with bulbar features. However, even recent North American studies use ALS to describe patients with only LMN signs[41,42] and some authors even separate MND and ALS as different disorders[43].

The term PMA may be used to mean late onset chronic forms of spinal muscular atrophy. However the evidence, based on clinical and genetic studies, suggests a real subdivision between spinal muscular atrophy and PMA. The latter being a disease of adult life which blends clinically and pathologically into the other subtypes of adult onset MND, while spinal muscular atrophy is principally an infantile and childhood disease usually of proximal distribution with an autosomal recessive

inheritance[44,45].

A patient with both a combination of PBP and PMA may arbitrarily be classified by some as PBP[46]. Whether PBP ever remains isolated to the brainstem, as the name implies, without spread to other levels is uncertain. There is increasing evidence, with the widespread use of magnetic resonance imaging that PLS, a numerically small group, and much debated entity, is part of the spectrum of MND but with exclusively upper motor neuron (UMN) signs[32,34].

The distribution of pathological changes does not necessarily correlate with clinical features even in well studied cases[47,48] and ALS, PBP, PMA and PLS, the usually accepted principal clinical subtypes in adults, are almost certainly varieties of a single disease with the common pathological feature of anterior horn cells loss and variable pyramidal tract involvement.

"Lou Gehrig's disease" is the euphemism often used by lay American's, after the most famous first baseman in major league history. Gehrig died in 1941 but his declining batting average and cinemagraphic evidence has been used as an indirect measure of his muscular strength pointing to the onset of his illness in 1938[49]. *"Creeping paralysis"*, a particularly vivid description of its effect, is sometimes used to describe MND[50].

The most famous Britons to be affected are David Niven, actor, and Professor S. Hawking, present Lucasian professor of mathematics at Cambridge University, who has been described as the greatest theoretical physicist since Albert Einstein[51]. As described both in a recent television documentary of his life and work and in his book[52], Hawking was told, in 1963, that

he had MND and could expect to live for two years[52]. His illness demonstrates a striking dichotomy between his great disability and his handicap, which is slight, at least as far as theoretical physics is concerned. His illness also raises important questions about predicting prognosis in MND.

The spelling of the word "neuron" in MND is also a source of some disagreement. Gould medical dictionary[38] gives both "neurone" and "neuron" as acceptable. The word is derived from the Greek for sinew, string, nerve, related to the Latin "nervus" and to the English "sinew". It refers to the complete nerve cell, including the cell body, axon, and dendrites. Walton's authoritative textbook on neuromuscular disorders[53] uses "neurone" but in most medical journals and in particular, neurological journals, the spelling "neuron" is in most widespread and becoming preferred although the *Lancet* uses "motoneuron" or "motorneurone" or "motorneuron". In North America the "e" in "neuron" is uniformly deleted although American authors publishing in British Journals may include the "e"[54]. "Neuron" is used throughout this thesis except when quoting a different spelling used by other authors.

WHY MEASURE THE INCIDENCE OF MOTOR NEURON DISEASE?

Despite recent advances in the understanding of those forms of MND which have a genetic basis[45,55,56] and although conditions have been, and continue to be, described which may mimic MND (table 2-1), for the vast majority of patients with sporadic adult onset disease the cause is unknown, the subject of much speculation and a wide variety of diverse hypotheses of aetiopathogenesis[57-59].

The possibility that environmental factors play a role in MND, particularly in the light of studies from the Western Pacific[60] (Chapter 2), is an appealing and recurring theme[61]. However, this hypothesis is not supported by the traditional teaching that the distribution of MND in developed countries is uniform and static[62-66]. A recent editorial[67] has challenged this view, suggesting that the distribution of MND in time and place may not be as uniform as previously believed. Clearly any non-random distribution in place and time is important to identify as a clue to potential environmental risks.

As well as studying temporal and geographic trends, incidence studies offer an opportunity to collect population based data to help clarify some of the issues alluded to above and discussed in more detail in the subsequent chapters, ie accurate demographic features, clinical description, appropriate classification and prognosis. Finally, and importantly, reliably measuring the size of a problem allows the appropriate planning and allocation of health care resources.

CHAPTER 2:

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

INTRODUCTION

"It is from well-arranged medico-statistical and topographical inquiries that we are ultimately to expect a vast increase to our knowledge of the remote causes of disease...The value of these researches...can scarcely be estimated too highly."

Streeten Green, written in 1840[68].

The last published review of the epidemiology of MND was 10 years ago[66] although the preparation of this thesis coincided with a further analysis by Kurtzke[69]. A thorough reappraisal of previous research is appropriate as the background to the incidence study which forms the basis of this thesis. The aims of this chapter are therefore to:

(1) Critically review all publications concerned with the mortality and incidence of adult (>15 years) onset MND in defined populations. Publications were specifically reviewed for any evidence of a non-random distribution in place both between studies and within populations. Some incidence studies also calculate, or include, a prevalence survey but studies exclusively of MND prevalence are not incorporated in this analysis as they do not add further to aetiological considerations.

(2) Review secular trends in this disease.

(3) Examine the reports of clusters of MND which might provide clues to environmental influences.

(4) Compare the epidemiology of sporadic MND with the Western Pacific forms and summarise the results of the intensive search for the cause of this MND variant.

(5) Identify standards for future epidemiological studies of MND and possible research directions.

METHODS OF DATA RETRIEVAL FOR REVIEW

This review was conducted according to recent guidelines for medical reviews[70,71]. A comprehensive search by individual year using Cambridge Compact Disc Medline from January 1965-June 1991 was used to identify all publications in English, or with English abstracts, dealing with the frequency (mortality or incidence) of adult onset MND in defined populations worldwide. The references in these publications were used to cross check the thoroughness of this search and to locate papers published from 1950-1965. In addition any papers dealing with survival or prognosis, which may contain incidence data and reports of clusters, were specifically sought. All papers were reviewed in the original.

Many population-based studies of MND have been published which vary widely in their quality. For the purposes of systematic analysis these were divided into mortality studies, based only on death certificate data [72-86], and incidence studies divided according to their methodology. Valid comparisons between studies can only be made if similar methodological standards and diagnostic criteria are applied. While most epidemiological studies included the syndromes of amyotrophic lateral sclerosis (ALS), restricted progressive bulbar palsy (PBP) and progressive muscular atrophy (PMA) some studies were confined to ALS. The best incidence studies used multiple sources of case ascertainment, and/or were based on recognised systematic medical documentation systems[87-97]. The second group of incidence studies were based on more than just tertiary referral records but there was some doubt about the completeness of case finding[98-106]. The third group were those in which incidence had been

calculated using single hospital records, usually neurology departments, or where data were incomplete in review, or where the diagnosis was based on unverified hospital discharge data[107-117]. There are a large number of published series of patients with MND but these were not included if not specifically dealing with incidence or the population denominator was unclear[118-123]. Some syndromes may mimic or resemble idiopathic MND but such studies of motor neuronopathy or neuropathy with recognised cause were excluded (table 2-1).

ANALYSIS OF EXISTING STUDIES

Mortality studies (Tables 2-2a,b)

According to the rules for selection of cause of death for primary mortality tabulation by the World Health Organisation, MND should be coded as the underlying cause even if it appears as a contributing factor[72]. However, this may not be followed in standard practice and some studies have used rates for MND classified as the "underlying cause" and excluded patients with MND whose deaths were certified as due to another cause[73] while others have separated the two groups[78] or used rates based on wherever the diagnosis appears on the death certificate[79]. Comparison of rates for subgroups of MND (ie ALS,PBP,PMA) based on death certificate data are complicated by changes in the International Classification of Diseases (ICD) and non-standardised methods of diagnosis. ICD-9, introduced in 1979, was a further change from ICD-8 with respect to MND[66] (see Chapter 4). ALS had previously been recorded as a distinct entity (code 348.0, ICD-8), although some studies use ALS to refer to all

types of MND[80]. In ICD-9 a new code, ICD-335, was created for all anterior horn cell diseases with 335.2 for "motor neurone disease", which contains "ALS; MND (bulbar) (mixed type), and PMA (pure)" (Table 4-1). A further ICD is planned for 1993. Death certificate data alone are therefore unlikely to be reliable enough for comparing rates of MND subgroups or even for comparing rates between different countries, particularly when these overlap ICD changes, and because of the confusion which exists over diagnostic criteria (see below).

Age specific mortality rates, where given, usually rise to a peak between 60 and 75 years, followed by a sharp decline, but this simply may reflect difficulties with diagnosis in the very elderly. In England and Wales, for birth cohorts after 1900 followed up separately over time, mortality increases continuously with age (C.Martyn, personal communication), the same finding has been reported from Sweden[75]. Rates in males are consistently higher than females, usually around 1.5:1.

When international mortality figures were last reviewed in detail[72], a rise from 1952 to 1960 followed by a sharp fall until 1971 was observed in Japan while in contrast, a rise in European and Australasian rates and stationary figures for the USA were noted. There is more recent evidence from the UK[73], Sweden[75], USA[76,77], France[79], Norway[82] (Fig 2-1) and most recently, Scotland (Dr.R.J.Swingler, personal communication, paper in preparation) that mortality rates are continuing to rise with time (table 2-1a), Fig 2-1 gives the typical scale of the increase which has been observed in these studies.

In the USA overall ALS mortality increased 46% for men and 49% for women between 1977 and 1986; the greatest increases in

age specific mortality have occurred in the older age groups[77] but increases are also apparent in middle age groups[76]. The question arises if this trend is artefactual, a result of improvement in diagnostic accuracy and increased case ascertainment (particularly in the elderly where age specific rates are high), or due to changes in ICD coding. However, mortality from MND does not correlate with the number of neurologists in the UK[73] or the physician/population ratio in the USA[81]; there has been much less of a parallel increase in the number of neurologists in the UK than USA; technological advances such as nuclear magnetic resonance imaging and the identification of syndromes which mimic MND are likely to reduce, rather than inflate rates and the disease is distinctive and of such high lethality that significant changes in reporting seem unlikely. On this basis it seems likely that the death rate increase is real and the apparent decline in age specific mortality is probably a measurement artifact. Mortality statistics may be adequate for following trends in total MND rates within countries.

The interpretation of variation in mortality with place is complicated by changes over time, the use of different age bands for age specific rates, and variable methods in the extraction of death certificate information. A comparison of standardised mortality rates for the age bands between 60 and 74 years (where random error and diagnostic bias are probably least) is presented in table 2-2b; these data are extracted from those mortality studies in table 2-2a where this was possible. Higher rates are observed in the UK compared with Finland and the USA.

Whether the incidence of MND (as opposed to trends) can be

studied adequately on the basis of mortality data alone is uncertain[78]. Although 70-90% of patients diagnosed with MND have this recorded on their death certificate[72,73,124,125], only one study from Japan has examined the false positive rate of death certificate coding (in 1965) by an extensive attempt to verify the diagnosis from other sources. As many as one third of males were coded as dying of MND without having it, but the accuracy was better for females[72].

Incidence studies (Table 2-3a,b,c,d)

1. Crude rates The best incidence studies are presented in table 2-3a together with the methods, crude incidence with calculated 95% confidence intervals[126], prevalence rates (where stated) and notes. Although crude incidence may differ between populations because of differences in age structure, when the studies were divided according to the quality of their methodology, in general, the crude rates tended to reflect the likely degree of case ascertainment. There was a significant difference between the mean crude rate of those studies in table 2-3a when compared with all other studies (table 2-3b and 2-3c) (difference = 0.64/100,000/year 95% CI 0.15-1.13) and when studies in table 2-3a were compared with those which relied on single hospital case ascertainment (table 2-3c) (difference 0.75/100,000/year, 95% CI 0.21-1.3). However, there were exceptions; for example, a low crude rate was seen in Israel, based on a comprehensive survey of Jews as part of a national neurological disease register, and in Sardinia, which used five separate sources of case finding. The claim of a low incidence in Mexico[100] was based on individuals with access to a government health programme and

while medical facilities may have been excellent for those with access, it is not certain that all affected individuals with MND were identified. A lower mortality in Mexico than any other of 33 countries, including others in the developing third world, was observed in a large comparative analysis of average age adjusted rates, at least around 1950[86]. If this observation is not artefactual then it may be evidence of an ethnic "resistance", *or* a result of environmental factors.

2. Age and sex specific incidence rates, standardised rates

Age and sex specific rates in all incidence studies, except Rochester, show a steady rise to a peak, usually between 60 and 75 years with a sharp decline after this (Fig 2-2). In Rochester the rate appears to continue to rise with age, although the numbers are small and confidence intervals for the older age groups are so wide that a decline cannot be excluded. This is of considerable interest from an aetiological viewpoint; if a true decline occurs in the elderly then the disease is perhaps more likely to reflect an environmental influence rather than simply a result of age related neuronal attrition. The majority of reports show a male predominance with a range between 1.2:1 to 2.0:1, but some show no sex difference[99] or even a female predominance[80]. Incidence rates with time, although reported as increasing, are unreliable in studies with small numbers[88]. In Israel this increase was considered to be due to causes other than improved case ascertainment[89].

Meaningful direct, statistical comparisons of age and sex specific rates between studies are complicated by methodological differences, the use of different age bands and because overlap

with the same years of study are necessary to minimise possible differences due to changing incidence over time. The age specific rates for males and females combined from three of the best incidence studies[88,89,94] are plotted in figure 2-2 to demonstrate the range. It can be seen that there are differences in incidence between the studies from Rochester and Israel and the 95% confidence intervals for these two studies (not shown) suggest the difference is real. When the rates for the age bands 45-74 years (likely to be the most reliable for comparative purposes) for males and females are standardised to the Scottish population (table 2-3d), the differences between populations are also apparent. When age standardised rates (over 45-74 years) for males and females combined from those studies in table 2-3a (excluding NW England where insufficient data for this calculation are provided) are plotted against their degrees north latitude (Fig 2-3), there is a positive correlation (p value for the slope 0.05) with a factor of around three times higher in northern latitudes. It could be argued that this observation strengthens the case for differences in the distribution of MND for, while this correlation may still be due to better case ascertainment, only the best incidence studies, which used multiple resources, are included. If real it may be due to genetic or environmental factors and is akin to the much debated correlation of multiple sclerosis prevalence with latitude[127].

3. Clusters There are reports of conjugal[128,129] and other non-consanguineous clusters of MND outside the Western Pacific, with rates much higher than would be expected by chance. Examples include people who work[130,131] or live[132-134] in close proximity; play in the same sports team[135]; have been war evacuees[136]; share an environmental peculiarity such as high soil selenium[137]; or a common occupational exposure such as leather[138] or textile[139] workers. Toxins from freshly caught fish were implicated in a cluster in Wisconsin[140]. In one example, all those affected were of Ashkenazi Jewish extraction[133]. It is not clear if the high incidence in Filipino men in Hawaii is because of a genetically susceptible pool with a high predisposition to develop MND or whether other factors are responsible[98,141]. Other studies show a significant[142] or non-significant[73,80,81,97] uneven distribution but most studies that have examined distribution within a population have demonstrated geographical uniformity. It is difficult to know whether small clusters are purely due to chance, particularly when the overall population incidence is not known[143]. A recent publication from north west England[96] attempted to provide further data in this regard by analysing the distribution of 173 cases according to postal areas and allocated through a grid reference to 338 electoral wards. Several wards had a significantly higher than expected rate but, as the authors point out, the actual number of wards showing this non random distribution may not have been greater than the expected normal variation.

One intriguing attempt to demonstrate clustering of MND in relation to an infectious aetiology has examined the correlations between infectious disease notification rates in 1931-39 with

mortality from MND in 1968-78. There was a specific positive correlation for poliomyelitis but not for other infectious diseases; nor did poliomyelitis correlate with other leading causes of death[144]. The suggestion has been made that the rising rate of poliomyelitis during the early decades of this century accounts for the present increasing trend in MND mortality (due to subclinical infection). There is, however, no such correlation in Scotland and no support for viral infection from laboratory studies[145]. Although late neurological deterioration after poliomyelitis may resemble MND[146], the relationship between previous poliomyelitis and sporadic MND remains a matter of debate.

4. Western Pacific forms of MND The Western Pacific clusters are found in: (i) Guam, the southernmost and largest of the Mariana islands, where the Chamorro Indians are affected[147-149]; (ii) the Kii peninsula of Japan[150] and (3) the Auyu and Jakai people of West New Guinea[151]. In Guam, the most extensively studied of these endemic variates, the clinical features resemble sporadic MND/ALS, but in the same population there is also a high incidence of a parkinsonism/dementia complex (PDC) and some patients have a combination of ALS and PDC. The pathology of these Guamanian diseases includes extensive neurofibrillary tangles in the cerebrum and brainstem of most patients, and in the spinal cord of a minority, as well as anterior horn cell loss in those with ALS[152,153]. This difference suggests that the sporadic and Western Pacific forms may have a different aetiology but should the cause of these high incidence foci be clarified then widespread repercussions for the under-

standing of sporadic MND are possible.

As a result of systematic surveys carried out in the early 1950's prevalence rates 50-100 times greater than in developed countries were established. Since then it was thought that these rates were declining[154-158], however, the accuracy of some later reports has been questioned and the most recent prevalence survey of three villages, based on small numbers, suggests that rates are still as high as in the mid decades of this century[159]. Disease duration is thought to be similar to that in developed countries while the age of onset may be increasing[153,159].

An environmental cause, or at least a genetically determined host response to an exogenous factor seems likely[141,160-162]. The disease is confined to a particular area of the Mariana islands despite a shared original migration pattern[163]; there is no evidence for Mendelian inheritance[160] and the disease is of no higher incidence in offspring of affected than non affected Guamanians. MND does not develop amongst those who have had a brief exposure to the implicated environment[164] and the latency for the development of MND, as judged by studies of Chamorro migrants to the United States, is long[165,166] implying that an early exposure may be crucial, or any proposed environmental factor must be slowly acting, or ageing is interacting with an earlier environmental factor. Attempts to transmit the disease have failed[167].

The putative environmental cause is unknown. The suggested declining incidence coincided with adoption of a lifestyle closer to Western standards so factors associated with a primitive

lifestyle may be important. Neurotoxins in the seeds of the nut Cycad Circinalis (false sago palm), and used by the natives of Guam for the production of flour, are thought by some to be responsible[168]. A degenerative motor system disease with similarities to MND has been produced in primates by feeding the cycad derived toxin - BMAA (α-amino-ß-methylaminoproprionic acid)[169,170] but motor neuron pathology can also be induced by other experimental methods[171]. Doses required for these experiments are high and washing of the seeds, as is the custom, removes all but minute traces of BMAA[172], probably to such low levels that toxicity is unlikely[173]. Gadjusek and others suggest an alternative mechanism[158,174,175]. In New Guinea low concentrations of calcium and magnesium and high levels of aluminium, silicon, titanium, chromium, iron and manganese are present in the well and spring water of those villages in which MND is found and not in those which lie on the major large rivers which originate in the central highlands. The biochemical abnormalities in the water or diet in Guam are less certain but intraneuronal deposits of calcium and aluminium suggest that basic defects in mineral metabolism might impair transport of neurofilament proteins, leading to neurofibrillary tangle formation[176]. The interested reader is referred elsewhere for details of the extensive debate[177,178].

SUMMARY AND CRITERIA FOR THE IDEAL STUDY OF MND INCIDENCE

Mortality statistics in MND may be sufficient for studying trends with time, and possibly variation in place, but are likely to underestimate rates in the elderly, particularly in medically deprived areas, where age specific rates may be higher than reported (see chapter 5 for discussion of deprivation and MND). Death certificate data are subject to changes in coding practice and there is little information on the frequency of false positive coding. Nonetheless recent studies of mortality do show rising rates with time, particularly in older age groups. This is a consistent finding in a number of countries, and it may be real rather than due to ascertainment bias but, if so, its cause is uncertain. Kurtzke also concluded that there was "...evidence to support a real increase in the frequency of ALS"[69]. If rates really are increasing, then this complicates comparisons between studies in different places conducted over different periods.

There are certainly variations in reported incidence rates in place, most of which can be explained on the basis of differences in case ascertainment with higher rates tending to be from more complete studies. However, there may be real differences of two to four fold between well studied populations in developed countries, suggesting a non random distribution of MND. The evidence for an environmental factor in the aetiology of the Western Pacific forms is now very strong. The precise factors responsible are unknown but may, if discovered, have important implications for research into the cause of sporadic MND. Areas of interest for future epidemiological research include studies

of MND incidence in racial minorities in developed countries; the development of sensitive methods for studying the distribution of MND within populations, such as the computer assisted geographical mapping techniques by grid reference[96]; prospectively designed studies; and attention to life events and environmental exposures which may be remote from the development of MND.

Criteria for the ideal study of MND incidence

From this review the standards for studies of MND incidence should be:

Standardised diagnostic criteria: The reader must be able to understand clearly what is meant by MND. There are no universally accepted criteria for the diagnosis and there is lack of agreement between neurologists in different countries presented with the same case summaries, particularly when the disease is clinically less fully developed, but pathologically proven[179].

A practical consensus statement for clinical and epidemiological studies is required which deals with the problems of defining the clinical limits of MND (see chapter 1), reducing inter observer error in the interpretation of physical signs (for example when is a retained reflex in a wasted corresponding myotome an UMN sign?) and to define the subgroups of MND which may have a different prognosis. A subcommittee of the World Federation of Neurology has recently drafted proposals for a system of classification of ALS, but this is so extraordinarily complex, and dependent on detailed electrophysiological evaluation, that it is quite unsuitable for application in large scale epidemiological studies. In chapter 3 diagnostic criteria which

can be applied to large epidemiological studies of patients who will have been investigated by different centres, to different degrees with varying investigations, is presented in full.

Complete case ascertainment: A study design ensuring complete case ascertainment is of overwhelming importance when studying variation of incidence in time and place, seeking putative environmental factors, or when studying prognosis. In developed countries most patients are likely to have attended regional neurological services but complete case ascertainment *cannot* be guaranteed by studies which rely exclusively on data from such sources. In particular, studies from specialised centres[180,181] are likely to be biased in favour of younger patients and possibly unusual forms of MND. The elderly, where age specific rates are high, but where diagnosis may be more difficult, are particularly likely to be missed without searches using multiple sources of case ascertainment. However, special care is required in the elderly as the diagnosis may be particularly difficult due to frailty, coexisting disease, or death from other causes before the passage of time has clarified the diagnosis. Multiple sources of case ascertainment should include neurologists; a review of hospital discharge data; an approach to primary care physicians for identification of patients who may not reach tertiary care centres, and finally, death certificate monitoring. Patient organisations or family care workers may provide useful information but cannot be used as the sole source as this is likely to lead to an underestimate of the true incidence and contamination by other diseases.

Well defined denominator and standard presentation of rates by age, sex and race: Accurate demographic information of the population at risk must be available so that appropriate denominators can be used. This may be a problem in developing countries. The denominator in open upper age bands is sensitive to changes in the overall population age structure and because numbers are small in this age group, changes in age specific incidence within populations over time, or differences between populations, may be misleading and result from the different age structure of open upper age bands. Results of incidence studies may be interpreted differently by the use of variable upper age bands, this is illustrated in figure 3-2. Therefore, information should be provided in five year age bands for the total population to allow comparison over time and between studies for a given age band, or combination of age bands.

Prospective design and large population base: Retrospective studies allow the passage of time to clarify diagnostic problems but are disadvantaged in other ways. Prospective data collection allows the application of standardised diagnostic criteria including electrodiagnostic tests. The low incidence of MND means such studies require a large population base and hence wide collaboration and rigorous case monitoring and follow up.

No incidence studies are available which fulfil all these criteria and it is on this basis that The Scottish Motor Neuron Disease Register (SMNDR) was established with a view to conducting a *prospective*, population based, collaborative study of MND incidence, distribution and prognosis and providing a resource

for research activity into MND in Scotland. This is the first such study of MND with this design.

Table 2-1: Syndromes which may mimic or resemble MND and are important to distinguish from idiopathic MND

Physical factors:

- Cervical spondylotic myeloradiculopathy[182]
- Radiation myelopathy/plexopathy[183-185]
- Cranial irradiation and intrathecal chemotherapy[186]
- Following severe electric shock[43,187,188]

Metabolic/Endocrine disorders:

- Hexosaminadase deficiency[189,190]
- Adrenoleukodystrophy (adrenomyeloneuropathy)[191]
- Hyperinsulin neuronopathy[192]
- Thyrotoxicosis[193]
- Phosphate deficiency/hyperparathyroidism[194,195]

Related to malignancy or disturbed immunity:

- Meningeal metastasis with radiculopathy/cranial neuropathy
- Multifocal neuropathy and antibodies to gangliosides[196-200]
- Ganglioside therapy[201]
- Plasma cell dyscrasias[202,203]
- Subacute motor neuronopathy ?ALS, with lymphoma[204]
- Other paraneoplastic ?renal cell carcinoma[205,206]
- Foramen magnum tumours[207]

Infections:

- Post-polio syndrome[146,208-211]
- Human immunodeficiency virus:mononeuritis/myelopathy[212-214]
- Syphilitic amyotrophic meningomyelitis[215,216]
- Cysticercosis[217]

Toxins/Drugs:

- Lead[218,219], mercury[220], manganese[221,222], selenium[137], aluminium[223]
- ß-N-oxalylamino-L-alanine (Neurolathyrism, Africa/Asia)[224]
- α-amino-ß-methylaminoproprionic acid in Cycad seeds on Guam?[168]
- Domoic acid ingestion from contaminated mussels in Canada[225]
- Solvent poisoning[138,226]
- Pesticide exposure (pyrethrin and chlordane based)[227,228]
- Amitriptyline overdose?[229]
- Hoigne's syndrome (pseudoallergic reaction) with penicillin[230]

Vascular:

- Rheumatoid arthritis with arteritis and neuropathy[231]
- Ischaemia of the anterior horns of the spinal cord[232]
- Multi-infarct state with bulbar palsy

Other primarily neurological diseases or MND associated with other disease:

- Benign fasciculations and cramps[233]
- Syringomyelia (without sensory signs)[234]
- Peroneal muscular atrophy with pyramidal features[235,236]
- Spastic paraparesis (various causes)[237,238]
- Cyst of the conus medullaris[239]
- Amyotrophy in multisystem disease eg Joseph disease[240]
- MND with dementia of various types[40,241]
- Spinal monomelic amyotrophy, focal cervical poliopathy[242-245]
- X-linked bulbospinal atrophy[246,247]*

Notes: A differential diagnosis of the idiopathic anterior horn cell disorders is not included. * May be classified with adult onset MND.

Table 2-2a. Studies of adult onset MND based only on mortality (death certificate) data.

Location	Year(s)	Range of mortality over study period (crude rate/100,000)	Notes	Reference [n]
Japan	1952-71	0.4-0.6	Rising rate from 1952 and then a fall after 1960.Includes worldwide mortality data 1954-1971 compared with Parkinson's disease which did not change	[72]
England/Wales	1959-1986	1.2-1.6	Increasing mortality over study period Standardised mortality ratio 79 in 1968 129 in 1986. Non random distribution in place	[73,74]
Sweden	1961-85	1.0-2.5	Figures divided into ALS and MND as a whole. Rise greater for ALS. Age standardised rate doubled over study period	[75]
United States	1962-84	age/sex specific rates only	Rising rates,with substantial changes particularly amongst the elderly	[76-78]
France	1968-82	0.7-1.5	Steadily increasing rate especially for >55years	[79]
Finland	1963-72	0.9	More common in women (0.87:1).Clustering in south east	[80]
United States	1968-78	0.9	Highest rates west of Mississippi	[81]
Scotland	1968-87	1.2-2.1	Significant rise with time Non random distribution in place	*
Norway	1969-85	1.6-2.8(m) 1.2-1.8(f)	Substantial rises especially in men and elderly	[82]

Notes: Listed in ascending order of first year of data collection. Studies of individual USA states[83-85] not included. For the USA and England and Wales notes incorporate more than one study.
*R.J.Swingler,personal communication

Table 2-2b: A comparison of age specific mortality rates per 100,000 between countries from studies in table 2a where this information can be derived.

	Country					
	England and Wales[73]		United States[77]		Finland[80]	
	Male	Female	Male	Female	Male	Female
Age Band	Age and sex specific rates:					
60-64years	5.8	4.6	4.9	3.5	4.5	3.5
65-69years	7.7	5.5	6.1	4.1	6.0	6.1
70-74years	8.5	5.8	7.6	4.7	2.8	3.5
	Mortality rates standardised to the 1989 Scottish population (age 60-74 years):					
	7.5	5.3	6.4	4.1	4.2	4.4

Table 2-3a: Incidence studies (all retrospective) of adult onset MND most likely to have complete or near complete case ascertainment.

Location	Years	Methods	ALS	PBP	PMA	Population (millions)	Cases (n)	Incidence Crude/100,000/yr (95% CI)	Prevalence /100,000	Notes	Reference [n]
Rochester,USA	1925-84	Mayo clinic diagnostic index of Rochester residents	Y	Y	N	0.36	44	2.0 (1.4-2.7)		Updated previous study(1925-77) small but ns increase in incidence	[87,88]
Israel	1959-74	National neurological disease register	Y	Y	Y	21.8	246	0.7 (0.6-0.8)		Increasing incidence in >60yrs	[89,90]
Sardinia,Italy	1965-74	Hospital archives,national statistics,neurology departments, General practitioners	Y	N	N	1.49	96	0.6 (0.5-0.7)	1.5	Uniform distribution Rates higher in agricultural workers Young mean age of onset (56 years)	[91]
North Sweden	1969-80	Neurology department, questionnaire to others, Death certificates	Y	N	N	0.65	128	1.7 (1.4-2.0)	4.8	No significant clusters Male to female ratio 1.1:1	[92]
Varmland county, Sweden	1970-81	Inquiry to clinics of medicine, geriatrics, death certificates	Y	?	Y	0.28	89	2.6 (2.1-3.2)	8.5	Higher rate ($p<.01$) in this county than remainder of Sweden	[93]
Denmark	1974-86	Computerised hospital data base for 2 counties	Y	Y	N	1.05	186	1.4 (1.2-1.6)	3.1	Female preponderance in patients >60yrs with bulbar onset	[94]
Middle Finland	1976-81	Hospital discharge data, death certificates	Y	N	N	0.24	36	2.4 (1.7-3.3)	6.4	Incorporates a case control study	[95]
NW England	1976-86	Neurology department, hospital discharge data	Y	Y	Y	1.84	173	1.9 (1.6-2.2)		Small area analysis shows clusters but due to chance?	[96]
SW Ontario, Canada	1978-82	Hospital notes ALS society case register Death certificates	Y	Y	Y	1.71	139	1.6 (1.3-1.9)	4.9	Uneven distribution between counties (non significant)	[97]

Notes: Studies listed in ascending order of first year of data collection. Y=Yes; N=No; ALS=amyotrophic lateral sclerosis; ns=non significant; PBP=progressive bulbar palsy; PMA=progressive muscular atrophy; NW=north west; SW=south west.

Table 2-3b: Incidence studies (all retrospective) of adult onset MND where case ascertainment is likely to be incomplete.

Location	Years	Methods	ALS	PBP	PMA	Population (millions)	Cases (n)	Incidence Crude/100,000/yr (95% CI)	Prevalence /100,000	Notes	Reference [n]
Hawaii	1952-69	Hospital records,neurologists in private practice,mortality data	Y	Y	Y	0.63	118	1.0 (0.8-1.2)		High incidence amongst Filipino men	[98]
Parma,Italy	1960-80	Neurology,general,orthopaedic	Y	N	N	0.40	78	0.9 (0.7-1.1)	2.3	Non significant increase in incidence over study period	[99]
Mexico City	1962-69	Government health programme, neurological physicians	Y	Y	Y	0.50	16	0.4 (0.2-0.6)	0.8	Supported by low mortality as well as incidence	[100]
Ferrara,Italy	1964-78	"All possible sources"	Y	N	N	0.39	37	0.6 (0.4-0.8)	2.1	Unremarkable	[101]
Pennsylvania	1968-75	Neurologists and major hospitals	Y	Y	Y	0.26	31	1.5 (1.0-2.1)	6.4	Similar to remainder of USA	[102]
Turin,Italy	1971-80	Neurology records,discharge data private neurologists,notes reviewed	Y	Y	Y	2.29	161	0.7 (0.6-0.8)	2.6	No clusters	[103]
Nova Scotia	1974-1984	Neurology and rehabilitation hospitals	Y	?	N	0.82	169	2.1 (1.0-3.0)		High incidence	[104]
Benghazi,Libya	1980-85	Not clear.All patients evaluated in a single unit.State health care	Y	N	N	0.52	23	0.9 (0.6-1.3)	3.5	Small numbers	[105]
North England	1981	Discharge data,consultants verification,death certificates	Y	?	N	?	78	2.2 (1.7-2.7)		Crude mortality 2.0	[106]

Notes: Studies listed in ascending order of first year of data collection.
Y=Yes, N=No; ALS=amyotrophic lateral sclerosis; PBP=progressive bulbar palsy; PMA=progressive muscular atrophy

Table 2-3c: Incidence studies (all retrospective) of adult onset MND which rely exclusively or principally on tertiary referral centres for case ascertainment.

Location	Years	Methods	ALS	PBP	PMA	Population (millions)	Cases (n)	Incidence Crude/100,000/yr (95%CI)	Prevalence /100,000	Notes	Reference [n]
Odense,Denmark	1948-75	Neurology services	Y	Y	Y	0.43	118	0.8 (0.7-1.0)	2.5	No secular trends observed	[107]
Poznan,Poland	1955-65	Neurological services/clinics	Y	Y	N	2.55	73	0.8 (0.6-1.0)	2.2	Uniform distribution	[108]
Sardinia,Italy	1957-80	Neurology department chart review	Y	Y	Y	1.49	182	0.5 (0.4-0.6)	3.6	Non random distribution	[109]
Lothian,Scotland	1961-81	Hospital discharge data, incomplete case record review	Y	Y	Y	5.0	161	?1.9 (1.6-2.2)		Incomplete case ascertainment	[110]
Florence,Italy	1967-76	Single hospital search	Y	Y	N	1.19	83	0.7 (0.5-0.8)	2.1	No particular distribution	[111]
Scotland	1968-77	Hospital,death certificates,no verification of diagnosis	Y	Y	Y	5.0	725	1.6 (1.5-1.7)		Highest rates in north and east	[112]
Palermo,Italy	1973-84	Neurology/surgery departments	Y	N	N	1.24	57	0.4 (0.3-0.5)	1.7	Incomplete case ascertainment	[113]
Cantabria,Spain	1974-85	Single neurology department	Y	Y	Y	0.51	62	1.0 (0.7-1.2)	3.5	Stable incidence over period	[114]
Messina,Italy	1976-85	Neurological centres	Y	Y	Y	0.65	41	0.6 (0.4-0.8)	2.5	Small numbers	[115]
Limoges,France	1977-85	Single neurology department questionnaire to others	Y	N	N	0.74	54	0.9 (0.7-1.1)	7.3	No special features	[116]
Western Norway	1978-88	Neurology department	Y	Y	?	0.40	84	1.6 (1.3-1.9)	3.7	Peak incidence 61-65 years	[117]

Notes: Studies listed in ascending order of first year of data collection.
Y=Yes, N=No; ALS=amyotrophic lateral sclerosis; PBP=progressive bulbar palsy; PMA=progressive muscular atrophy

Table 2-3d: A comparison of age and sex specific incidence and age standardised incidence, 45-74 years, by country.

	Country							
	Rochester*	Israel*	Sardinia	Sweden 1	Sweden 2	Denmark*	Finland	Canada
Reference	[87,88]	[89,90]	[91]	[93]	[92]	[94]	[95]	[97]
Age band	Age specific rate:							
	m/f	m/f	m/f	m/f	m/f	m/f	m/f	m/f
45-54years	2.0/2.6	2.1/1.2	2.2/0.9	1.0/1.0	5.9/3.2	2.1/0.8	4.6/5.1	3.0/2.0
55-64years	9.5/5.2	3.3/1.8	3.2/1.8	7.8/4.2	9.0/4.2	5.2/3.5	10.3/11.8	5.5/4.0
65-74years	13.2/12.6	2.9/1.4	6.6/1.5	10.0/5.8	12.3/6.5	6.2/5.0	13.7/8.4	9.0/5.5
	Incidence age standardised to the 1989 Scottish population (age 45-74 years only):							
	7.5/6.5	2.7/1.5	3.7/1.4	5.7/3.5	8.6/4.5	4.2/3.0	9.0/8.4	5.4/3.7

Notes: See also table 2-3a (age specific rates not given for NW England study). Rates/100,000/year.
In some studies age specific rates are extrapolated from graphed values because of differing age bands employed.
m= male, f= female 1= Varmland County, Sweden 2= Northern Sweden. * see also figure 2-2.

Fig 2-1: Mean annual age-adjusted death rates /100 000 population for Motor Neuron Disease in Norway, standardised to total 1980 Norwegian population.

(Flaten 1989)

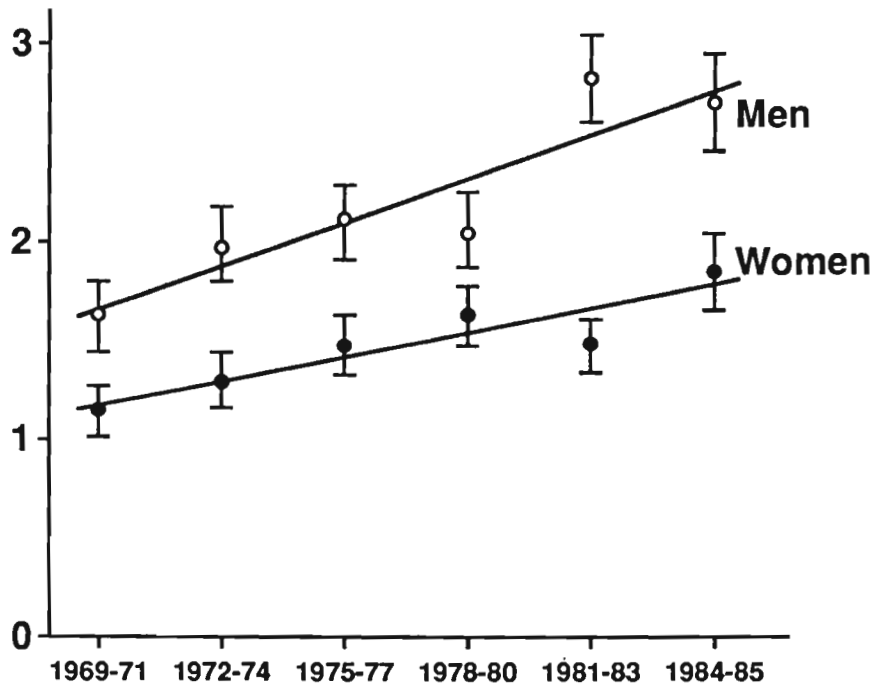


Fig 2-2: Age specific incidence of adult onset MND (total male & female for 3 population based studies)

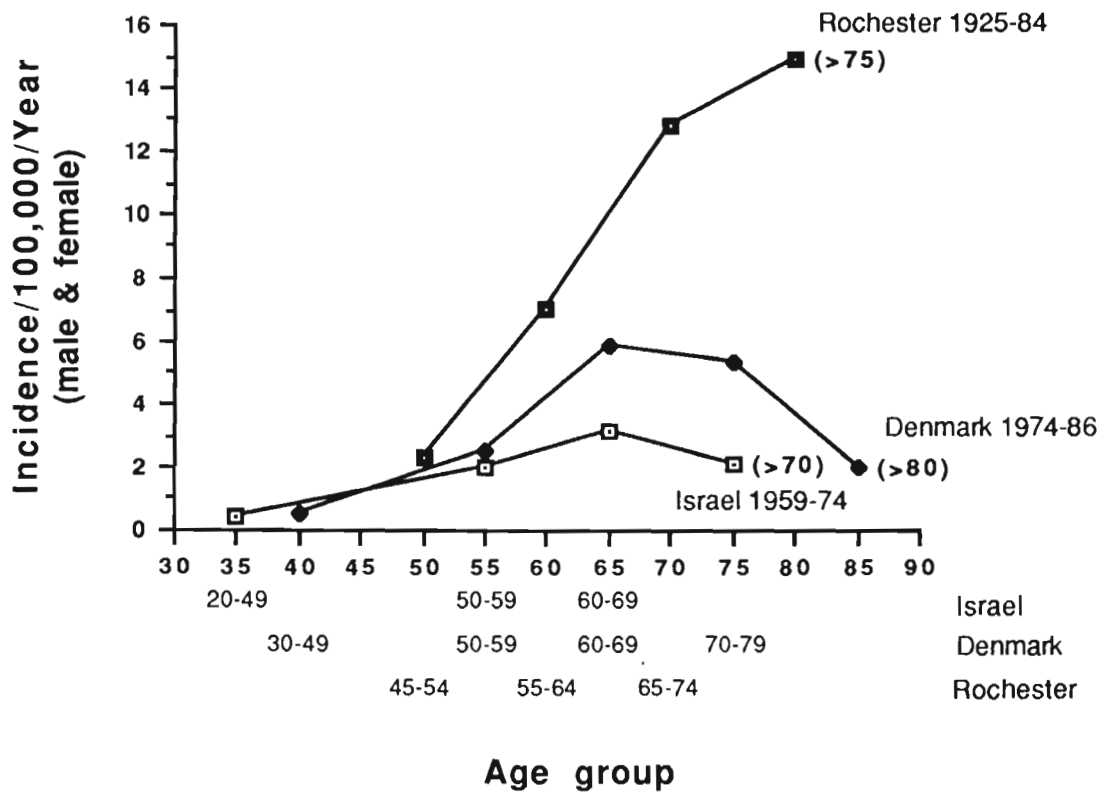
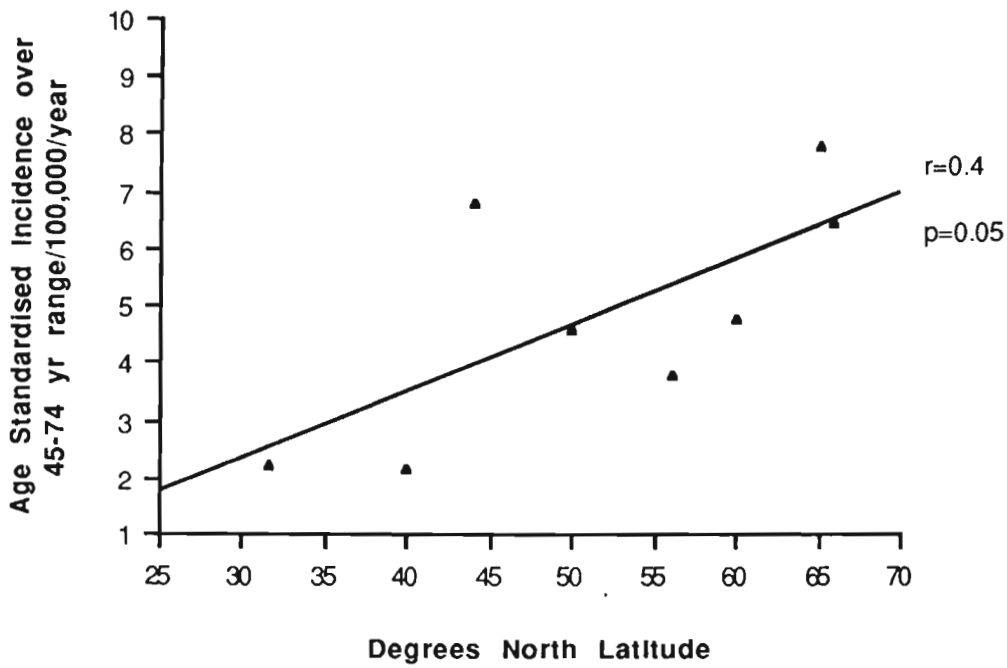


Fig 2-3: Correlation of age standardised incidence of MND with mean degrees north latitude in 8 population based studies



CHAPTER 3

THE SCOTTISH MOTOR NEURON DISEASE REGISTER: METHODOLOGY, INCIDENCE, DEMOGRAPHY AND CLINICAL FEATURES OF PATIENTS DIAGNOSED 1989-1990

INTRODUCTION

" It is sometimes said that clinical observation has little more to offer neurology, yet clinical observation continues to discover new syndromes and to reinterpret old symptoms and I foresee great scope for it still."

Lord Brain[248]

Scotland is in the north of the United Kingdom (UK) and covers an area of 30,414 square miles between 54 38' and 60 51' 30" north latitude and between 1 45' and 6 14' west longitude[249]. The population estimate for 1989 was 5,090,700 of whom 18% were over 65 years[250]. The country is divided into 9 regions, 3 island areas, 53 districts and 1211 postcode sectors and is served by 3041 general practitioners. Neuromedical services are provided by 19 consultant neurologists and 4 consultant clinical neurophysiologists who are likely to see most but not all patients with MND.

In January 1989 the SMNDR was launched with the aim of prospectively achieving complete case ascertainment in order to reliably study the incidence, demography, clinical features and prognosis of MND in Scotland and to provide a resource for research into this disease.

METHODS OF THE SCOTTISH MOTOR NEURON DISEASE REGISTER

1. All Scottish consultant neurologists and neurophysiologists agreed to collaborate and acted as the principal source of case notification. They were requested to complete a simple registration form (table 3-1) which was forwarded to the study

coordinators based at the Western General Hospital, Edinburgh for inclusion on a centralised database. Collaborators were encouraged to register patients when the diagnosis of MND was first entertained so that suspected, as well as definite cases, could be followed up, although the threshold of individual collaborators with respect to the registration of suspected cases varied.

2. The two family care officers employed by the Scottish Motor Neurone Disease Association (SMNDA) offered patients the option of self-referral to the register.

3. In 1990 and 1991 a letter was sent to all GP's in Scotland, asking for details of any patients with MND in their practice diagnosed after January 1st. 1989.

4. The Information and Statistics Division of the Common Service Agency for the Scottish Health Service provided a list of all patients discharged from Scottish hospitals in 1989 and 1990 coded by International Classification of Diseases (ICD) 9 as code 335 (anterior horn cell disease). The records of all patients older than 15 years, not already included on the register, were obtained and reviewed before inclusion.

5. A request was made to neuropathology departments for any patients diagnosed at post mortem.

6. All death certificates for 1989-90 identified from the General Register Office for Scotland were examined when ICD-9 335 was recorded as the underlying cause of death or as a contributing factor. GP practice records with their letters and summaries from hospital consultations were then requested from Health Boards.

7. Pedigrees were traced in families where a genetic cause seemed likely or possible. Information of personal details of

unaffected or affected relatives (parents, children, siblings, aunts, uncles and cousins) were obtained from the proband wherever possible to allow tracing of death certificate coding and in some cases, clinical notes.

After registration, clinical details included in discharge summaries or outpatient correspondence and the reports of neurophysiological investigations, were obtained to allow classification of MND subtypes based on clinical features (see below). After the patient's death the complete hospital and GP records were scrutinised and pathology reports obtained when available. Figure 3-1 shows the structure of the SMNDR.

Patients were included on the register, ie considered incident, if the diagnosis of MND had been made or suggested for the first time after December 31st 1988. At registration, the patient's GP was informed of the aims of the study. Follow up of all patients was achieved principally through GP's with a six monthly questionnaire concerning any revision of the diagnosis, any change of GP (to allow transfer of follow up) and simple clinical features, such as difficulty speaking or swallowing, limb weakness the date and place of death and if other family members were affected. Collaborators, who were informed of the study's progress by a monthly newsletter, were also encouraged to send copies of follow up correspondence from hospital clinics. A paper file was maintained for each patient and the Dbase IV management system for microcomputers was used to construct a computerised database for compiling features of key interest and to permit organised retrieval of data. Hospital ethical approval was obtained.

The 1989 population estimate for Scotland and its

regions[250] (derived from the last population census in 1981) was used for the calculation of rates and standardised incidence ratios. A census in 1991 has not yet published population figures. Age specific incidence was calculated using age at diagnosis, usually in relation to the first hospital admission for investigations. The significance of differences between the means for ages according to sex was examined using the Student's t-test. Age adjusted standardised incidence ratios (of observed to expected cases) were calculated for each of the 9 regions and 3 island areas using the indirect method[251]. Confidence intervals (CI) were calculated using the Confidence Intervals Analysis Programme[252].

Diagnostic criteria

A set of simple but specific criteria suitable for application to this, and other large scale studies was devised, using aspects of the World Federation of Neurology Subcommittee on Neuromuscular Diseases approach[253]. The criteria for diagnosis are as follows:

The term "motor neuron disease" is used to encompass any adult (>15 years) onset progressive motor system disorder (sporadic or familial) with the following categories:

1. Clinically definite MND: A *combination* of lower motor neuron (LMN) signs, clinically *or* by electromyography (EMG), and upper motor neuron (UMN) signs (table 3-2), not due to longstanding neurological disease, (eg previous stroke or recognised compressive mononeuropathy), involving the brainstem *and* implicating involvement of one or more spinal regions. Three spinal regions were used for classification of physical signs, they were:

C1-T1 (cervical region; neck and upper limb), T2-L1 (thoracic region), L2-Sacral segments (lumbosacral region). If signs were limited to the brainstem and only 1 spinal region (eg only upper limb signs as the sole manifestation of involvement outside the brainstem) then both UMN and LMN signs were required in that region, otherwise it was not considered necessary for both UMN and LMN signs to be present in each of the involved regions. Normal or brisk deep tendon reflexes in the presence of a clearly wasted corresponding myotome, eg triceps jerk in wasted triceps muscle, were used as evidence of UMN involvement.

Qualifications: In addition the following were mandatory: a progressively deteriorating course; the absence of sensory signs (including visual abnormalities) apart from mild vibration sense loss in the elderly; absence of sphincteric disturbance, parkinsonism, dementia and causes of syndromes which may mimic MND (table 2-1), after appropriate investigations and follow up.

Patients in this group were assigned a category which gave an indication of the clinical pattern of the MND as follows:

(1-1) ALS/PBP. Clinically definite MND which began with limb symptoms but later developed bulbar features.

(1-2) PBP/ALS. Clinically definite MND which began with bulbar symptoms and later developed limb symptoms or began with bulbar and limb symptoms simultaneously.

2. Clinically probable MND: (2-1) PBP: A syndrome in which dysarthria and dysphagia of UMN or LMN origin are the predominant features (but which may be accompanied by sterno-mastoid weakness as the only [potentially] extrabulbar LMN sign) in the absence of LMN limb signs but which may be accompanied by

UMN limb signs (eg extensor plantar response) but not symptoms (eg difficulty walking).

(2-2) Spinal ALS (2 regions) and (2-3) Spinal ALS (3 regions): Two and three regions (cervical, thoracic and lumbosacral) involved respectively, with a combination of UMN and LMN signs, not necessarily both in the same region, but without bulbar features and given the above qualifications, in particular exclusion of cervical spondylotic myelopathy. Patients registered with monomelic atrophy were not included in the calculation of incidence data.

(2-4) PMA: An exclusively LMN motor disorder, including absent deep tendon reflexes in affected myotomes, involving at least two regions with a clearly progressive course supported by consistent neurophysiological investigations (see below).

(2-5) PLS: An exclusively UMN motor system disorder (after at least two EMG examinations separated by at least six months) affecting all four limbs with or without involvement of the brainstem, in the absence of a family history of gait disturbance and with no evidence of multiple sclerosis or MND mimic syndromes after CSF immunological studies, visual evoked responses and magnetic resonance imaging of the brain or cervical cord. Patients with unspecified spastic paraparesis were explicitly excluded. Diagnostic categories are summarised in table 3-3 and the alternatives for the distribution of clinical signs are shown in table 3-4.

The above classification was applied (i) at registration (*initial diagnosis*) based on the documented features of the illness when patients first came to medical attention, or, if patients were identified through hospital discharge or mortality

data, retrospectively, again based on the features at presentation and supported by hospital consultation documentation. (ii) When the full extent of the disease was established after follow up, or all available data (hospital notes, GP records and pathology reports) had been reviewed after death, whichever came first (*final diagnosis*).

Additional notes: Criteria for neurophysiological diagnosis were not established prospectively and are difficult to apply rigorously given the variation in clinical practice between neurophysiologists. When available, particular attention was paid to the results of nerve conduction studies and EMG:

1. To exclude other causes of LMN disease, in particular, polyneuropathies, compressive neuropathies/radiculopathies, multifocal motor neuropathy[196,197] and myopathies.

2. To identify LMN involvement which was not evident on clinical examination and which could therefore be used to assist subgroup classification. Equal weight was given to the finding of dennervation potentials on EMG as to the clinical LMN signs (table 3-2) when determining the extent of regional involvement.

3. As a means of documenting spread of LMN abnormalities and therefore the progressive nature of the disease, if this was in doubt.

Myelography was usually performed when MND was incompletely developed and confined to spinal segments. An acellular cerebrospinal fluid (CSF) result was required before a clinically probable diagnosis was attached but CSF examination was not considered mandatory for the diagnosis if clinically definite, as defined above. In some instances support for the diagnosis was obtained with swallowing tests (Barium cine swallow) and muscle

biopsy. Anti-ganglioside antibodies were not routinely performed.

The diagnosis was considered proven by autopsy if this showed LMN and UMN neuronal loss in the brainstem or spinal cord and neuronal atrophy with loss of Nissl substance, corticospinal tract degeneration and the absence of extensive central chromatolysis, active neuronophagia, neurofibrillary tangles, abnormal storage material, spongiform change and extensive inflammation.

RESULTS

A total of 257 patients were registered with the SMNDR in 1989-90 but 28 patients were excluded from the main analyses because an MND like syndrome coexisted with other neurological disease; the diagnosis was subsequently shown not to be MND or did not fulfil the criteria above (Table 3-5). The details of these patients are presented in Appendix A. Unless otherwise stated, ages refer to those at diagnosis.

Of the 229 patients with proven, clinically definite or probable MND 132 (57.6%) were men (mean age at diagnosis 63.1 years, SD 12.2 years, range 19.6-84.2 years) and 97 (42.4%) were women (mean age at diagnosis 67.4 years; SD 11.0 years; range 30.4-90.7 years), giving a male to female ratio of 1.4:1. There was a significant difference in mean age between the sexes of 5.4 years (95% CI 2.3-8.6). For patients older than 65 years the sex ratio was 1.1:1 compared to 1.9:1 for those younger than 65 years, a significant difference. A summary of the descriptive statistics is presented in table 3-6.

Many patients were notified from multiple sources. However,

the first source of referral is shown in table 3-7. 190 patients (83%) were seen at some time by a neurologist and 188 (82%) had an EMG. Patients who had not seen a neurologist (n=37, 16%) were older than the remainder with a difference in the means of 7.6 years (95% CI 0.4-14.9).

Table 3-8 shows the clinical pattern of MND based on information at the presentation to medical attention (initial diagnosis) and the final classification with follow up (final diagnosis), after all records were reviewed, at the time of data censoring on January 1st. 1992 (this date also used for survival estimates in Chapter 6). Table 3-8 documents the natural progression of MND with most patients who presented with PBP developing spinal involvement (PBP/ALS) and many patients with only spinal disease (ALS), as the initial diagnosis, developing PBP (ALS/PBP). Patients with PMA and PLS were in the minority.

The site of onset of MND (table 3-9) shows an approximately one third division into those patients whose weakness began in the upper limb, lower limb and bulbar region. Men were more likely than women to present with weakness of the hand, a reflection to some extent of the sex differences in clinical subtypes (see below). However, onset in the lower limb showed no difference between the sexes. Women were significantly more likely to present with PBP and to have PBP as a component of MND at any stage of the illness, whereas males were more likely to have exclusively spinal disease (table 3-10). This was particularly true of women over 65 years where there was a relative risk of 4.5 (95% CI 2.1-9.6 years) compared to men over 65 years. Three patients presented with shortness of breath as the principal complaint and in one 60 year old male with PMA this was due

to a highly selective diaphragmatic palsy with EMG evidence of more widespread dennervation.

Eleven patients (5 %) had a family history of MND but none were related to each other, the pedigree details are contained in Appendix B. This group was younger than the sporadic cases; difference in means was 9.6 years (95% CI, 5.5-13.6). The pattern of familial disease suggested a probable or definite autosomal dominant inheritance in all but one family where X-linkage appears likely (a diagnosis of x-linked bulbospinal neuronopathy[247]). In some families (SF,RP-appendix B) premature death, or young age of unaffected members make interpretation of inheritance more difficult. These families formed a heterogeneous sample of different clinical subtypes both within and between pedigrees.

In 15 (6%) the diagnosis was proven by autopsy, the pathological details of these patients are included in Appendix C.

The crude incidence for Scotland was 2.25/100,000/year (95% CI 1.96-2.54/100,000/year). Age and sex specific incidence rates are presented in table 3-11 and figure 3-2 and continued to rise steeply to a peak between 75-84 years for women and 65-74 years for men (fig 3-3). There is then an apparent decline in rates over 85 years. The age adjusted standardised incidence ratios for individual regions showed some variation (table 3-12; fig 3-4). However, 95% confidence limits overlapped with unity, indicating none were significantly different from the expected at the $p<0.05$ level, although lower standardised ratios were observed in the north east and island areas.

DISCUSSION

The epidemiological method may provide important clues to the causes of MND by demonstrating temporal and geographical trends in distribution. Difficulties arise in delineating the optimum size for such a study: under-ascertainment and error in diagnosis will bias mortality studies based on very large populations, whereas random variation will lead to imprecise estimates if too small a sample is used. In this project size has not compromised diagnostic accuracy because data can be sought prospectively and studied over several years.

Some studies of incidence and/or clinical features in MND have relied on data collected from tertiary referral centres but, in general, such studies give a lower incidence than those which make a more concerted effort in case finding (Chapter 2). Only two other countries, both from Scandinavia[93,95], reported a higher crude incidence higher than Scotland but denominators were not provided in these papers so it is difficult to be sure that this is not due to differences in age structure. The previous study of MND incidence in Scotland[112], based on unverified hospital discharge data (1968-77), and therefore likely to be contaminated with diseases other than MND, gave a high crude average first discharge rate of 4.7 and 3.01/100,000/year for men and women respectively. Mortality statistics collected over the same period gave average rates of 1.57 and 1.18/100,000/year (see Chapter 4 for analysis and discussion of this source of data). A further incidence study confined to the Lothian region[110] was incomplete in tracing case records and reported a range of incidence over 1968-75 of 1.0-1.9/100,000/year. The female to male ratio is within limits previously described (between 1:1 and

1:1.5).

A finding of all studies that have examined age specific incidence, except that from Rochester, is a decline in rates in the most elderly age groups. Our data show that the highest age specific incidence of 9.9/100,000/year for males and females combined in the 65-74 year group was maintained into the 75-84 year group, given the confidence limits of this estimate (Table 3-11). Caution is needed in the interpretation of the apparent decline in age specific incidence in the most elderly. Presentation of the data with an upper age band of >75, years rather than >85 years (Fig 3-2), suggests that a true decline may not actually occur, given the confidence limits. Proper comparison with other studies needs careful attention to open ended upper age bands (see page 54). The decline in rates over 85 years is difficult to interpret, particularly because of the small numbers (n=2) and may be due to failure to diagnose the illness in this age group (see also chapter 5), rather than poor ascertainment of diagnosed patients. If rates really do continue to rise into old age rather than decline, as is generally reported, then senescence must make a major contribution to the development of MND.

The age pattern of this population based cohort is older than series which have been described based on referred samples, particularly neurology departmental records[181,254,255] (table 2-3c) and is the result of an unbiased patient group. The age differences between patients who were, or were not seen, by a neurologist (table 3-6) also implies that studies based only on neurology departmental records are unlikely to reflect the true demographic features of the disease. The diagnosis date (and

therefore the decision about whether a patient was incident or not) was standardised to the time when the diagnosis was first suggested as possible.

The registration of patients by different collaborators varied with respect to how far advanced the disease process was, hence some neurologists preferred to register patients when the diagnosis was first entertained and some preferred to allow the passage of time to remove diagnostic doubt. Delay in registration and the lower than anticipated rate of first registration by neurologists was largely due to this factor. Those patients who were eventually excluded (Table 3-5 and Appendix A), are a biased group but represent a sample for which the diagnosis MND was entertained and therefore form part of the differential diagnosis of this disease. Of particular note are patients who were eventually diagnosed as cervical spondylotic myelopathy. The absence of bulbar involvement (ie clinically probable MND) should be a cautionary sign and prompt appropriate investigation of the cervical spine.

The interpretation of the figures relating to the clinical subtypes is highly dependent on the way physical signs are used for the classification of patients. In this study, preserved reflexes in the presence of a corresponding wasted myotome were used as evidence of UMN involvement and therefore such patients were classified as having ALS included in their subtype (ALS; ALS/PBP; PBP/ALS). There may be little pathological basis for dividing sporadic MND into subgroups given the poor correlation between clinical pattern and pathological distribution of the lesions[47]. However, appropriate classification is important to standardise patients who will be included in clinical trials

and for prognostic reasons (see Chapter 6).

Differences in the sex ratio, age (women older) and the clinical patterns have been observed by others, including the predilection of women, especially those in the older age groups, to present with or develop PBP more commonly than men[94,181,256].

The 5% rate of familial MND is in accordance with other studies which range from 2.7-10%[65,257]. Patients with a family history were younger than sporadic cases and formed a heterogeneous group of disease pattern with examples of most subtypes represented, as reported by others[258,259] (see Appendix B for details). The likely dominant inheritance seen in most of the families has been reported as the most common pattern in adult onset MND[258,260,261] but inheritance was ambiguous in one of our kindreds (RP) and occasional recessive inheritance of MND may occur[262]. X-linkage appears to be the inheritance pattern in one family (JH) with a presentation of bulbospinal neuronopathy (Kennedy syndrome[56,247]). Although some familial MND is linked to chromosome 21, this disease is genetically heterogeneous[41]. The low frequency of familial MND and the decreasing likelihood that as age increases a patient who presents with MND has a family history[257] suggests that inherited, as opposed to somatic, mutations make only a small contribution to adult onset MND.

The distribution of patients within Scotland gives no clear evidence of non-random distribution and therefore in itself provides no evidence for an environmental etiology. Failure to demonstrate non uniformity may be due to the inadequate statistical power of this sample so far and in the future, as SMNDR

registrations accrue, distribution can be analysed by other means such as by postcode.

Table 3-1: SMNDR Registration form details.
(responses yes, no, uncertain)

General:

- Muscular weakness
- Progressive history
- Absence of sensory signs
- Seen by a neurologist

Distribution of signs:

- Bulbar signs
  - UMN bulbar signs
  - LMN bulbar signs
- Limb signs
  - UMN limb signs
  - LMN limb signs
- EMG performed?

Is there any suggestion of an alternative diagnosis?

Is there any associated disorder?

Is the patient aware of the diagnosis?

Date of onset

Date of diagnosis

Is the diagnosis definite/probable/suspected?

Table 3-2: Physical signs by region used in the classification of patients with MND

Region	Upper motor neuron signs	Lower motor neuron signs
Bulbar	Dysarthria (may be LMN)* Dysphagia (may be LMN)* Spastic,clumsy tongue Exaggerated jaw jerk/facial jerks Spastic tetraparesis Extensor plantar response(s)	Wasted tongue or cranial musculature Fasciculation of the tongue Dysphonia/weak cough Palatal weakness/nasal escape Wasting/weakness/fasciculation of sternomastoid
Cervical	Reflexes present in a wasted upper limb Finger jerks Spastic tetraparesis/extensor plantar(s),without bulbar signs	Wasting/fasciculation C2-T1 Paradoxical breathing/diaphragmatic palsy Absent upper limb reflexes
Thoracic	Spastic paraparesis Reflexes in wasted lower limb Extensor plantar response(s)	Paraspinal/abdominal fasciculation Paraspinal wasting, truncal weakness Intercostal weakness/reduced vital capacity
Lumbo/sacral		Wasting/fasciculation L2-S2 Absent lower limb reflexes

In deciding if bulbar involvement was or was not present, no attempt was made to distinguish symptoms due to LMN as opposed to UMN lesion(s).

Table 3-3: Summary of the diagnostic categories used by the SMNDR

1.Clinically definite MND	
1-1	ALS/PBP
1-2	PBP/ALS
2. Clinically probable MND	
2-1	PBP
2-2	ALS (2 regions)
2-3	ALS (3 regions)
2-4	PMA
2-5	PLS
3. Not MND	
3-1	Spastic paraparesis (unspecified)
3-2	Multisystem diseases
3-3	Miscellaneous

ALS= Amyotrophic lateral sclerosis; PBP= Progressive bulbar palsy;
PMA= Progressive muscular atrophy; PLS= Primary lateral sclerosis;

Table 3-4: Alternatives for the distribution of clinical signs in the limbs and trunk for the diagnosis of different categories of MND by the SMNDR (see text for qualifications)

1.Clinically definite:

The least extent permissible for diagnosis:

	Bulbar UMN
or	Bulbar LMN
and	UL (C) or trunk (T) or LL (L/S) LMN
and	UMN signs in the same spinal region

2-2. Clinically probable MND (ALS, 2 regions):

No bulbar signs, 2 spinal regions combining UMN and LMN signs eg:

LL	LMN (L/S)		
LL	UMN (T or C)		
LL	LMN (L/S)	Trunk	LMN (T)
UL	UMN (C)	UL	LMN (C)
		LL	UMN (T or C)

2-3.Clinically probable MND (ALS 3 regions):

No bulbar signs, 3 spinal regions combining UMN and LMN signs eg

LL	UMN (T or C)	LL	UMN (T)
	LMN (L/S)		LMN (L/S)
UL	LMN (C)	UL	LMN (C)

Note: If UL (C) LMN signs are present then cannot be certain that LL UMN signs are due to disease of the same (C) region or (T) region. UMN= Upper motor neuron; LMN= Lower motor neuron; UL= Upper limb; LL= Lower limb.C= Cervical; T= Thoracic; L= Lumbosacral.

Table 3-5: Summary of patients registered with the SMNDR but excluded from the main analyses (for details see Appendix A.)

A. Clinical features of MND but other neurological features coexisted (n=8).

MND associated with dementia or atypical pathological features	4
MND with extrapyramidal signs	2
Combined neuronopathy and neuropathy with polycythemia	1
Longstanding neurological disease making diagnosis uncertain	1

B. Diagnosis subsequently shown to be other than MND with follow up (n=15).

Cervical spondylotic myelo(radiculo)pathy	7
Cerebrovascular disease	2
Motor neuronopathy associated with lymphoma (paraneoplastic)	1
Polymyositis	1
Retrophyrangeal tumour	1
Neuropathy and hydrocepahlus	1
Demyelinating disease, probably late onset multiple sclerosis	1
Metabolic derangements and debility	1

C. Diagnosis uncertain but fail to fulfil SMNDR criteria for the diagnosis of clinically definite or probable MND (n=5).

Monomelic signs	1
Spastic paraparesis not otherwise specified	1
Possible PLS, possible multiple sclerosis	1
"Arrested" MND/ non-progressive	1
Brainstem lesion, non progressive	1

Table 3-6: Descriptive statistics comparing the differences between means (95% confidence limits) for selected variables

		n	mean(m) (years)	(Range)	sd	m1-m2	(95% CI)
1. Male (M) vs Female (F)							
Age at onset (years)	M	132	61.6	(14.6-83.4)	12.2		
	F	97	67.0	(27.9-89.2)	11.2	5.4	(2.3-8.6)
Age at diagnosis (years)	M	132	63.1	(19.6-84.2)	12.2		
	F	97	68.4	(30.4-90.7)	11.0	5.3	(2.2-8.4)
Age at death (years)	M	72	67.4	(41.4-84.5)	9.7		
	F	72	70.0	(39.7-90.7)	10.7	2.6	(0.8-5.9)
2. Sporadic (Sp) vs Familial (Fam)							
Age at onset (years)	Sp	218	64.3	(14.6-89.2)	12.0		
	Fam	11	55.6	(41.2-75.5)	12.6	8.7	(1.4-16.0)
Age at diagnosis (years)	Sp	218	65.7	(19.6-90.7)	11.8		
	Fam	11	58.1	(42.4-76.6)	13.3	7.6	(0.4-14.9)
3. Seen (N+) or not seen (N-) by a Neurologist							
Age at onset (years)	N+	192	62.3	(14.6-82.3)	12.1		
	N-	37	72.1	(53.2-89.2)	7.8	9.8	(5.7-13.9)
Age at diagnosis (years)	N+	192	63.8	(19.6-84.4)	12.0		
	N-	37	73.4	(53.5-90.7)	7.7	9.6	(5.5-13.6)

Table 3-7: First source of referral to the Scottish Motor Neuron Disease Register in 1989-90

Total number of incident patients	**229**
Collaborating neurologists/neurophysiologists	129 (56.5%)
Hospital discharge data	44 (19%)
General Practitioners	27 (12%)
Scottish MND Association family care officers	23 (10%)
Mortality data (death certificates)	5 (2%)
Pathology records	1 (0.5%)
Seen by a neurologist	**188 (82%)**
NCS/EMG performed	**190 (83%)**

Table 3-8: Clinical classification of MND subtypes at presentation and by January 1st. 1992

	At presentation (Initial diagnosis)				January 1992 (Final diagnosis)			
	M	F	Total		M	F	Total	
Definite MND								
1-1 Beginning in the limbs (ALS/PBP)	22	24	46	(20.1%)	47	33	80	(34.9%)
2-1 Beginning in the bulbar muscles (PBP/ALS)	21	32	53	(23.1%)	25	43	68	(29.7%)
Probable MND								
2-1 Progressive bulbar palsy (PBP)	5	15	20	(8.7%)	1	5	6	(2.6%)
2-2 Spinal ALS (2 regions)	8	3	11	(4.8%)	4	1	5	(2.2%)
2-3 Spinal ALS (3 regions)	54	20	74	(32.3%)	40	13	53	(23.1%)
2-4 PMA	20	2	22	(9.6%)	14	2	16	(7.0%)
2-5 PLS	2	1	3	(1.3%)	1	0	1	(0.4%)
Total	**132**	**97**	**229**	**(100%)**	**132**	**97**	**229**	**(100%)**

Table 3-9: Anatomical site of onset of muscle weakness

Site of onset	Male	Female	Total
Bulb (dysarthria or dysphagia)*	26	47	73 (31.9%)
Total upper limb ϕ	57	11	68 (29.7%)
Arm	25	4	29 (12.7%)
Hand	32	7	39 (17.0%)
Total lower limb	41	38	79 (34.5%)
Leg	28	26	54 (23.6%)
Foot	13	12	25 (10.9%)
Shortness of breath	3	0	3 (1.3%)
Uncertain	5	1	6 (2.6%)
Total	132	97	229

* Onset in bulb or simultaneously in bulb and limbs. ϕ Relative risk of a male having onset in the hand=5.94 (2.9-12.2)

Table 3-10: Relative risks (RR) and 95% confidence limits for the clinical subtypes of MND according to sex

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RR of a female having PBP as the initial feature (PBP; PBP/ALS as initial diagnosis)
Females = 47 of 97
Males = 26 of 132 RR= 2.5 (1.7-3.7)

RR of a female having PBP at any stage of MND
Females = 81 of 97
Males = 73 of 132 RR= 1.5 (1.3-1.8)

RR of a female over 65 years having PBP as the initial feature (PBP; PBP/ALS) as initial diagnosis
Females = 34 of 65
Males = 14 of 71 RR= 4.5 (2.1-9.6)

RR of a male presenting with spinal disease (ALS as initial diagnosis)
Males = 84 of 132
Females = 47 of 97 RR= 1.3 (1.0-1.7)

RR of a male having only spinal disease (ALS as final diagnosis)
Males = 91 of 132
Females = 47 of 97 RR=1.4 (1.1-1.8)

RR of a male presenting with PMA (PMA as initial diagnosis)
Males = 20 of 132
Females = 2 of 97 RR= 7.4 (1.8-30)

RR of a male with PMA only (as final diagnosis)
Males = 14 of 132
Females = 2 of 97 RR= 5.1 (1.2-22)

Table 3-11: Age-sex specific incidence rates for MND in Scotland (1989-90).
Numbers of patients given in 5 year age bands, incidence and 95% CI calculated for 10 year age bands between mid decades.

age band	Men Population	n	Incidence /100,000/yr(95%CI)	Women Population	n	Incidence /100,000/yr(95%CI)	Total Pop	n	Incidence /100,000/yr(95%CI)
15-24	407870	1	0.12 (0.00-0.58)	391983	0	0.00 (0.00-0.38)	799853	1	0.06 (0.00-0.30)
25-29	210796	(2)		201758	(0)		412554	(2)	
30-34	184169	(0)		182061	(1)		366230	(1)	
25-34	394965	2	0.51 (0.04-0.80)	383819	1	0.13 (0.00-0.62)	778784	3	0.19 (0.05-0.49)
35-39	167833	(2)		168056	(2)		335889	(4)	
40-44	172561	(4)		172776	(0)		345337	(4)	
35-44	340394	6	0.88 (0.38-2.11)	340832	2	0.29 (0.05-0.93)	681226	8	0.59 (0.29-1.10)
45-49	144006	(12)		149071	(2)		293077	(14)	
50-54	136881	(7)		145717	(7)		282598	(14)	
45-54	280887	19	3.38 (1.86-4.90)	294788	9	1.53 (0.80-2.70)	575675	28	2.51 (1.53-3.33)
55-59	131201	(22)		144283	(8)		275484	(30)	
60-64	123114	(11)		141079	(12)		264193	(23)	
55-64	254315	33	6.27-8.70)	285362	20	4.03 (1.97-5.05)	539677	53	4.91 (3.59-6.25)
65-69	113212	(30)		141953	(14)		255165	(44)	
70-74	73196	(22)		106321	(20)		179517	(42)	
65-74	186408	52	13.94 (10.01-17.75)	248274	34	6.84 (4.45-9.15)	434682	86	9.89 (7.80-12.0)
75-79	59099	(14)		99573	(21)		158672	(35)	
80-84	31927	(5)		70064	(8)		101991	(13)	
75-84	91026	19	10.44 (5.75-15.15)	169637	29	8.54 (5.45-11.65)	260663	48	9.21 (6.6-11.6)
>85	14979	0	0.00 (0.00-10.01)	50306	2	1.99 (0.35-6.30)	65285	2	1.53 (0.26-4.85)
Total	2460373	132	2.68 (2.22-3.14)	2630327	97	1.84 (1.47-2.21)	5090700	229	2.25 (1.96-2.54)

Table 3-12: Standardised incidence ratios for the nine Scottish regions and three island areas 1989-90 (Orkney and Shetland combined)

Region	Population (Total)	Observed n	Expected n	Standardised incidence ratio (95% CI)
Borders	102,700	8	5.36	1.49 (0.64-2.94)
Central	271,400	10	12.06	0.83 (0.39-1.52)
Dumfries/Galloway	147,600	4	6.86	0.58 (0.16-1.49)
Fife	344,800	11	15.60	0.71 (0.35-1.26)
Grampian	503,500	19	21.64	0.88 (0.53-1.37)
Highland	201,900	10	8.98	1.11 (0.53-2.05)
Lothian	742,900	42	33.06	1.27 (0.92-1.72)
Strathclyde	2,311,200	110	103.00	1.07 (0.88-1.29)
Tayside	392,500	13	18.62	0.42 (0.12-1.10)
Orkney/Shetland	4,1570	2	1.92	1.04 (0.13-3.76)
Western Isles	3,0630	0	1.54	0.00 (0.00-4.92)
Scotland	**5,090,700**	**229**	**229**	**1.00**

Fig 3-1: Organisation of the Scottish Motor Neuron Disease Register

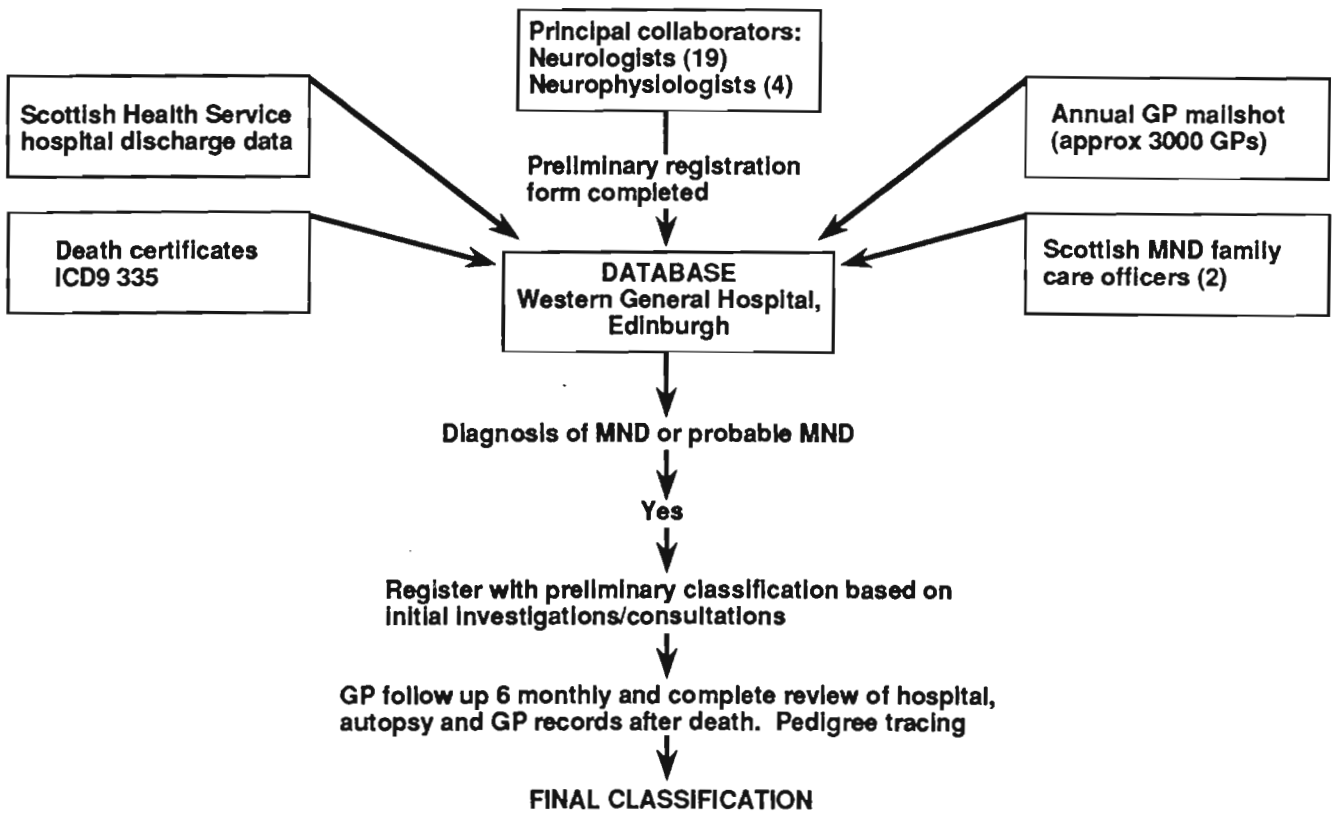
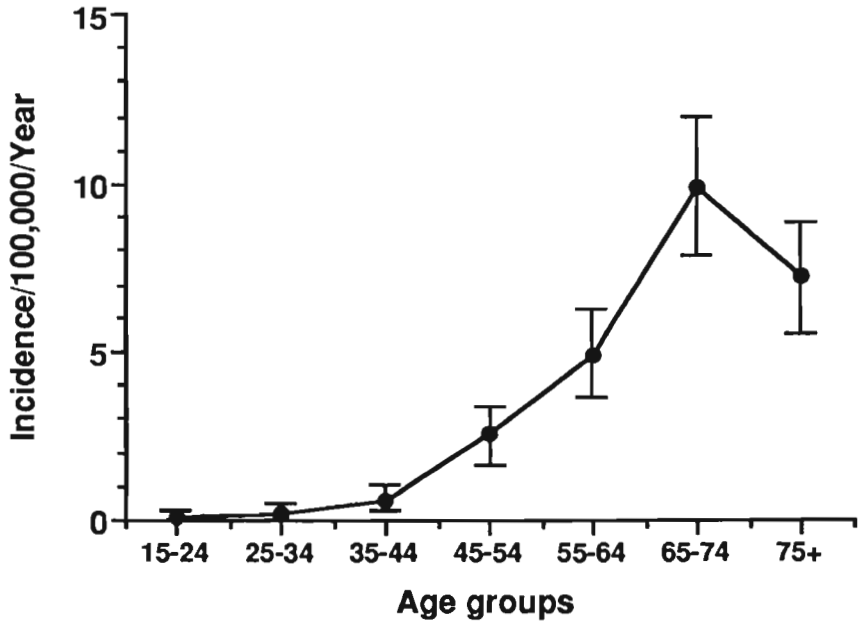


Fig 3-2: The Scottish Motor Neuron Disease Register 1989-90
Age specific incidence rates (n=229)



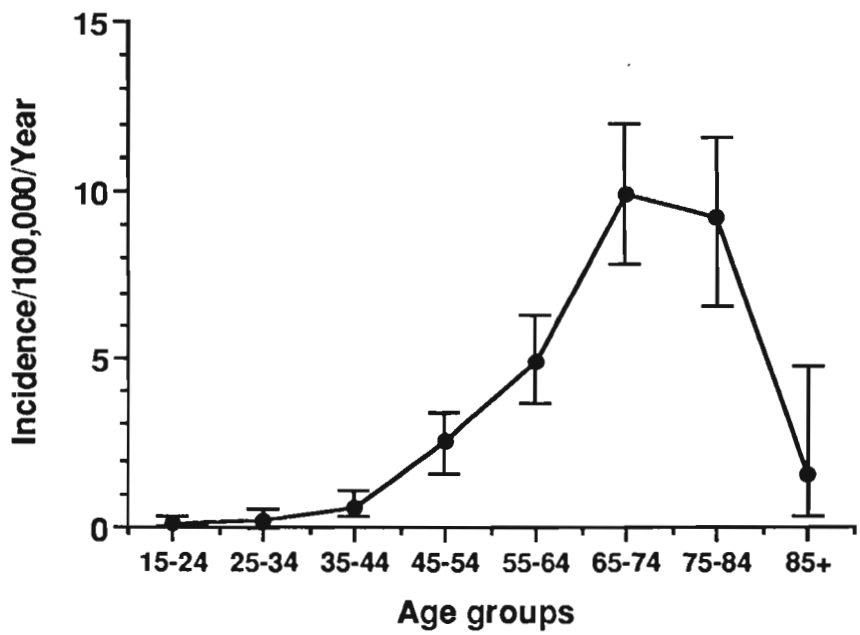


Fig 3-3: The Scottish Motor Neurone Disease Register 1989-90 Age and Sex Specific Incidence Rates

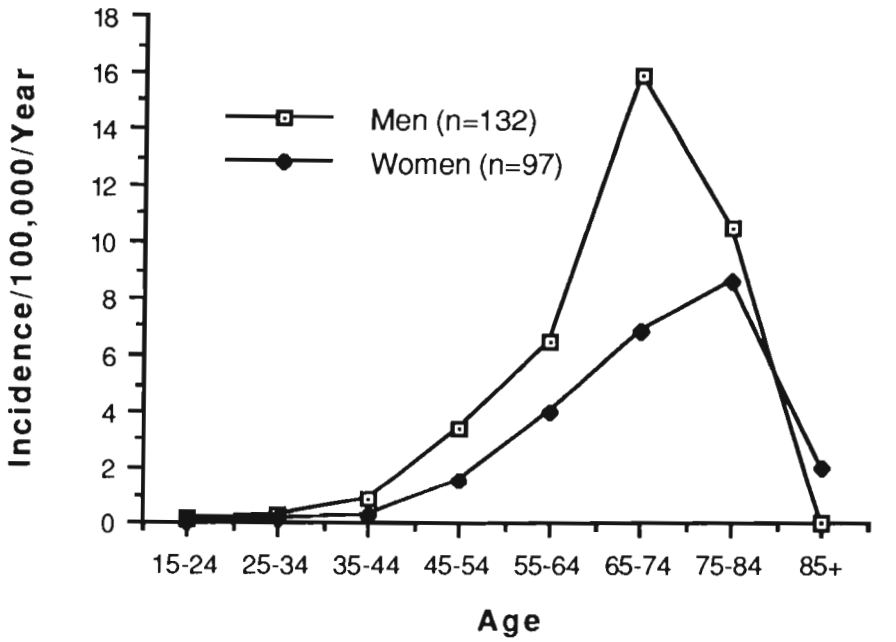
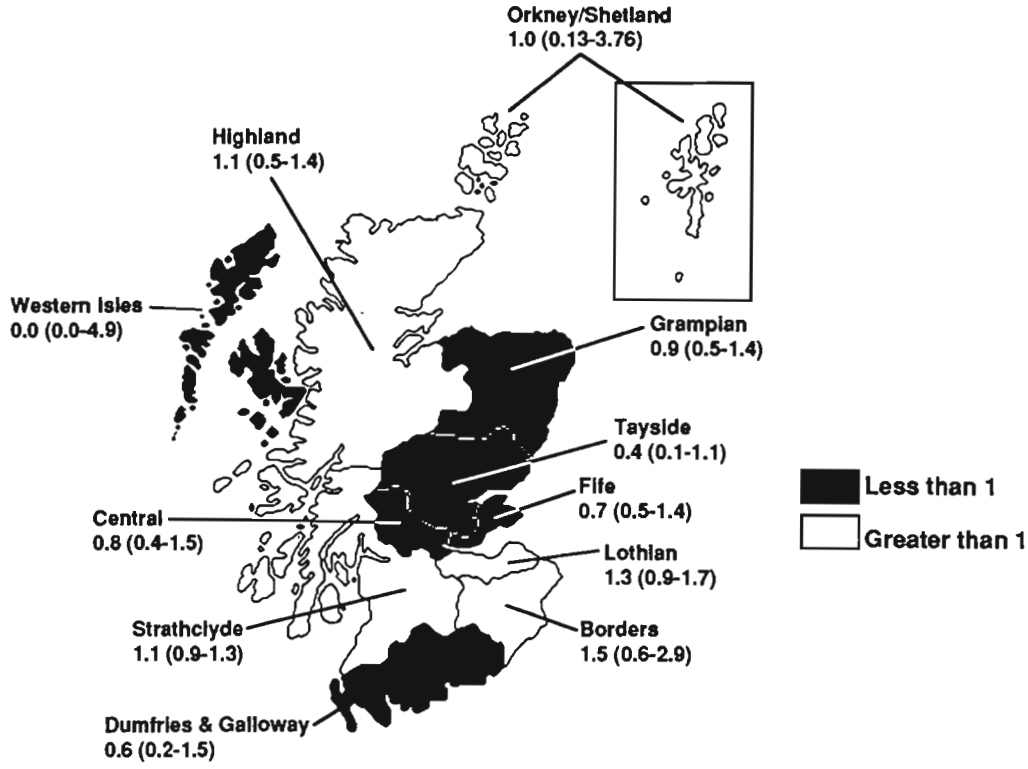


Fig 3-4: The Scottish Motor Neuron Disease Register 1989-90
Standardised incidence ratios by region (95% CI), n=229



CHAPTER 4

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

INTRODUCTION

" Physicians of the Utmost Fame
Were called at once; but when they came
They answered as they took their Fees,
"There is no cure for this Disease."

From "Henry King", Hilaire Belloc[263]

National Health Service managers, administrators and public health specialists use morbidity and mortality data to plan the appropriate allocation of health care resources. Therefore, it is important that this information is as accurate as possible.

Some investigators, using unverified hospital discharge rates, have reported an incidence of MND approximately two to three times that measured by other means[112]. This discrepancy suggests that a large but unknown number of patients coded as MND following hospital discharge do not actually have this disease.

More commonly, mortality statistics are used both to follow trends and as an indirect measure of incidence of MND[73,124] (see chapter 2), with the belief that such data have a high degree of a accuracy, given the generally fatal outcome of this disease within a year or two of diagnosis. In 1979 the ninth revision of the ICD[264] introduced an amended classification of anterior horn cell disease and the clinical subtypes of MND were included under the rubric 335.2 (table 4-1).

The accuracy of such routinely collected statistics depends on: (1) The proportion of incident patients admitted to hospital or dying from the disease (2) The precision of diagnosis at discharge from hospital or at the time of death (3) The satisfactory completion of Scottish Morbidity Record (SMR 1) forms and

death certificates (4) The appropriateness of ICD coding (5) The accuracy of transcription of information to the Scottish Hospital In-Patient Statistics (SHIPS) and Registrar General's computer file and (6) The efficiency of the linkage programme which retrieves first, rather than all, discharges and the satisfactory retrieval of death certificates for the relevant year.

There have been no formal studies to compare the accuracy of hospital discharge data with other case finding methods, or the extent to which these data will identify all patients who develop MND, yet this is an important requirement for studies which require an unbiased and complete sample of cases. Some information is available concerning the false negative rate of death certificates[73,124,125] but much less is available concerning the false positive rate[72]. In this chapter I have compared the accuracy of hospital discharge data and mortality statistics with the SMNDR.

METHODS

The SMNDR was considered as the "gold standard" for the purpose of this study, although 21% of SMNDR registrations in 1989-90 had been ascertained for the first time from SHIPS and 2% from mortality returns.

Morbidity data retrieval

The inpatient and day case records summary sheet of hospital morbidity in Scotland (SMR1) collects biographic, administrative and clinical information relating to every hospital death, discharge or transfer and includes a section pertaining to diagnosis which should "be completed by the doctor on discharge of pa-

tient"[265]. Clerical staff complete the remaining details and code the assigned diagnoses according to the ICD-9. This form is the basis for data transferred to the SHIPS computer, although it has now been replaced by a computerised patient administration system in a number of hospitals.

A request was made to the Information and Statistics Division of the Common Services Agency for the Scottish Health Service for details of all patients coded as ICD-9 335 in any part of their discharge form for 1989 and 1990, and which, through a record linkage system, was restricted to first discharge with this diagnosis. This was available in the August following the year of interest. The hospital records of all such patients in Scotland who were not already registered with the SMNDR were requested, with the permission of the consultant in charge of the patient, through the relevant medical records officer (see chapter 3). Patients who fulfilled the criteria for probable or definite MND, who were not already included on the SMNDR, and who had been diagnosed on or after January 1st 1989 (incident), were therefore eligible for inclusion in the SMNDR and accordingly registered. Other patients had been coded correctly but were discovered to be prevalent to the SMNDR (diagnosis made before January 1st 1989), despite first admission in that year. The diagnoses of all patients coded as ICD-335 who did *not* have MND were recorded and the records examined to try and determine the reason for the error. The SMNDR was also used to identify all patients diagnosed as definite MND and first discharged from hospital in 1989 and 1990 who did *not* appear in the SHIPS.

Mortality data retrieval

A list of all deaths older than 15 years, coded as ICD 335 in position 1 or 2 on the death certificate, was retrieved by the Registrar General's Office for Scotland approximately 1 year after the end of the year of interest (see chapter 3). This information enabled the retrieval of General Practice records, which contain a copy of all hospital correspondence, through the relevant Health Board. This information was treated along the same lines as that derived from SHIPS (see above), SMNDR records were searched to determine the false negative rate of retrieval for mortality statistics.

RESULTS

Morbidity data

A summary of the SHIPS data in relation to the SMNDR is displayed in table 4-2. Of a total of 379 patients older than 15 years discharged for the first time in 1989-90, 141 were already registered with SMNDR and 27 were known to be prevalent from other sources, leaving 211 for whom hospital records were reviewed for diagnostic details. 112 did not have MND, ie the false positive rate was 30%. 52 MND patients included on the SMNDR (23% of incident cases) did not appear on SHIPS in the two years examined. SHIPS overestimated the incidence of MND by a factor of 1.6. Table 4-3 displays the utility of SHIPS in terms of sensitivity (84%) and positive predictive value (70%) of a diagnosis of MND as determined by ICD 335. If it is assumed that all patients discharged from hospitals in Scotland who did not have MND were *not* coded as ICD-335 then, given this very large true negative rate, an hypothetical specificity would be close

to 100%.

Table 4-4 gives the diagnosis in the 112 patients miscoded as MND. The largest group were patients with a pseudobulbar palsy due to cerebrovascular disease (38%). In 18% the coding accurately reflected the medical summary but the diagnosis was incorrect, either because of a failure to meet standard criteria for diagnosis, or because a "probable" or "possible" diagnosis of MND was disproven at follow up. 12% of miscoding appeared to be due to a transcription error, as no possible source of confusion for ICD 335 could be determined from the records.

Mortality data

Summary statistics relating the death certificates coded as ICD 335 in relation to the SMNDR are displayed in table 4-5. 27/281 deaths,(10%) contained false positive errors giving a positive predictive value for mortality returns of 90%. Again, miscoding of patients with pseudobulbar/bulbar palsy was the most common source of error. 12 (44%) of these errors were due to misdiagnosis although coding was correct, 15 (56%) were due to miscoding of other conditions (Table 4-6).

Seven of 95 SMNDR patients who died with MND were not retrieved by the Registrar General, giving a false negative rate of 6%. However, inspection of these returns revealed that MND was recorded as a cause of death in 3 cases, so presumably there was a transcription error at some point in retrieval. As the death rate of patients on the SMNDR will continue to rise, at least until 1991-2, when a steady state of mortality will reflect incidence more closely, it is not possible to calculate the sensitivity of a death certified as MND.

DISCUSSION

Morbidity data

This audit demonstrates that SHIPS is inaccurate. 30% of patients coded with ICD 335 did not have MND and therefore these data cannot, in their crude form, be used as a reliable guide to the incidence of MND in Scotland which would have overestimated the rate for 1989-90 by a factor of 1.6. This figure will fall slightly if the same audit is repeated at a later date as the number cases prevalent with respect to the SMNDR will be less however the problem of false positive coding will persist unless measures are taken to correct its cause. 49 of 229 (21%) of incident patients were identified by SHIPS as the first source of referral for the SMNDR and therefore this resource was necessary to accurately determine the incidence of MND in Scotland.

There are three major reasons for these errors. Firstly, while the importance of accurate coding *may* be appreciated by many doctors, this task seems to receive a low priority. Although medical staff make the diagnosis, they do not take primary responsibility for the supervision of diagnostic coding, which is delegated to clerical staff who may not be able to interpret adequately the nuances of ambiguous medical terminology. In some cases records staff are left extracting information from poorly worded letters rather than specifically listed discharge diagnoses and hence take medical conditions out of context eg for "pseudobulbar palsy due to cerebrovascular disease" some patients were assigned to the wrong ICD or to both ICD-335.2 and 437.9.

Secondly, the ICD classification does not allow practitioners to indicate whether a diagnosis is firmly established,

requiring further information, or largely speculative. This is in contrast to clinical practice where revision is often required and the passage of time clarifies a diagnostic problem (for example the differential diagnosis of spondylotic cervical myelopathy and MND). It is this flaw, when the diagnosis did not meet generally accepted minimal criteria for probable or definite MND[266] (Chapter 3), which accounted for 18% of the diagnostic inaccuracy (Table 4-4).

Finally, some of the errors arose because coding with the ICD-9 can be ambiguous, for example the alphabetical listing directs "bulbar (progressive) (chronic)" and "bulbar-pseudo (not elsewhere classified)" to ICD-335.2, which may be inappropriate.

Although the accuracy of a general sample of morbidity information[267] and for a number of other specific diseases in Scotland[268-271] has previously been examined, and while many epidemiological studies of MND have collected hospital discharge data as part of a case finding exercise[91,92,94,95], some of whom have commented on their inaccuracy[96], none have formally evaluated their utility for this disease. Neither have previous studies been able to compare accuracy with a more or less independent case finding method such as the SMNDR.

The results indicate that more diligent efforts to ensure correct coding are required. The nature and uses of SHIPS should be made clear to the medical staff responsible for discharge documents. Doctors should be encouraged to use clear and unambiguous terminology, preferably within a standardised discharge format. Guidelines issued to area medical committees in 1990 have emphasised that a senior member of the clinical team should

be responsible for coding[272]. Regular audit of case records is important in this regard and quality assurance within the Information and Statistics Division has now been established whereby experienced staff will blindly recode a random sample of SMR records to quantitate the accuracy of existing coding. As a result of this review sources of error will be discussed with coding staff and the SMNDR will continue to monitor SHIPS returns to see if accuracy improves.

Mortality data

Interpretation of variations in time and place which might be used to generate aetiological hypotheses depends on an understanding of the accuracy of the data on which such comparisons are based. In this study, mortality data were much more accurate than SHIPS, as might be predicted. However, some of the problems relating to discharge data also apply to death certificate coding, in particular the miscoding due to other neurological conditions, mainly bulbar palsy of various causes, in turn due to the difficulties with the ICD coding system.

Whether the incidence of MND can be studied adequately with mortality data alone is controversial[78] (see Chapter 2). Other studies of the accuracy of mortality data have shown that 70-90% of patients diagnosed with MND have this condition recorded on their death certificate[72,73,124,125]. In Scotland mortality data also have a low false negative rate. Only one other study from Japan has examined the false positive rate of death certificate coding (in 1965); an extensive attempt to verify the diagnosis from other sources showed that as many as one third of men were coded as dying of MND without having the

disease, but the accuracy was better for women[72]. SMNDR mortality statistics were much more accurate than this.

These findings have important implications for epidemiologists interpreting trends in MND frequency. There is evidence from a number of countries that the mortality from MND has increased steadily over the past 30 years[73,75-77,79,82] and this is also the case in Scotland[273]. This increase may be real, rather than due to ascertainment bias or improved diagnostic skills, but it would be helpful to confirm this with other sources, eg incidence data.

From this analysis, it can be inferred that changes in the ICD coding system, or alterations in coding practice, are likely to have an effect on both morbidity and mortality rates which could be mistaken for a real variation in disease incidence. Whether these results are applicable to other countries is uncertain but the anomalies in ICD-9 will apply everywhere.

Table 4-1: International Classification of Diseases-9 (1979); 335, anterior horn cell disorders.

335.0 Werdnig-Hoffmann disease

Infantile spinal muscular atrophy

335.1 Spinal Muscular atrophy

Kugelberg-Welander

Adult spinal muscular atrophy

335.2 Motor Neuron Disease

Amyotrophic lateral sclerosis

Motor neuron disease (bulbar) (mixed type)

Progressive muscular atrophy (pure)

335.8 Other

Table 4-2: Summary of the Scottish Hospital In-Patient Statistics (SHIPS) in relation to the Scottish Motor Neuron Disease Register (SMNDR)

	Discharge or diagnosis date 1989	1990	Total
Discharged from Scottish hospitals for the first time, coded ICD 335 and aged >15 years	171	208	379
Already registered with SMNDR as diagnosed on or after 1.1.89 (incident)	51	90	141
Already known to SMNDR as MND diagnosed before 1.1.89 (prevalent)	9	18	27
Hospital records reviewed for patients not known to the SMNDR showed:			
Coded correctly but notes indicated prevalent to SMNDR	34	14	48
Diagnosis MND (first notification source for SMNDR)	26	23	49
Diagnosis not MND (false positive, see table 4)	50	62	112
Records could not be located	1	1	2
Total records reviewed	111	100	211
Therefore SHIPS correct in diagnosis, whenever this made (true positive)	120	145	265
Diagnosis of MND, no hospital discharge in either 1989 or 1990, not on SHIPS *	10	32	42
Discharged from hospital but not on SHIPS	7	3	10
Total ie definite or probable MND,on SMNDR, but not on SHIPS (False negative)	17	35	52
Incident patients as defined by the SMNDR ("gold standard")	111	118	229

SMNDR Scottish Motor Neuron Disease Register. * Diagnosis of MND made as an outpatient.

Table 4-3: Sensitivity and positive predictive value of a diagnosis of Motor Neuron Disease as determined by the Scottish Hospital In Patient Survey (SHIPS) compared to the Scottish Motor Neuron Disease Register (SMNDR), 1989-90.

	Scottish Motor Neuron Disease Register		
	MND	Not MND	Total
Scottish Hospital In Patient Statistics			
ICD 335, 1989-90	265	112	377 ϕ
Not ICD 335	52	*	-
Total	317	*	

ϕ 2 records missing. * The presumed but unmeasured high true negative rate would produce a specificity close to 100%
Sensitivity of SHIPS = True positive/True positive + False negative x 100 = 84%
Positive predictive value of SHIPS = True positive/True positive + False positive x 100 = 70%

Table 4-4: Classification of 112 patients miscoded as MND by The Scottish Hospital In Patient Statistics.

	1989	1990	Total (%)
1.Diagnosis when coding was incorrect:			
Pseudobulbar palsy due to:			
(a) Cerebrovascular disease	23	20	43 (38%)
(b) Multiple sclerosis	1		1
Bulbar palsy (eg carcinoma lung with vocal cord paresis; dysphagia due to oesophageal carcinoma; multiple cranial neuropathies; myasthenia gravis; unspecified,non progressive)	5	7	12
Neuromuscular disease, usually with "neuron" in diagnosis eg "lower motor neuron weakness", "motor neuropathy"	3	12	15
Muscular atrophy due to polio	4	2	6
Not MND but physician refused release of further information	1		1
2.Coding correct,but insufficient medical evidence for MND	4	16	20 (18%)
3.No reason apparent for the error in coding (transcription error):			(12%)
Neurological disease (but MND not mentioned)	5	5	10
Non neurological disease	4		4
Total	**50**	**62**	**112**

Table 4-5: Summary statistics relating to 1989-90 death certificates coded as MND ICD 335 (position I or II)

	1989	1990	Total
Death certificates coded as ICD 335 (as retrieved by The Register General)	148	133	281
Died, known to have MND but prevalent to SMNDR	61	46	107
Died, known to SMNDR and incident	21	64	85
Further GP records requested for review	66	23	89
Unable to trace records	3	0	3
Death certificate coded as ICD 335 but diagnosis incorrect or insufficient evidence for diagnosis (False positive)	14	13	27 (10%)
True positive (281-27)			254
Registered with SMNDR, died 1989-90 but not retrieved by Register House (False negative)	2	5	7* (6%)
Incident patients 1989-90 (SMNDR)	111	118	229
SMNDR patients who died	26	69	95

Notes: SMNDR = Scottish Motor Neuron Disease Register.
* 3 of these patients had MND on the death certificate in position I and therefore are an error of retrieval rather than misdiagnosis. Positive predictive value of mortality certification as ICD 335: (281-27)/(281x100) = 90% The true positive death rate (as judged by the SMNDR) is not yet stable to allow calculation of sensitivity.

Table 4-6: Errors in mortality data (n=27) with respect to adult onset MND. Diagnosis shown is based on review of medical records and death certificates.

1. Bulbar or pseudobulbar palsy due to cerebrovascular disease, multiple sclerosis or unspecified (non-progressive)	11
2. Motor neuropathies, radiculopathies, "lower motor neuron weakness"	5
3. Multisystem neurological disease	2
4. Probable cervical spondylosis	1
5. Diagnosis unknown or uncertain but insufficient evidence for MND	8

Note: 15 did not have MND in the body of the death certificate but were coded ICD 335; 12 had MND on the death certificate ie coding correct but MND misdiagnosed.

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

" To restore the human subject at the centre - the suffering, afflicted, fighting, human subject - we must deepen a case history to a narrative or tale; only then do we have a "who" as well as a "what", a real person, a patient in relation to disease - in relation to the physical."

Oliver Sacks[274]

One framework for research into the aetiology of MND, is to consider the potential interaction of ageing with environmental factors which might be temporally remote from the onset of clinical disease[275]. Support for this hypothesis is derived from the study of the Western Pacific forms of MND[276], the low concordance observed in twin studies[277], and reports of MND or MND-like diseases in relation to a variety of exogenous toxins[218,220,221,226,278]. Case-control studies have also suggested that a number of environmental factors may be of potential importance in increasing risk for subsequent MND (see table 5-1). This case-control study was planned to examine the following hypotheses relating to controversial issues:

1. Preceding trauma

"... trauma-and particularly major trauma to the limbs, is in fact a risk factor for amyotrophic lateral sclerosis...it seems a lead worth pursuing in this otherwise hopeless disorder"

J.F.Kurtzke[46]

This statement is based on evidence from the close temporal relationship of physical trauma to the development of MND in numerous anecdotal case reports[279-286], in uncontrolled series of patients published as recently as 1991[43] and evidence from case-

control studies, some of which have suggested a possible link between blunt trauma, electric shock, surgical procedures or hard physical labour/manual work[101,287-292] (Table 5-1). The interpretation of many studies is limited by methodological problems which risk introducing important sources of bias, particularly when patients are a selected group[290,291], or, as is often the case, the investigators cannot avoid the recall bias inherent in asking patients who have a vested interest in explaining their disease. Furthermore, case-control studies based on a diagnosis included on death certificates may result in associations which are the consequence of the disease itself eg superficial injury[78]. The potential relationship of MND with trauma is important, not only for aetiological considerations, but for medico-legal proceedings. Therefore, this case-control study sought to further examine this putative association.

2. Occupation, environmental toxins and xenobiotics

Exposure to single large doses of a neurotoxic substance, or more prolonged cumulative exposure to low doses, could produce motor neuron cell loss. Occupational groups might provide clues to such possible environmental risks; for example, it has been suggested that leather[73,138], textile[139], agricultural[91,112,293] and manual workers[292] may be at increased risk. Occupational exposure to a variety of minerals and metals is also a potential mechanism of neuronal attrition[220,223,294].

Williams et al, observed a patient who developed MND following intoxication by the insecticide pyrethrum[227,228], which is metabolised quickly to safer substances in mammals but

not insects, whom it paralyses and kills. This observation suggests that some toxic substances may have the capacity to produce MND directly or, that a genetically determined biochemical aberration, combined with the "wrong" environmental factors might predispose to the development of disease (ecogenetic/xenobiotic hypothesis[295]). Patients with MND may have a defect of sulphur oxidation and methylation which results in a high cysteine to sulphate ratio[296,297]. Therefore, an individual with poor S-oxidation capacity on a genetic basis who acquires a second insult, for example by the consumption of large amounts of sulphur containing compounds (eg the brassicae group of vegetables) might then be prone to develop MND[295].

Accordingly information was sought about all occupations; the subject's perceived toxic environmental exposure; the consumption of brassicae (cabbage, cauliflower or brussel sprouts) and an interest in the cultivation of vegetables.

3.Social class and the environment in childhood

The risk for MND could be related to factors associated with socio-economic deprivation, or affluence. Measurement of social class is fraught with difficulty, particularly for women employed in the home. To avoid some of these difficulties, Carstairs has devised a measure of socio-economic deprivation in Scotland[298] using information available from the last (1981) census which allocates a numerical score to individual postcode sectors (which contain an average of 6000 persons). Using the z-score technique to give a single score, the percentage values are combined for each postcode sector based on the four variables of car ownership, degree of overcrowding, unemployment and social class. The scores are distributed into seven categories within 0.3, 0.8, 1.5

and >1.5 standard deviations (sd) either side of the mean (+0.3sd to -0.3sd as the middle category). One important advantage of this method is that it can be applied to males and females, regardless of occupation, whether working or not. When standardised mortality ratios (SMRs) based on this scale are calculated, a number of common causes of death (eg cancer of the lung) show a highly significant trend (Fig 5-1a), with higher ratios from deprived areas.

In contrast fig 5-1b also shows the SMRs based on the 533 deaths from MND (ICD 335), in Scotland 1980-85, male and female. This demonstrates the reverse trend, that is, higher SMRs in individuals who live in areas of greater affluence. Confidence limits overlap with unity, and the Chi squared value for the Poisson regression is 2.21 (ns), but the graph does follow a "dose response" relationship. Because of concern about accurate diagnosis of the cause of death in the elderly, particularly for a rare neurological disease, the total group has been divided into those aged 20-74 years (fig 5-1c) and aged >75 years (fig 5-1d). It is then apparent that elderly people largely account for the overall trend in SMR with the Chi squared for the regression being 3.2 ($p < 0.1$) for those >74 years. This observation *may* reflect a failure to diagnose MND in elderly patients from deprived areas which probably are not so well supplied with medical services as affluent areas. Alternatively, if environmental factors associated with affluence *do* predispose to MND, the reason for the difference in the two age groups may be that the elderly have benefited less than younger people from improvements in the standard of living since the second world war. This observation argues strongly against factors associated with

deprivation increasing the risk for subsequent MND but this issue can also be addressed by the case control study.

A related question is the issue of the childhood environment and the risk of infection, particularly with poliovirus. Although late deterioration after poliomyelitis is well recognised[146,208-211,299], the majority of case-control studies which have examined the frequency of preceding poliomyelitis in patients or family do not support a causal association[288-290]. Also the vast majority of patients with MND cannot recall an episode of poliomyelitis. The hypothesis linking the two diseases, expounded by Martyn[74], hinges on the concept that a subclinical infection depletes motor neurons and renders the individual susceptible to age related neuronal depletion, or a second insult. Unfortunately past exposure to poliomyelitis cannot be distinguished serologically from antibody due to immunisation, introduced in the early 1950's.

In an attempt to look for indirect evidence of a link between the two diseases Martyn noted a specific positive correlation of MND mortality 1968-1978 with poliomyelitis notification rates 1931-39 in England and Wales; poliomyelitis did not correlate with other leading causes of death[144]. In addition, the suggestion has been made that the rising rate of poliomyelitis during the early decades of this century accounts for the present increasing trend in MND mortality. Population based epidemiological investigations in the 1950's identified the major determinants of seroconversion as absence of domestic amenities, domestic overcrowding and large sibship size[300,301]. With improvements in hygiene the proportion of children who escaped infection in the relatively "safe" period (from a clinical disease

point of view) increased and paralytic poliomyelitis became a disease of areas well supplied in terms of standard of housing[74].

Two possible predictions with respect to patients with MND can be made from this information: either, (1) If conditions are of a high standard of hygiene in childhood then later exposure to poliovirus might result in greater, albeit subclinical, nervous system damage because of greater vulnerability of motor neurons at this age and therefore childhood affluence should correlate with risk of MND[74], as suggested by the recent observation in Scotland described above[302], or (2) If childhood was spent in circumstances of poor domestic hygiene then the number of individuals exposed to poliovirus infection would be greater and thereby increase subsequent risk of MND, if the two are related[144].

Therefore this case control study design sought to seek any difference in the childhood environment with respect to standard of housing, domestic amenities, overcrowding and social class of the patient's father.

METHODS

Throughout, "case" or "patient" refers to a person affected with MND, "control" refers to an unaffected person and "subject" refers to either case or control.

Patients

Incident patients in Scotland with MND were identified from the Scottish Motor Neuron Disease Register (SMNDR) (Chapter 3).

The method of identification of the 103 patients included in the case-control study is described in table 5-2. Only patients with a mixture of upper and lower motor neuron signs were included (SMNDR classification = ALS; ALS/PBP; PBP/ALS). In each case the permission of the consultant neurologist or physician concerned and the patient's GP was sought before inclusion in the study.

Controls

After discussion of the nature of the study with each patient's GP, an age and sex matched community control was identified from the practice age and sex register, usually computerised, as the person with the date of birth nearest to that of the patient. In this way selection bias in obtaining controls was avoided as the GP's age and sex register constitutes a complete list of patients registered with a given practice (ie no records are missing because the patient is unwell). One control was identified for each patient. In two instances, after repeated attempts, the first control could not be located and then the next subject in the age and sex register was approached. One control refused to cooperate and in this instance the GP also declined further help, so a neighbouring practice assisted. The only potential reasons for exclusion of a control was dementia or psychological disturbance of such an extent to prevent adequate cooperation with a questionnaire; in fact, in no instance did this happen.

Data collection

I visited the case and then the corresponding control, in all regions of Scotland, in their respective homes, usually on

the same day, after arrangements had been made in advance of the visit. For patients, details of the history and clinical features as obtained by the SMNDR were verified and updated if discrepancies existed. A neurological examination was performed particularly to confirm the distribution of physical signs, which may have changed since registration with the SMNDR. Very particular care was taken in the establishment of dates of symptom onset. Case and control were treated in an identical fashion as far as the questions pertaining to antecedent factors were concerned. An equivalent date was assigned to controls corresponding to the onset of symptoms due to MND in the patients and only events prior to this date were recorded. Some prior indication of the nature of the questions was given in advance of the visit and information was collected by standardised questionnaire. The spouse of the case was invited to contribute to the answers and then, whenever possible the control's spouse was also used for help in ascertaining an accurate response. If no spouse was available for the case then the control's spouse was also excluded.

The standardised questionnaire (Appendix D) recorded the dates, anatomical location and nature of *all trauma requiring medical consultation*, including fractures; blunt trauma; operations requiring a general anaesthetic; and any electric shocks resulting in loss of consciousness, injury or post shock residual symptoms. Trauma which may have been associated with the onset of weakness was excluded by taking the history of the illness at the outset of the patient's interview. If the subject reported a fracture or injury near the time of the patient's symptom onset and there was any question of a weak limb predisposing to a

fracture eg a foot drop resulting in upper limb fracture, then the trauma was excluded from analysis. Following the interviews all the GP practice records, which included reports from accident and emergency departments and results of x-rays, for the case and control, were scrutinised to ascertain any injuries or operations requiring medical consultation which may have been omitted during the subject's interview. Systematic GP records began with the introduction of the National Health Service around 1948 and are transferred to the new GP when a patient moves to a different area and so represent a valuable source of unbiased information prior to the development of MND. In one pair access to the notes was denied by the GP but information regarding trauma was provided in letter form. In this way an account was obtained of the subjects' recall of traumatic events (fractures, blunt trauma requiring medical consultation and operations); trauma according to the GP records and this information could be analysed separately or on the basis of best information from both sources.

A detailed lifetime employment history was obtained and classified according to the Office of Population and Censuses and Surveys (OPCS)[303]. Details of toxic exposures (solvents, lead, minerals and ores) with regular contact over a period of 12 months or more were recorded. Structured questions about cigarette smoking and a history of atherosclerotic disease were also included.

A lifetime residential history was recorded of residences of more than 2 year's duration (limited to a maximum of the six of greatest duration if there were more than this number but always including residential details for the first 10 years of childhood). For each residence information was collected on its

location whether urban (city or town), or rural (village or isolated house); the availability of domestic amenities (a garden, separate bathroom with a fixed bath, running hot water, and flush lavatory); and residence size, (number of occupants per room and per bedroom).

Data were entered, as they were collected, into a microcomputer using dbase IV (Borland Inc.), for subsequent analysis by The Statistical Package for the Social Sciences (SPSS-X and SPSS-PC) using Chi square for categorical data and rank test for continuous data. Confidence intervals were calculated using a computerised analysis programme, applying a matched case control method[126,252].

RESULTS

Patient Characteristics

The age and sex distribution of the patient group were representative of the total population of incident patients with MND, 1989-90. There were 61 males (mean age 63.4, range 35-85 years) and 42 females (mean age 67.1 range 28-86 years). However, not surprisingly, the mean survival from symptom onset of patients who died before I could include them, was shorter than the 49 patients involved in the case-control study who had died by January 1st 1992, with a difference in the means of 6.4 months (95% CI -0.1-12.9). All patients had a mixture of upper and lower motor neuron signs in the limbs; 71 (69%) also had a bulbar/pseudobulbar palsy (ALS/PBP; PBP;ALS), the remainder had multilevel spinal disease without bulbar signs (ALS). The age of controls was identical to that of patients, a result of the matching process.

1.Trauma

Tables 5-3a shows the total number of fractures by case or control and sex. There was no significant difference in the distribution of fracture frequency by case or control for men or the total group, although the Chi square for females was just significant ($p<0.05$). With matched case-control analysis there was an overall non-significant excess of fractures in patients (table 5-3b) and a significant excess of fractures (with a very wide confidence interval) occurring within the prior five years before symptom onset, this remained significant when only those fractures documented by the GP's records were included (table 5- 3c). Table 5-3d shows the details of patients' fractures within 5 years of symptom onset. For the 4 patients with fractures within one month of symptom onset limb weakness could not have been responsible for the fracture, after this the increasing interval between fracture and symptom onset makes error even less likely. Figure 5-2 shows the distribution of fractures in case and control by interval before first MND symptoms (or equivalent in control) and figure 5-3 the odds ratios for a fracture at variable intervals before symptom onset.

There was no significant difference in the number of non-bony traumatic events requiring medical attention, number of operations, electric shocks or blood transfusions (Tables 5-4 to 5-7). There was no correlation between the site of fracture or injury and the anatomical area in which the weakness began. Patients were as good as controls (kappa=0.8) in recalling the true number of events when GP records were combined with subject's recall and analysis of the results based on the patients' account only produced no further positive associations.

2. Occupation, environmental toxins and xenobiotics

No single occupational group was significantly over represented, although the numbers in each of the 16 categories defined by the OPCS were small. The highest odds ratio (OR) of 3.0 (95% CI, 0.5-30) was in unskilled and labouring occupations. Overall and for men, patients were significantly more likely to have engaged in manual work than controls (table 5-8).

There was an excess of patients who perceived they had been exposed to some agents of potential toxicity (Table 5-9a) with an odds ratio for lead exposure of 5.3 (95% CI, 1.5-11.0). Table 5-9b details the nature of lead exposure in cases.

No difference was found in the number of times per week that patients ate members of the brassicae or in the frequency with which they undertook vegetable gardening.

3.Social class and the environment in childhood

There was a non-significant trend for patients to have had no hot water or a fitted bath (Table 5-10). However, this was not supported by any difference in the availability of a flush toilet; home space, as judged by the presence of a garden or the number of individuals per room in the house or rural versus urban living. No patients gave a history of paralytic poliomyelitis although 4 patients and 6 controls had contact with a family member with poliomyelitis (OR 0.7; 0.1-2.8). The frequency of the common childhood infections was the same in patient and control groups. The social class of patients' and the patients' fathers social class did not differ from that of controls. There were no associations with pet ownership, vascular disease, hypertension or tobacco use.

DISCUSSION

Sources of bias

The case-control method as a technique for establishing aetiology is relatively weak, subject to many potential sources of bias, rarely proves cause and effect, and rather than explain all cases, simply identifies risk factors[304-306].

In this study clinical homogeneity was achieved with predetermined specific diagnostic criteria for inclusion, ie a mixture of multilevel spinal involvement with or without bulbar palsy. *Selection bias* was minimised by using incident, rather than prevalent, population based patients. Despite attempts to include all incident patients in a given time period and achieving a representative group in terms of demographic variables, there was a non significant trend towards longer survival in those included in the case-control study. There were practical difficulties in timing appropriately involvement of patients at a stage when the diagnosis was secure but distress was not caused by approaching moribund patients. However, it seems unlikely that factors associated with a longer survival are systematically related to the issues examined.

Recall bias is a major source of systematic case-control study bias. This was reduced by not giving specific information to subjects about the hypothesis under examination and, in addition, as far as trauma was concerned, I was able to verify events by the use of General Practice records. These are unbiased for the knowledge of subsequent development of MND, and are a complete medical history, at least for events after 1948 when the National Health Service was introduced. Recall bias did

not, however, appear to be influencing the account of injuries obtained from patients' as all subjects, whether case or control, approximated the true trauma rate (ie best information combining both sources) equally well, and when the results were analysed on the basis of subject recall only, no false positive associations were made.

Unlike trauma, where this could be checked, recall bias may have been contributing to the findings related to environmental toxins, as there was no reliable way of verification of this information by independent means. On the other hand, the problem of *over-matching* may be spuriously masking an association between occupational related factors and MND as, for example, certain large employers in small towns engaged both patient and control, or a rural residence for the patient (and thereby a likely association with agricultural occupation) was also likely to apply to the control. However, overmatching will not have resulted in spurious false-positive associations. Controls were identified in an unbiased fashion from the community in which the patients lived,

Non-respondent bias, for example that resulting from a mailed questionnaire[291,307], was avoided by my personal approach as was *membership bias* by not identifying cases primarily from charitable bodies (in Scotland, The Scottish MND Association) as in some studies[290,307].

Exposure suspicion (interviewer) bias was possible but a standardised questionnaire was used; pre-specified hypotheses were tested, every effort was taken to avoid eliciting a biased account from patients and results were analysed after data collection were complete. By only recording events before

symptom onset any associations were more likely to represent primary rather than secondary phenomena.

Any study has constraints in terms of time and resources. *Wrong sample bias* may have resulted from the numbers it was possible to include (103 cases matched one to one), thereby reducing statistical power of the analysis, particularly when some factors are observed in only a few individuals.

Finally, *insensitive measure bias* may be operating if the questions asked are not a good reflection of the putative exposure or mechanism under examination. Taking a dietary history to estimate the ingestion of sulphur containing compounds is a very crude guide to this and questions about the absence domestic amenities may be too indirect to measure risk of enteroviral infection.

Discussion of risk factors

1. Trauma

This study lends some further support to the cumulative evidence which claims an association of physical trauma, particularly fractures, with MND. An overall non-significant trend was mainly due to the much higher fracture rate in the five years before symptom onset. However, these findings are not supported by any relationship of MND to non-fracture or operative trauma.

One of the largest case-control studies[288], in two parts, identified patients from (i) death certificates (with information from the spouse) and (ii) cases known to the ALS research group (selected collaborating neurologists) versus a mixture of hospital and neighbourhood controls. This study was vulnerable to selection bias, recall bias, and potential non-standardised data

collection. However, the two different methodological approaches of this study were consistent in their conclusion, that mechanical injuries were two to three times more frequent in both sexes heralding MND. A further study claiming a relationship of MND to trauma was limited to males, cases were ascertained from death certificates and used military records collected prior to the development of MND as the source of information on trauma, thereby avoided the major problem of recall bias. Lifetime operations, injuries and fractures were more than twice as common in cases[287]. A recent study which made a concerted effort to achieve patient homogeneity, used a selection of control groups, tested specific hypotheses and attempted to minimise recall bias, failed to demonstrate any such relationship[308].

When considering the cause of, or associations with, disease, the judgment of the relevence of any association should be based on a number of factors[309]. Case-control studies are generally less persuasive than *cohort studies* but follow up of a group of patients with fractures to the development of MND would require such enormous numbers and such a long time and as to make it impracticable. How *specific* is the association? Trauma has a potential role in Parkinson's disease[310], Alzheimer's disease[311] and dystonia[312] and so this may weaken the argument with respect to MND. However, the association of MND and trauma is *consistent*- almost all comparisons of this relationship in MND have been positive, whether or not statistically significant[69] (table 5-1). Was the association *hypothesis testing* or is it *hypothesis generating*? In this case-control study I ventured to test prespecified null hypotheses (the major issues outlined above). Given the number of questions, however, some "significant" asso-

ciations could have occurred by chance (1 in 20 at the p=0.05 level). There does not appear to be a clear *biological plausibility*, unless tissue damage in some way influences motor neuron function, perhaps mediated by trophic factors. It has not been possible to demonstrate a *dose-response relationship* (eg in those patients with fractures, that MND developed earlier); the association is not *strong* (ie not a common ocurrence in patients); on the other hand, it could be argued that there is a *temporal relationship*, of fractures with MND (clustered in the years before symptom onset).

2. Occupation, environmental toxins and xenobiotics

All the potential environmental toxins for which information was sought resulted in an OR of more than 1.0 and 95% CIs did not overlap with unity for exposure to lead and solvent/chemicals (ie significant at $p<0.05$ level). Combining all the factors increased the statistical power of an association between environmental toxins and MND, in a non-specific way (Table 5-9a). However, this result must be interpreted with great caution as there was no way to avoid recall bias (see above).

The major nervous system effects of lead intoxication are encephalopathy and motor neuropathy. The descriptions of selective motor involvement and amyotrophy date from Aran[21] but upper motor neuron signs have also been described in patients with lead poisoning[313]. Lead is widespread in the environment, with large increases in deposits (for example in quiescent Greenland ice caps) which correspond to the onset of industrialisation in the mid eighteenth century and have accelerated since

the use of leaded petrol[219]. Individuals are likely to have quite variable exposures[314], for example due to occupation or dietary habits[315]. The evidence for an association of lead and MND[218,219] and the possibility of interactions of lead and other minerals in MND is controversial[294,316,317]. A role for lead has been suggested based on findings of increased levels in spinal cord, muscle, plasma or CSF in patients with MND[318-321]. However these measurements are likely to be a crude reflection of the direct motor neuron exposure. Other case control studies have also suggested that lead exposure may be important in the aetiology of MND[322,323] (table 5-1) with the most recent study from the Mayo group[308] reporting a significant exposure in men, OR= 5.5 (95% CI, 1.44-21.0).

Some solvents are neurotoxic, usually producing a peripheral neuropathy, toxic encephalopathy[324] or extrapyramidal syndrome[226]. The case reports of MND associated with insecticide use[227,228] and a possible association with tolulene use in Sweden[325] and with textile[139] and leather workers[138] make it conceivable that occupational exposures are important in increasing the risk for MND. There is no support from this study to suggest that the consumption of brassicae is greater in MND patients than controls[295].

3. Social class and the environment in childhood

No correlation was found with *highest* social class of the patient or the patient's father. An occupational history which included manual work had an OR = 2.6 (95% CI, 1.1-6.3), thus there is no further support, from this study, for the possible correlation of MND mortality with affluence[302].

Although some factors related to socio-economic deprivation in early childhood (the absence of hot water or a bath) showed a trend towards patients being relatively deprived, the evidence based on this study is weak and does not favour a role of factors related to deprivation, particularly communicable diseases, including poliomyelitis, as playing a part in the aetiology of MND. These findings are consistent with others who have also failed to show any relationship to home space[288], or poliomyelitis[288-290,326].

It has been suggested that MND may not have a single etiology, but rather, a vulnerable motor neuron cell population is depleted by a variety of environmental or other factors acting with age to produce MND as the final common pathway[308,327]. The finding that some factors examined in this study have a limited association with MND favours the hypothesis that the aetiolgy of MND is multifactorial and that the environment may be important in increasing an individual's risk for the subsequent development of MND.

Table 5-1: Published case control studies of motor neuron disease (in English, 1965-91). Listed in chronological order of study.

Case (n)	Control (n)	Significant associations (*)	Odds ratio (OR) (95% Confidence interval) (#)	Non significant associations (♦)	Notes on methods	Reference [n]
79	78	Nil	Trauma (single subject)		Retrospective series based on hospital records	[281]
74	74	Lead exposure Fractures(<5yrs)	2.9 (1.4-5.9) 3.4 (1.0-11.0)		Neurology department patients No difference in bone lead level	[322]
109	109	Carcass exposure	1.5 (?)	Tonsillectomy,rural urban living,	Selected group,postal survey neighbourhood controls	[307]
25	50	Milk intake	8.8 (2.1-36.6)	Heavy metals,trauma Athletic activity	Selected patients (mean age 44 years) control selection?	[328]
504	504	Operations Injuries	2.1 (1.1-4.2) 2.4 (1.3-4.6)	Socioeconomic, status,occupation	Death certificates for ALS (m) matched to military records	[287]
712	637	Injuries: male :female (f) Operations:(f)	2.5 (1.7-3.7) 4.1 (2.5-6.7) 1.9 (1.3-2.7)	Alcohol,POW,smoking stay on Guam, gastrectomy [329]	Based on death certificates; controls for deceased patients selected from surviving spouse (widows for female patients and widowers for male patients)	[288]
158	158	Injuries: male :female	1.6 (1.0-2.9) 2.4 (0.8-8.7)	Home space,animal, contact,polio,job	ALS research group of neurologists, control selection?	[288]
63	61	Injury to back Electric shock	2.7 (1.2-6.5) 3.0 (1.0-9.1)	Fractures,head injury polio	Neurology department ?Source of controls	[289]
40	40	Exp to dogs	4.4 (1.7-11.3)	Other pet exposure	Neurology clinic patients, neighbourhood controls	[330]
105	164	Exp to metals	4.1 (1.6-10.2)	Pets,exercise diet,anaesthetics	Referred patients,incomplete reply to questionnaire	[323]
40	40	Exp to dogs	7.5 (1.7-67.6)	Animals, animal hides	ALS clinic, neighbourhood controls	[331]
66	66	Nil		Nine heavy metals	Neurology department based,	[332]

Table 5-1 (cont)

518	518	Job with electrical exposure Electric shock Trauma Relative with PD	3.8 (1.4-13.0) 2.8 (1.0-9.9) 1.6 (1.0-2.4) 2.7 (1.1-7.6)	Polio,lead and hide exposure	Selected ALS society Controls from friends	[290]
66	66	Nil		Skeletal fracture	Neurology centre, neighbourhood controls	[333]
135	85	Injuries: male+female	2.8 (1.6-4.9)	Nil else tested	Selected patients < 45 years Controls with multiple sclerosis	[291]
1593	3168	Conditions eg pneumonia (related to MND) only		Parkinson's disease Dementia	Designed to study conditions associated with MND at death	[78]
100	100	Nil		Operations,polio fractures,milk intake, metal exposure	Highly selected A variety of control types	[326]
72	216	Injuries (all) Agricultural job Less education Physical jobs	2.1 (1.2-3.7) 1.8 (1.0-3.2) 2.2 (1.1-4.0) 2.0 (1.1-3.6)	Operations, toxins, milk consumption	Hospital controls,questionnaire for some information, injuries exclusively from medical files.	[101]
77	80	Hard labour	2.5 (1.3-4.8)	Athletic effort Pets,metals,trauma	Neurology clinic patients, mean age 59 years,hospital controls	[292]
6	12	Nil		Trauma,consumption of fish.Many others	A small cluster from death certificates	[140]
1375	2245	Farm workers	1.7 (1.1-2.7)	A large number of other jobs	Based on death certificate and census information	[293]
45	90	Nil		Several medical conditions	Population based.Negative association with hypertension in men: OR 0.11 (0.01-0.88)	[334]
74	201	Lead exposure in men	5.5 (1.4-21)	Exertion,family history of NDD, rural living,trauma/surgery	Patients with clinical homogeneity,semi-quantitative	[308]

* = Lower 95% CI > 1.0; # As given or calculated by me; ϕ = Lower 95% CI < 1.0; NDD= Neurodegenerative disease

Table 5-2: Patients included in the case control study

Patients registered with the SMNDR with diagnosis date May 1990-October 1991 inclusive	180
Died before inclusion possible	39
Diagnosis "possible" MND	29
Familial	4
Permission for interview refused by	
Consultant	1
General Practitioner	1
Relative	1
Did not speak English	1
Moved to distant parts	1
Seen with age and sex matched controls	**103**

Tables 5-3a,b,c,d: Data relating to fractures.

Table 5-3a: Fractures by case, control, sex and number based on the best information combining patients' recall and GP records

	Number of fractures according to sex															
	0		1		2		3		4		6		7		Total	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Case	29	20	20	13	7	9	1	0	1	0	1	0	2	0	61	42
Control	26	31	21	7	7	3	3	1	2	0	1	0	1	0	61	42

Chi square value: for male and female = 4.6, DF= 6 (ns)
for males (M) = 2.0, DF= 6 (ns)
for females (F) = 8.2, DF= 3 ($p < 0.5$)

Table 5-3b: Matched case-control analysis, all subjects lifetime history of fractures, yes or no (*). Numbers in parenthesis are based on GP records only **

	Male	Female	All
Case and control	21	5	26 (12)
Case only	11	17	28 (26)
Control only	15	6	21 (21)
Neither	14	14	28 (44)
Odds ratio (CI)	0.7(0.3-1.7)	2.8(1.1-8.8)	1.3 (0.7-2.5)

* Based on best information combining patient's recall and GP records.
** Pre 1948/childhood fractures which are not recorded in GP notes account for the differences with true rate. OR for only GP recorded fractures = 1.2 (0.7-2.3)

Table 5-3c: Matched case-control analysis of fractures within five years of symptom onset. Numbers in parenthesis are based on GP records only

	Male	Female	Total
Case and control	0	0	0 (0)
Case only	7	8	15 (14*)
Control only	0	1	1 (1)
Neither	54	33	87 (88)
Odds ratio	∞ (1.87 - ∞)	8 (1.1-348)	15 (2.3-654)

*Fracture occurred overseas
Odds ratio based on GP records only = 14 (2.1-606)

Table 5-3d: Details of patients with MND who sustained a fracture within five years of symptom onset

Age of onset	Fracture mechanism	Fracture site	Interval until MND	Site of MND onset
69	Fell (trip)	Bilateral Colles	1 month	Dysarthria
35	Fell (drunk)	Right Colles	1 month	Right hand
73	Assaulted	Multiple ribs, Right metacarpal	1 month	Dysphagia
79	Fell (?trip)	Nasal bones	1 month	Dysarthria
67	Fell (?trip)	Right first metacarpal (compound)	3 months	Right footdrop
58	Fell from roof	Right lateral malleolus	6 months	Left hand
73	Fell (trip)	Left distal radius	10 months	Left hand
48	Road traffic accident	Left Tibia and fibula	11 months	Right footdrop
74	Uncertain	12th thoracic vertebra	25 months	Right hand
55	Fell (trip)	Left Colles	30 months	Dysarthria
27	Assaulted	Mandible	34 months	Right footdrop
72	Fell (trip)	Left Colles	39 months	Left leg
60	Fell from roof	3 ribs	48 months	Right hand
70	Road traffic accident	Left tibia and fibula*	50 months	Right footdrop
56	Fell from roof	Right tibia	54 months	Right leg

* All fractures above recorded in GP records, except this (occurred overseas)

Table 5-4: Distribution of injuries requiring medical attention, by case, control and number of injuries. Combines information based on patient's recall and GP records.

	Number of injuries								
	0	1	2	3	4	5	7	8	Total
Case	27	29	19	9	10	7	2	0	103
Control	33	28	21	13	6	1	1	0	103

Chi square value 1.4, DF= 7 (ns)

Table 5-5: Distribution of operations requiring general anaesthetic, by case, control and number of operations. Combines information based on patient's recall and GP records

	Number of operations							
	0	1	2	3	4	5	8	Total
Case	15	36	20	19	5	6	0	103
Control	13	35	22	19	9	2	2	103

Chi square value 5.7, DF= 7 (ns)

Table 5-6: Electric shocks (patient recall)

	Yes	No
Case	8	95
Control	4	99

Chi square 1.4, DF=1 (ns)

Table 5-7: Blood transfusion (patient recall)

Yes	No	Total
11	92	103
15	88	103

Chi square 0.7, DF= 1 (ns)

Table 5-8: Matched case-control analysis of occupation (manual versus non manual)

	Male	Female	Total
Case and control	37	5	42
Case only	15	8	23
Control only	5	4	9
Neither	4	25	29
Odds ratio (95% CI)	3.0 (1.0-10.5)	2.0 (0.5-9.0)	2.6 (1.1-6.3)

Table 5-9a: Matched case-control analysis of environmental/occupational toxins

	Minerals	Lead	Solvents/ Chemicals	Pesticides	Any of these
Case and control	3	3	6	10	28
Case only	8	16	23	18	32
Control only	2	3	6	13	10
Neither	90	81	68	62	33
Odds ratio (95% CI)	4.0 (0.8-39)	5.3 (1.5-28)	3.8 (1.5-11)	1.4 (0.6-3.1)	3.2 (1.5-7.3)

Table 5-9b: Details of 19 patients with MND in whom lead exposure was reported over a period of more than 12 months.

Age	Sex	Details of lead exposure
65	Male	Plumber and labourer. Jointing and welding of lead pipes.
47	Male	Labourer and driver. Handling lead in roof work.
47	Male	Drain layer and labourer. Removing old lead pipes and fitting new.
55	Male	Electrician. Stripping and handling cables often with lead.
59	Male	Driver. Unloading and loading of lead cased containers and barrels.
50	Male	Plumber. Removing old lead pipes and fitting new.
57	Male	Roofer. Cutting and fitting of roof flashings.
76	Male	Painter. Stripping and application of lead paints over several years.
40	Male	Shipwright. Fitting of lead sheeting in boats.
59	Male	Maintenance engineer in a gas works. Jointing, welding lead pipes.
62	Male	Electrician. Handling of lead cables.
55	Male	Labourer. Removing of old lead pipes for new.
65	Male	Scrap metal dealer. Handling of scrap lead.
67	Male	Roofer. Cutting and fitting of lead flashings.
60	Male	Mechanic. Soldering and handling lead materials, car fume exposure.
73	Female	Foundry and metal worker. Working with lead materials.
56	Male	Glazier. Lead strips used over many years to support glass during fitting.
75	Male	Typesetter. Lead materials.
63	Male	Wire rope maker. Used molten lead in galvanising shop.

Notes: Reported exposure in six controls of a similar nature to the above (see table 5-9a).

Table 5-10: Matched case-control analysis of domestic amenities in the first 10 years of life

	No garden	No bath	No hot water	No flush WC
Case and control	24	49	45	11
Case only	25	25	27	17
Control only	28	19	17	19
Neither	26	10	14	56
Odds ratio (95% CI)	0.9 (0.5-1.6)	1.3 (0.7-2.5)	1.6 (0.8-3.1)	0.9 (0.4-1.8)

Fig 5-1: Age standardised mortality ratios in Scotland by deprivation category (1980-85) (1=affluent, 7=deprived)

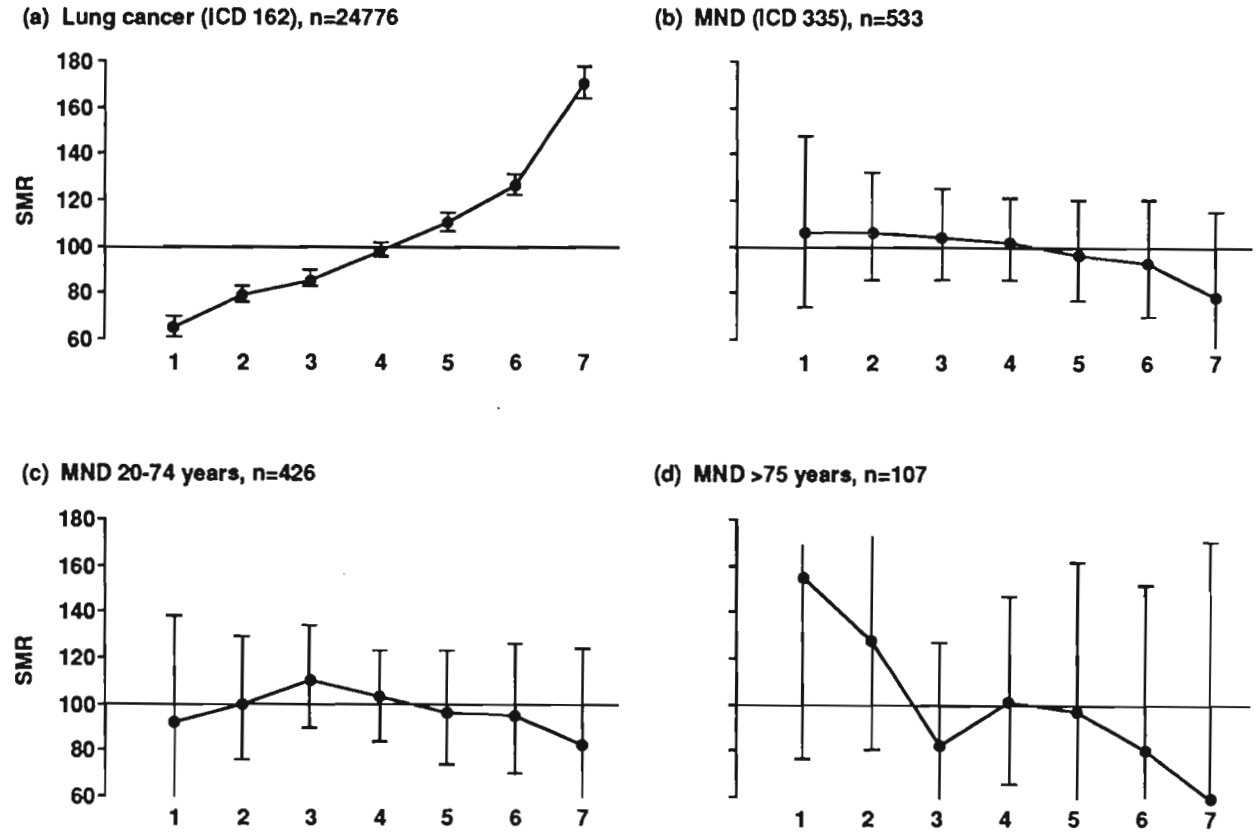


Fig 5-2: Distribution of fracture frequency by interval before onset of symptoms due to motor neuron disease

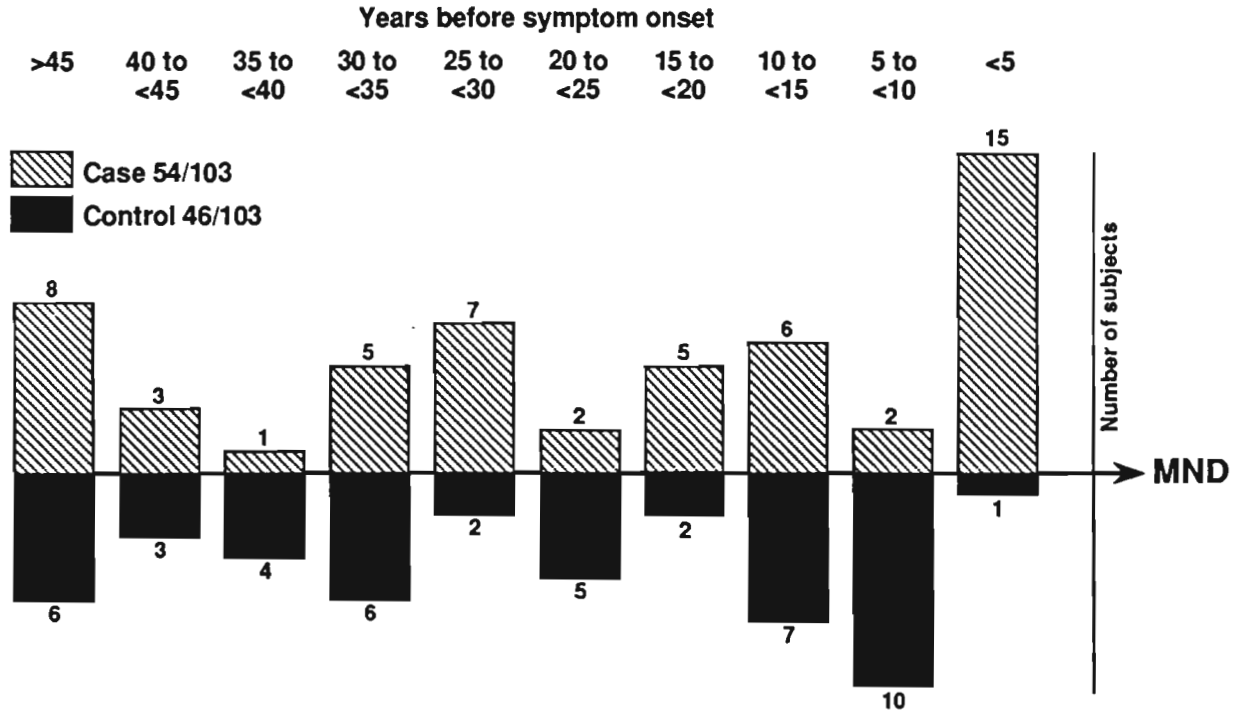
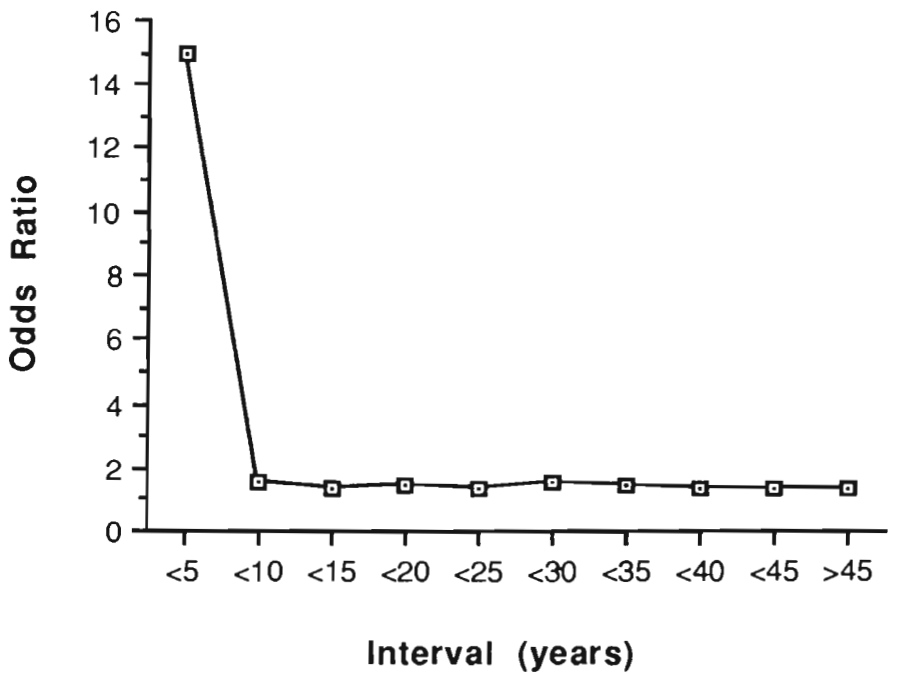


Fig 5-3: Odds ratio for a fracture occurring at various intervals before the onset of MND symptoms



CHAPTER 6

THE PROGNOSIS OF MOTOR NEURON DISEASE

INTRODUCTION

" Two years before [in 1963] *I had been diagnosed as suffering from ALS commonly known as Lou Gehrig's disease or motor neurone disease and given to understand that I only had one or two more years to live."*

Stephen W.Hawking, Lucasian professor of Mathematics, Cambridge University, written in 1988[52].

There have been many retrospective studies of prognosis in MND, usually in conjunction with incidence studies, and some are population based. Two prospective studies are based on patients referred to tertiary care facilities (table 6-1). Despite agreement on a generally poor prognosis for this disease the conclusions of individual studies differ in a number of important respects. Survival predictions can be hazardous, as illustrated by the opening quote and several questions remain unresolved or in doubt concerning the prognosis of MND:

(i) Can reliable predictions of outcome be made based on clinical features at presentation or during the course of the illness? Reference is still made to the "variable outcome" of this disease and while it is generally agreed that PMA has a more benign course[335] and that the presence of PBP is a poor prognostic sign[101,256,336,337], some studies have failed to demonstrate any clear prognostic variables and estimates of median survival, even for patients with a combination of upper and lower motor neuron signs, vary from 48 months[338] to 12 months[256] from diagnosis (table 6-1).

(ii) Is old age a poor prognostic variable and is age an independent risk factor, or does the increased frequency of PBP in older patients account for the suggested poorer prognosis with

increasing age[339]? Some studies of selected patients[255,340] contradict the more widely held view that increasing age is a poor prognostic factor.

(iii) Is their evidence for a subgroup of patients with MND who have a prolonged survival? Estimates of 5 year survival vary from 4-40%[93,341] and observations of "resistance" to progression for some patients have been made[48].

Unlike acute medical illness such as stroke, there are difficulties in obtaining precise estimates of a time of onset for a disease of insidious progression, while prognosis based on date of diagnosis may vary with local practice. Predicting outcome related to the clinical pattern of MND is also hindered by a lack of internationally accepted diagnostic criteria, confusion in terminology, or by too small numbers in some studies to show any difference, should this exist[88]. These factors can be improved by a prospective, population based study of well defined patients and allow reliable predictions based on presenting features and progress. There are no such studies to date which fulfil all these requirements[342] (chapter 2).

METHODS

Patients

This analysis of survival relates to all 229 patients included in chapter 3. Follow up was complete for a mean of 2 years (range 1-3 years). 57 patients (25%) had been seen in person, as part of the case control study, and 84% by a SMNDR collaborator. At the time of data censoring (January 1st 1992) there had been 144 deaths (72 males and 72 females).

Statistical methods

Data were collected and summarised using Dbase IV, a database management system for microcomputers (Borland Inc.) for subsequent analysis with The Statistical and Epidemiological Research Corporation (EGRET) package for survival analysis using the Kaplan Meier technique[343] and Cox's proportional hazards model. Calculations were based on day zero of follow up as either (a) the date of onset or (b) the date when the diagnosis had first been suggested as likely or probable. Patient groups were analysed overall and according to age, sex, and clinical subtypes as defined in Chapter 3.

Except for time zero, the numbers at risk, included below the survival curves (figures), for any given time of follow (eg 1 year, 1.5 years etc), are an approximate for that interval. This is because the Kaplan-Meir statistic generates survival intervals in fractions of years after each "failed" individual. Hence the quoted figures at risk represent the number at the nearest time interval generated in the calculation *before* that which I have plotted on the x axis and, at longer periods of follow up, are over-estimates. For example, for survival by sex, the number of males at risk 4.8 years from symptom onset was 11 and at 5.2 years was 8. The number plotted corresponding to 5 years of follow up is 11.

RESULTS

Follow up was complete and survival curves are included at the end of this chapter. The numbers at risk for any given time of follow up are included below the curves to further allow comparisons of numbers on which individual curves are based (see above). The numbers in each group at time zero are also included in table 3-8.

The overall 50% survival from onset was 2.5 years (95% CI, 2.2-3.0 years) and from diagnosis 1.2 years (95% CI, 1.0-1.4). There are no differences in the overall conclusions of survival curve comparisons according to clinical and demographic variables whether curves are calculated from the time of onset or from the time of diagnosis.

There were significant differences in survival with poor prognostic factors for: age (>65 years, $p<0.001$); gender (female sex, $p<0.01$) and clinical pattern (PBP, $p<0.001$). PBP remained a poor prognostic sign, whether considered as the presenting feature (initial diagnosis PBP; PBP/ALS), or as a component of the illness at any time (final diagnosis PBP; PBP/ALS; ALS/PBP). This conclusion is not altered by comparing patients with PBP with those with purely spinal disease (ALS) ie removing patients with PMA, who have an overall good prognosis ($p<.005$). Cox's proportional hazards model showed that the difference in survival between the sexes was accounted for by the greater proportion of females with PBP, although age remained a significant variable ($p<0.05$).

Five year survival estimates can only be based on time from symptom onset at this stage of follow up. Overall 5 year survi-

val from onset was 27.7% but the small numbers at this time of follow up result in a large degree of uncertainty with 95% CI for this estimate = 19.9%-36.0%. Five year survival was considerably less for patients with PBP as the presenting feature (PBP; PBP/ALS) = 3.5% (95% CI, 0.0-15%) or for patients with PBP as a component of the initial diagnosis (PBP; PBP/ALS; ALS/PBP) = 10.6% (95% CI, 3.8%-21.4%).

There were 15 patients on the SMNDR with survival for more than five years from symptom onset. Five had PMA subtype, 10 had ALS as the initial diagnosis and in only two did PBP develop, both in the few months before their death shortly after the censoring date.

DISCUSSION

The interpretation of the figures relating to the clinical subtypes is highly dependent on the way physical signs are used in the classification of patients. In this study, preserved reflexes in the presence of a corresponding wasted myotome were used as evidence of UMN involvement and therefore such patients were classified as having ALS included in their subtype (ALS; ALS/PBP; PBP/ALS). In any event, there may be little pathological basis for dividing sporadic MND into subgroups given the poor correlation between clinical pattern and pathological distribution of the lesions[47,48]. However, appropriate classification is important to standardise patients for prognostic studies and planning treatment trials[344].

Familial cases (n=11) were not excluded from the survival analysis as previous studies have suggested, and this sample

confirmed, that their survival does not differ significantly from sporadic adult onset MND and demographic and clinical features are stronger predictors of outcome than whether the disease appears to be inherited[345]. It is possible that patients who are older at diagnosis were identified at a later stage of their disease and hence have an apparently shortened survival but the difference in survival according to age is also observed based on time from onset so this observation is likely to be real.

Studies which use retrospective approaches, or are based on referral centres, are more likely to be biased towards younger patients and produce much longer estimates of survival[338,341]. A study design ensuring complete case ascertainment is of major importance when estimating prognosis in MND.

My findings are similar to another population based, but retrospective study in Denmark[94,256]. Christensen et al described 186 patients identified from hospital discharges, including geriatric units. 11% were from outside neurology departments and the mean age of this cohort (66.9 years for men and 62.4 years for women) makes significant ascertainment bias unlikely. The median survival of this group was 12 months (95% CI 10-14 months) from diagnosis (23 months from onset), the 3 year survival 12%, 5 year survival 4%. Old age and a bulbar onset were poor prognostic factors.

With respect to the questions posed in the introduction, these results suggest that: (i) In well defined cohorts survival can be predicted with a high degree of confidence, that (ii) the higher mortality rate in females is largely related to the increased frequency of PBP, but old age remains a significant independent poor prognostic variable. (iii) As far as longevity

with MND is concerned, all survivors beyond five years from symptom onset presented with PMA or ALS, without PBP, and in only 2 did PBP develop, late in the course of the illness.

Reports of patient "resistance" to progression in ALS[48] with 5 year survival of 20% are likely to be because the disease remains confined to spinal segments (numerically a much smaller group) or to referral bias of atypical cases. Three of the four patients surviving for more than 5 years in the study by Christensen[256] did not have bulbar symptoms until the fifth year after diagnosis.

Clearly the clinical pattern of disease is of major importance in predicting outcome from MND and needs to be considered when making decisions about patient management, advising those affected with this disease and planning treatment trials[344].

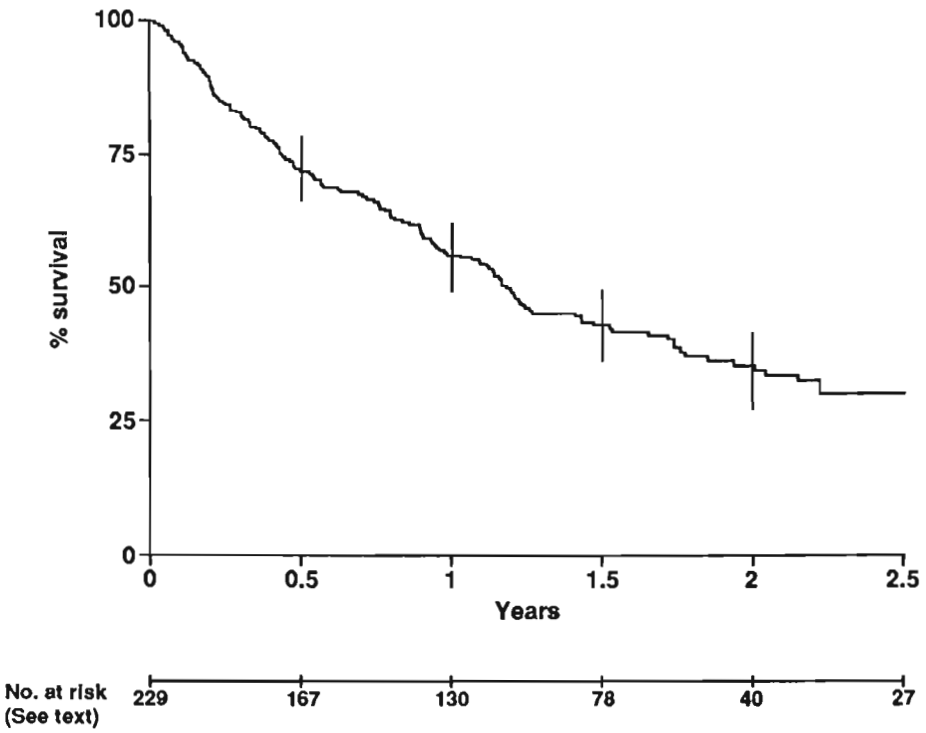
Table 6-1: Studies of prognosis in motor neuron disease. All published English language studies (1965-91), listed in order of year of publication.

Case numbers	Population based?¶	Prospective?	Mean age at onset (years)	Actuarial analysis?	Median survival from onset (months)	5 year survival (%) (#)	Comments, Poor prognostic features (pp=)	
50	No	No	2 groups selected by duration of MND	No	13 (group 1) 38 (group 2)		Short report ?definitions selected from a larger group	[346]
140	No	No	49	No	30 (bulbar) 55 (spinal)		Young cohort,small subgroups analysed,pp=bulbar onset	[337]
13	No	No	70 (selected)	No	>80		Short report,old age does not mean poor prognosis?	[340]
92	No	No	38	No	>72 in 54% >120 in 29%		Hospitalised patients, benign prognosis in Africans?	[347]
100	No	Yes	Not stated	Yes	40	25%	Selected patients. (10% at 10 years)	[48]
5	No	No	49	No	96		Restricted to 1 family Variable survival	[348]
118	Yes(3)	No	57	Yes	34	20%	pp=bulbar onset ?due to age	[339]
668	No	No	56	Yes	36 (from diagnosis)	39%	Highly selected cohort (ALS foundation)	[341]
210	No	No	54	Yes	30	20%	Young cohort, pp=bulbar onset	[336]
36	Yes(1)	No	60	Yes	27	8%	pp=PBP (explained by age)	[95]
128	Yes(1)	No	59	Yes	30 (PBP) 36 (All)	28%	Almost equal male/female ratio	[92]
89	Yes(1)	No	66	Yes	25	4%	Older patients	[93]

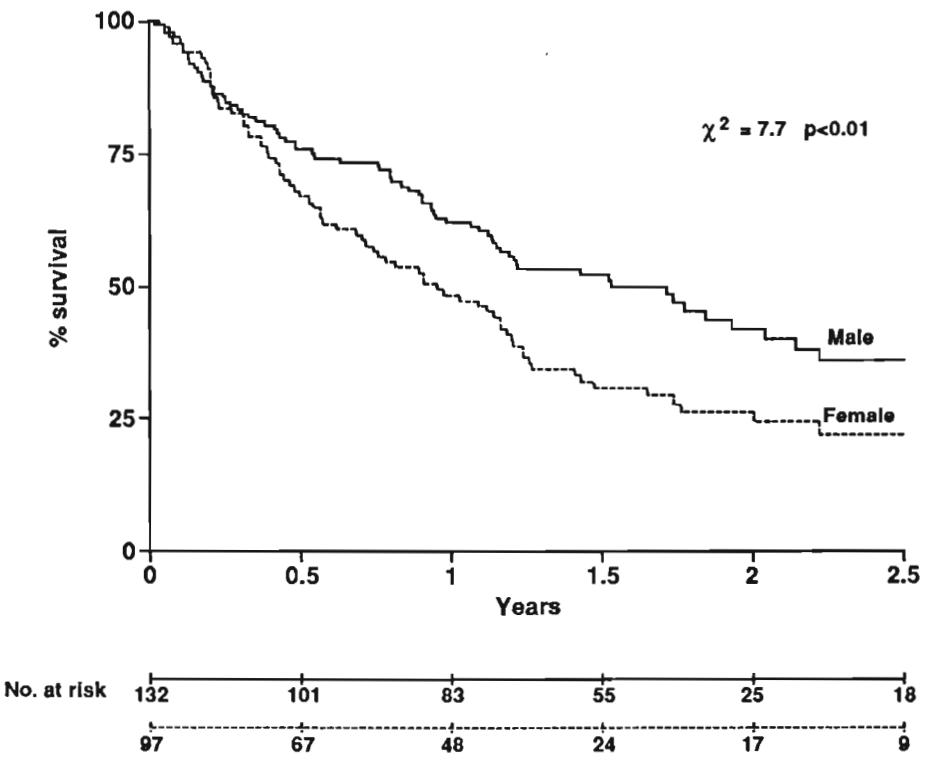
318	Yes(1)	No	56	Yes	36	29%	Based on neurological disease register,16% at 10 years	[349]
155	No	No	48	Yes	>72 (from diagnosis)	56%	Restricted to adults with PMA	[335]
44	Yes(1)	No	67	Yes	24	15%	Small numbers but complete	[88]
27	No	No	50	Yes	24	8%	Familial MND only	[258]
397	No	No	57	Yes	48	35%	Young patients	[338]
72	Yes(2)	No	59	Yes	24 (PBP) 48 (ALS) 72 (PMA)	<10%	pp=PBP. Incorporates a case-control study	[101]
57	Yes(3)	No	54	Yes	33	30%	Likely to be incomplete case ascertainment	[113]
194	No	Yes	59	Yes	36	32%	Uses disability score	[350]
837	No (despite paper's title)	No	57(m), 60(f)[ALS] 49(m)54(f) ["benign ALS"]	Yes	38	28%	Population defined by 1hour's travel from the clinic! Plateau in survival of younger patients	[119]
51	Yes(3)	No	61	Yes	33	24%	No significant differences between sexes or subtypes	[351]
186	Yes(1)	No	64	Yes	12	4%	Good study pp=old age and bulbar onset	[256]
149	No	No	46 (only) familial)	Yes	24	23%	Analysis of published reports of familial ALS (strictly defined)	[345]
84	No	No	61	Yes	28	25%	pp=PBP,not due to age or sex	[117]

Notes to table 1: In many studies, ALS (with and without bulbar features) is used synonymously with MND. m=male, f=female.
Total group; according to actuarial analysis if used, if not then average survival. ϕ Case ascertainment likely to be
(1) = Complete or nearly complete; (2)=Probably incomplete; (3)= Based on tertiary referral sources (See Chapter 2).

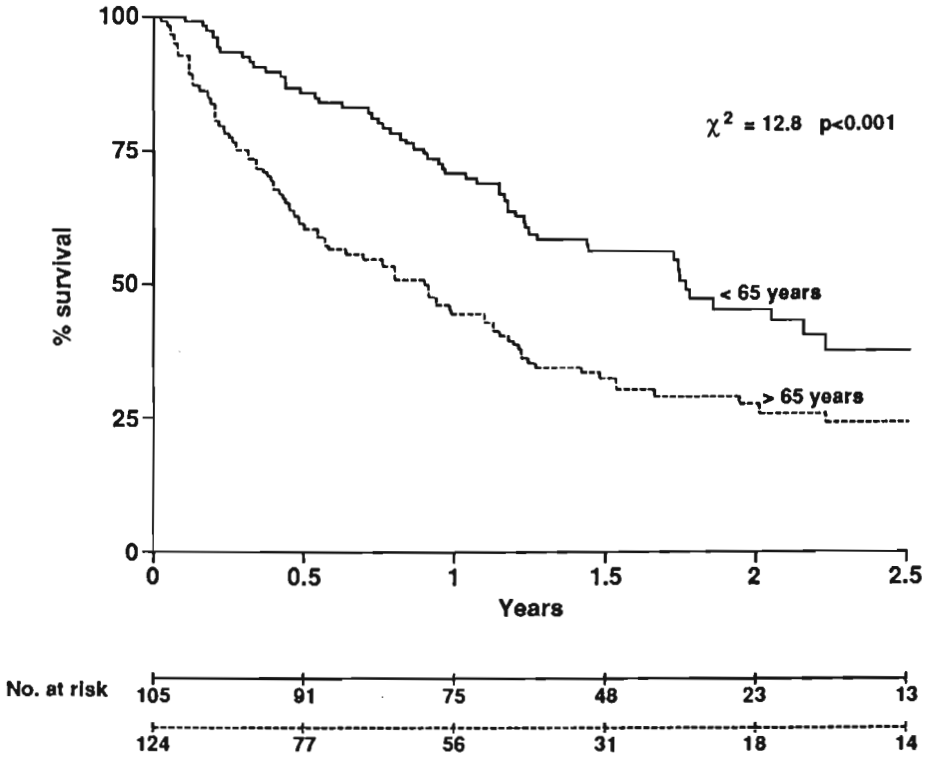
The Scottish Motor Neuron Disease Register 1989-90
Survival from diagnosis, all patients



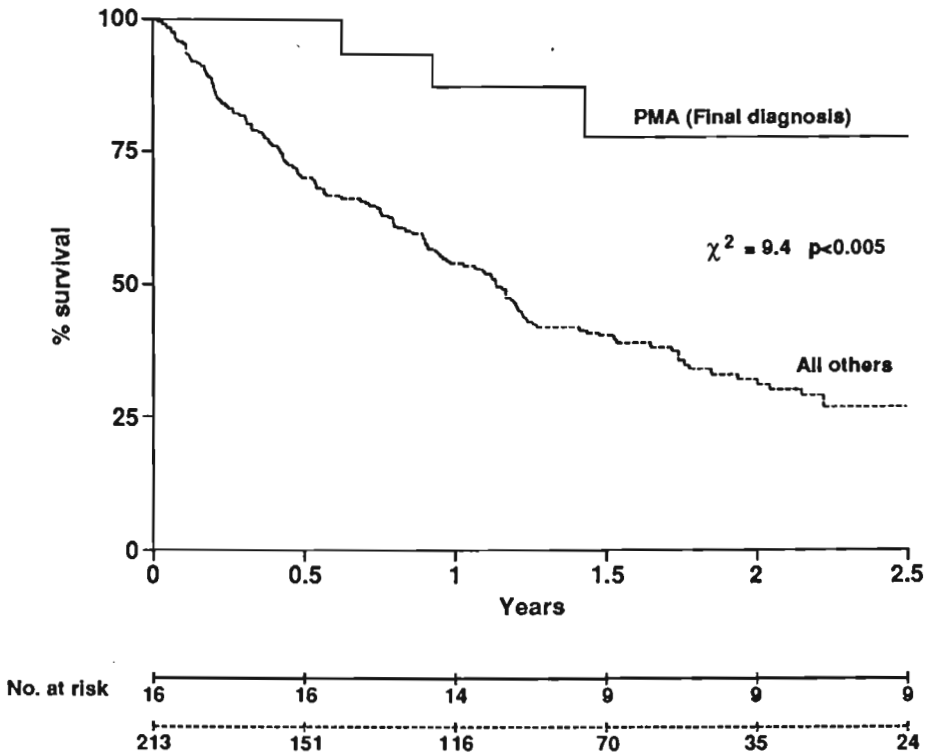
Survival from diagnosis by sex



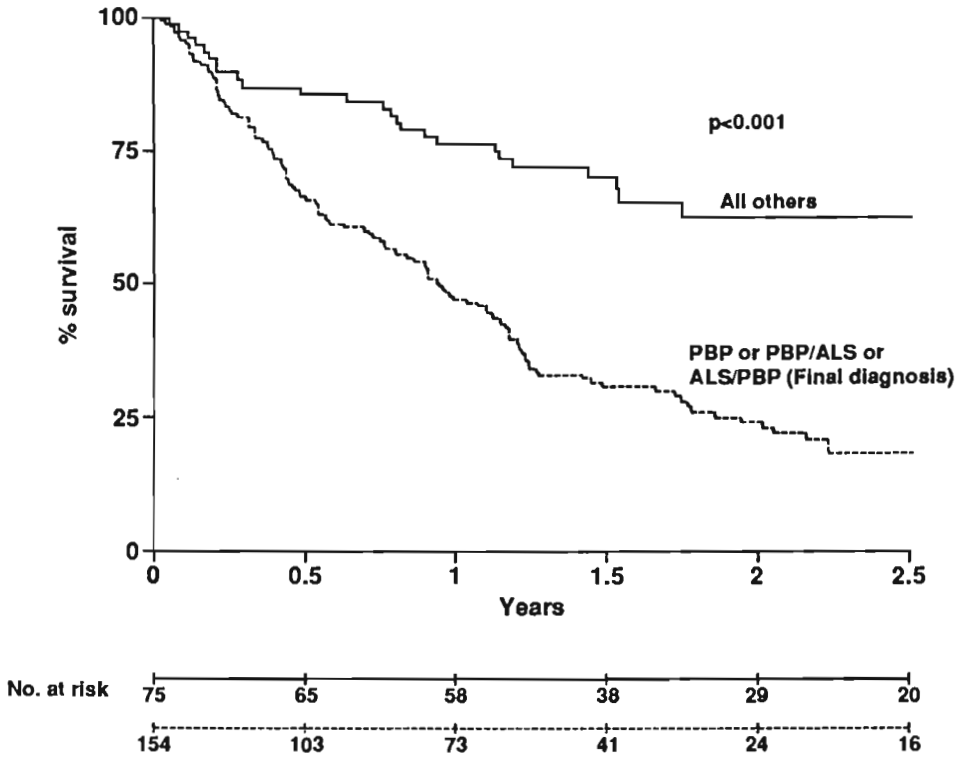
The Scottish Motor Neuron Disease Register 1989-90
Survival from diagnosis by age

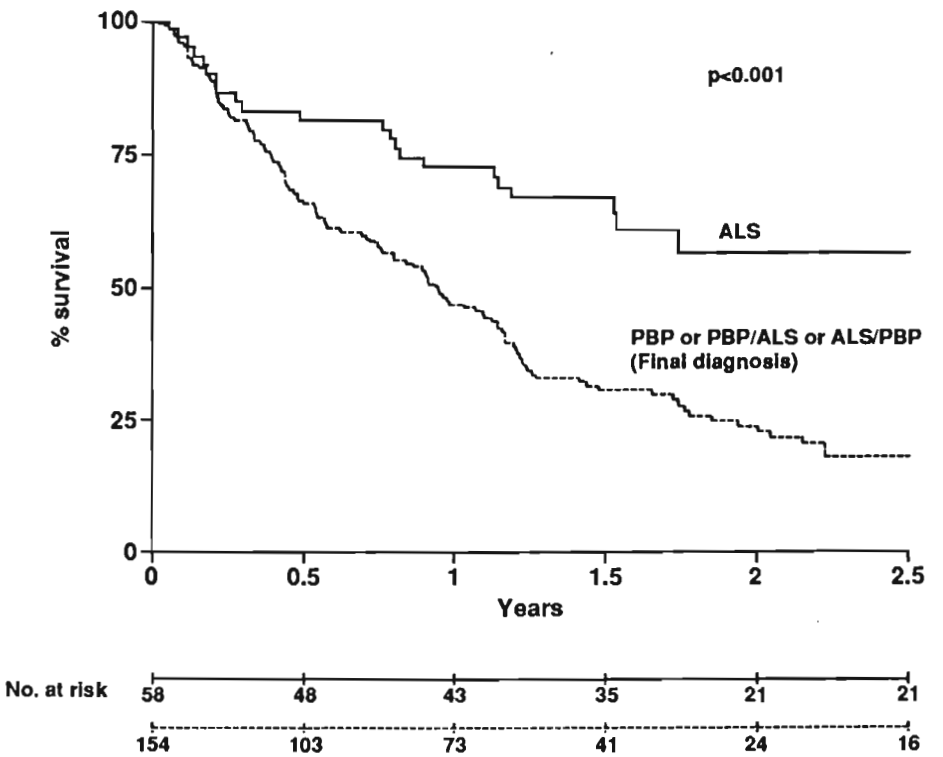


Survival from diagnosis, progressive muscular atrophy

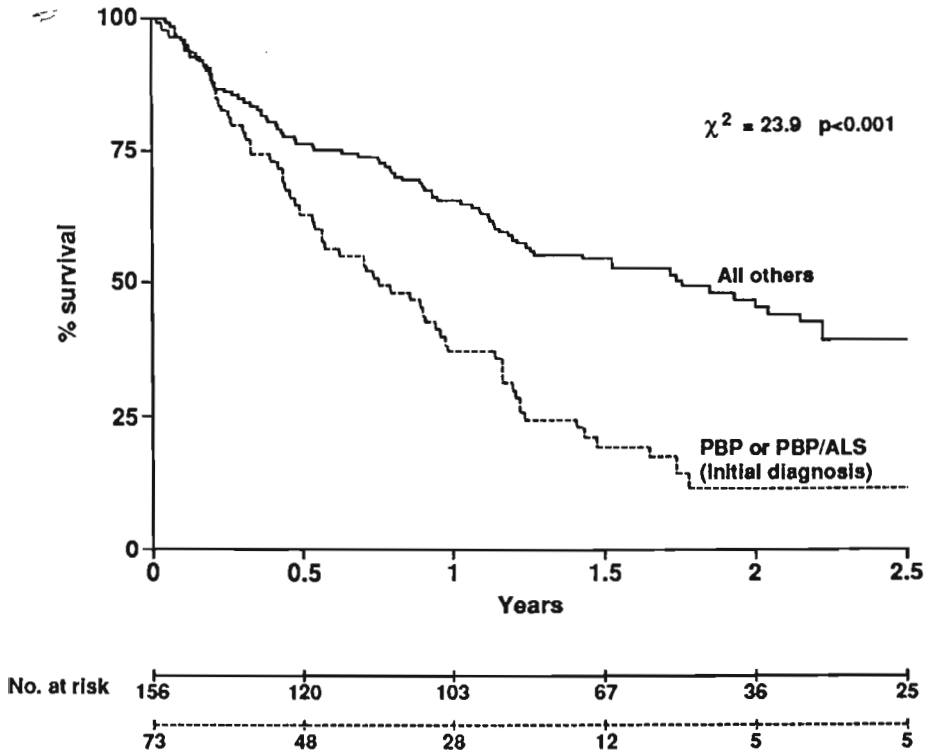


The Scottish Motor Neuron Disease Register 1989-90
Survival from diagnosis, bulbar palsy at any stage

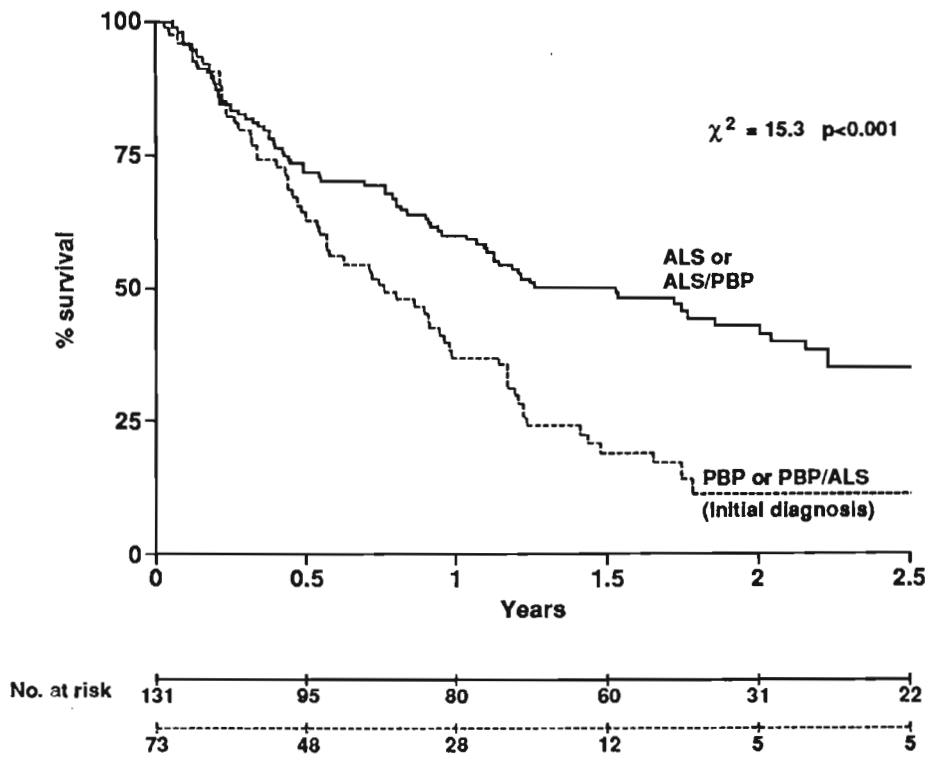




The Scottish Motor Neuron Disease Register 1989-90
Survival from diagnosis, bulbar palsy at presentation

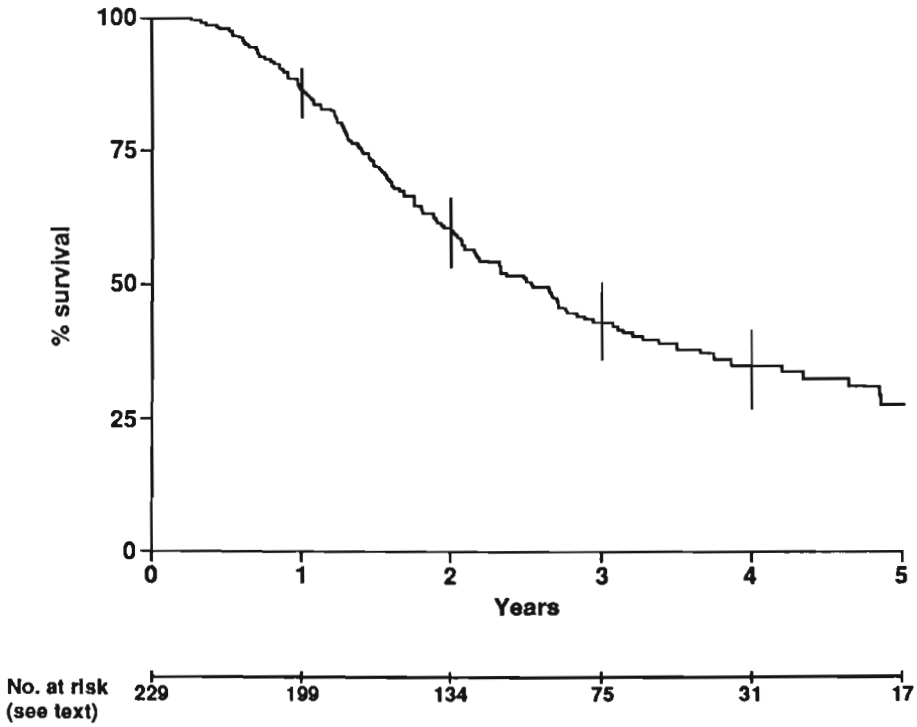


No. at risk						
	156	120	103	67	36	25
	73	48	28	12	5	5

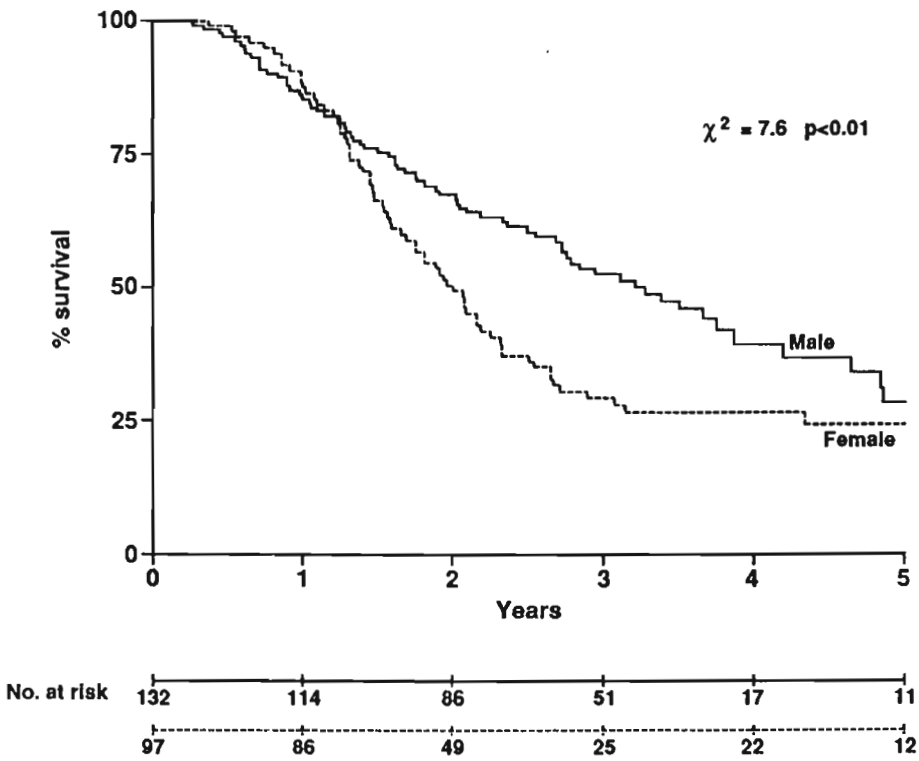


No. at risk						
	131	95	80	60	31	22
	73	48	28	12	5	5

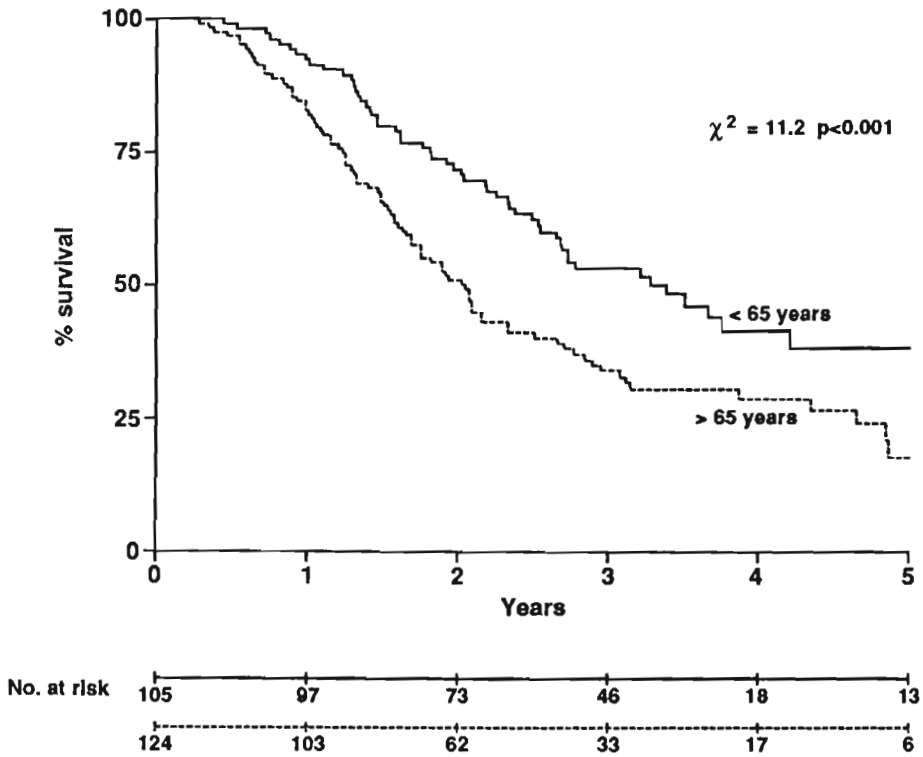
The Scottish Motor Neuron Disease Register 1989-90
Survival from symptom onset, all patients



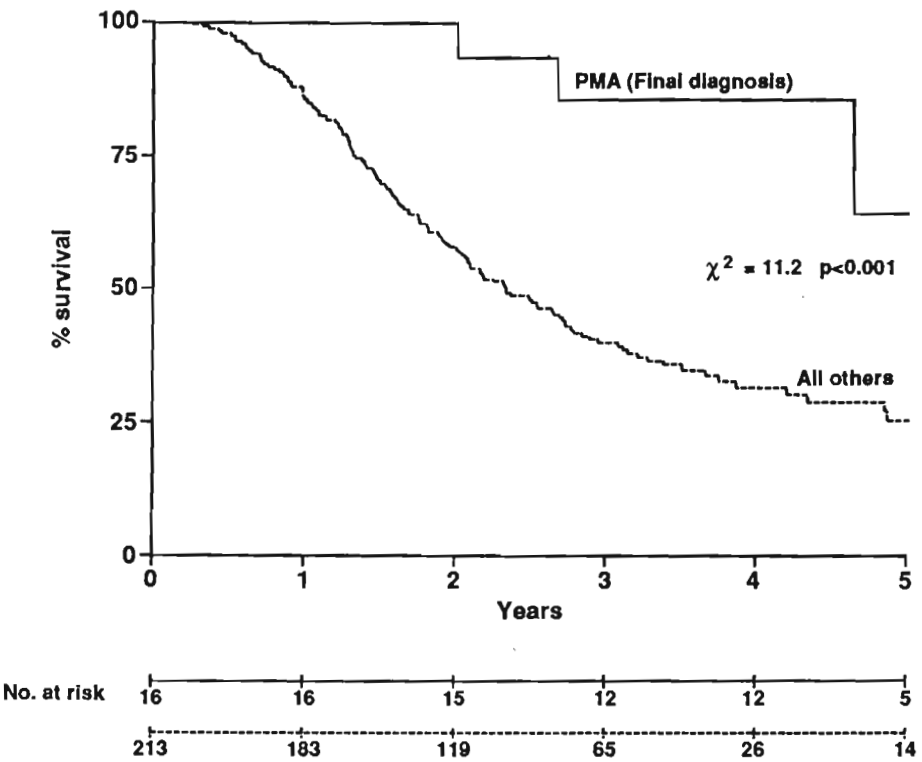
Survival from symptom onset by sex



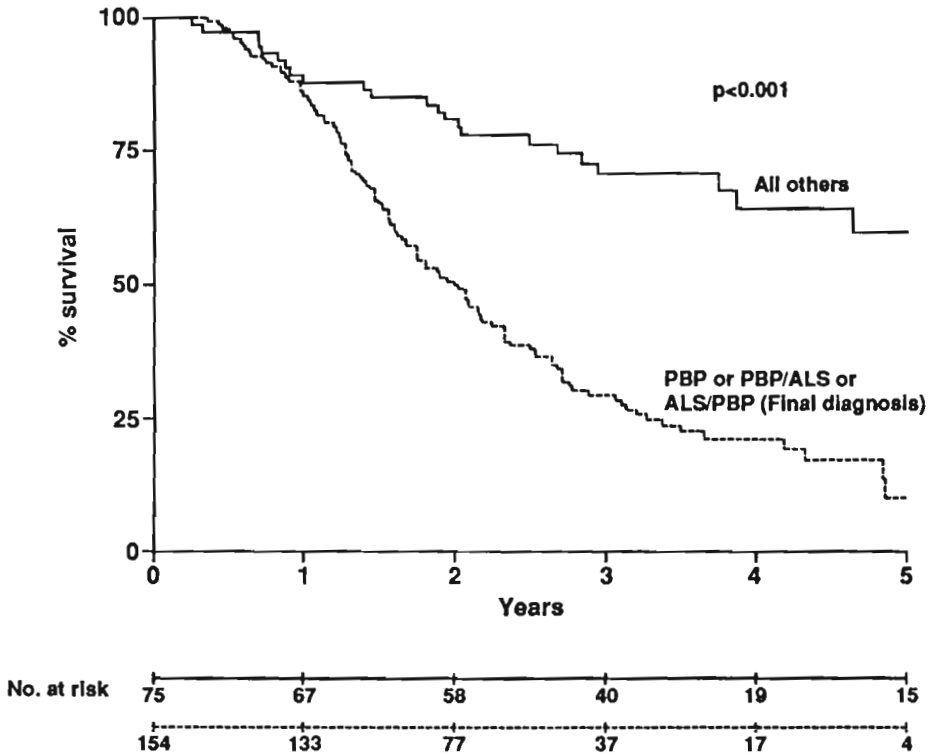
The Scottish Motor Neuron Disease Register 1989-90
Survival from symptom onset by age

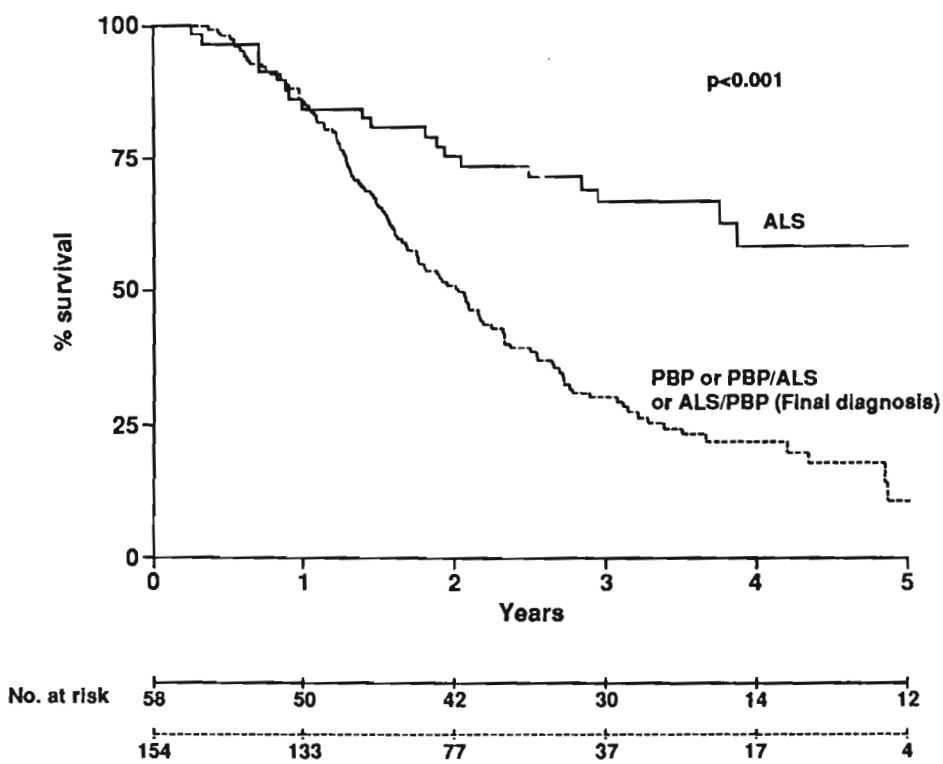


Survival from symptom onset, progressive muscular atrophy

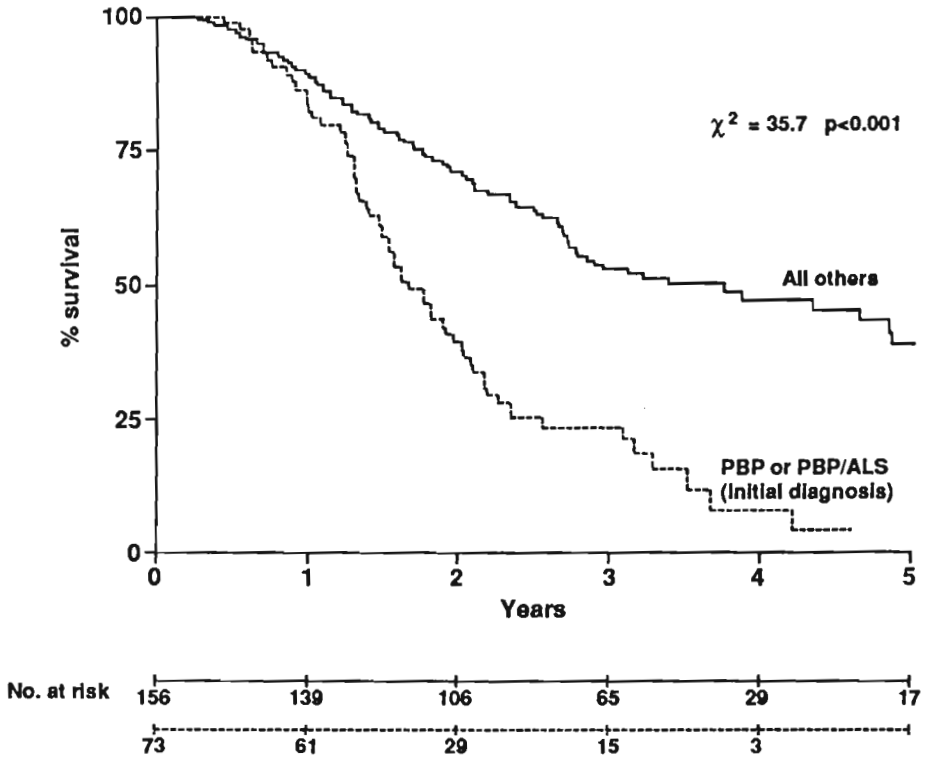


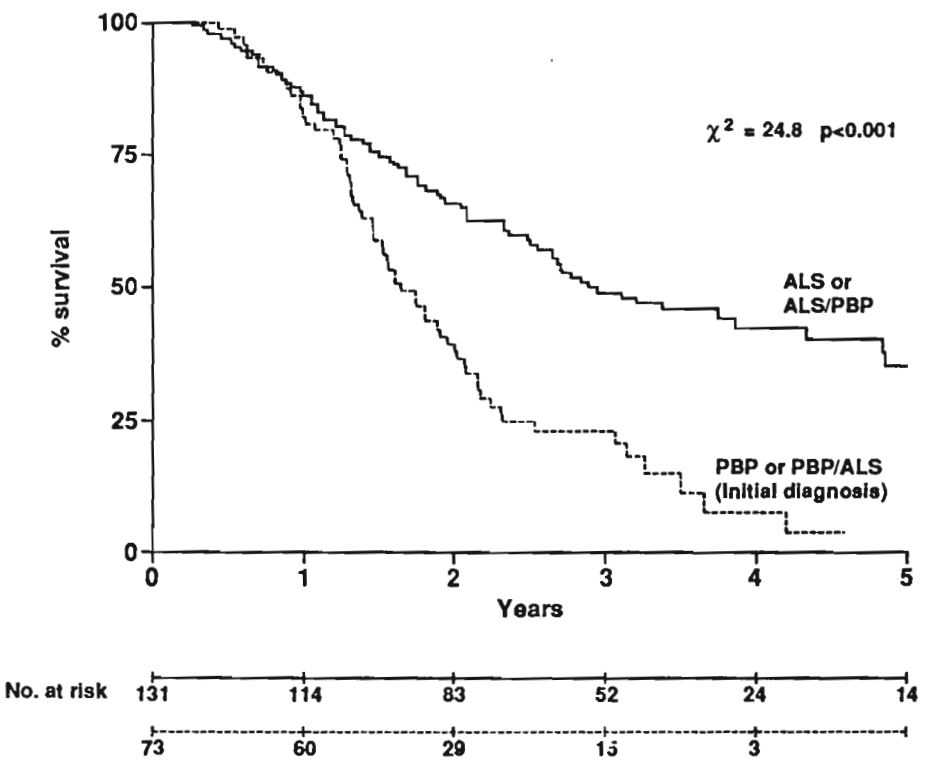
The Scottish Motor Neuron Disease Register 1989-90
Survival from symptom onset, bulbar palsy at any stage





The Scottish Motor Neuron Disease Register 1989-90
Survival from symptom onset, bulbar palsy at presentation





CHAPTER 7

CONCLUSIONS. MAKING USE OF THE WORK INCLUDED IN THIS THESIS

" The best test of a physician's suitability for the practice of neurology is not his ability to memorise improbable syndromes but whether he can continue to support a case of motor neurone disease and keep the patient, his relatives and himself in a reasonably cheerful frame of mind."

Professor W.B.Mathews[352]

" I realised that a man's intelligence is not the sum of what he knows but the soundness of his judgement of people and his power to understand and to help them."

Yevgeny Yevtushenko[353]

I have highlighted the need for standardised diagnostic criteria for MND. Although there is no real difficulty in recognising the disease at an advanced stage, there may be considerable diagnostic uncertainty at presentation to medical attention and there is confusion over the terminology used to describe MND. Accurate diagnosis is essential if patients are to be advised appropriately, epidemiological studies are to be compared usefully and well defined patients are to be recruited in treatment trials. This study outlines simple but comprehensive diagnostic criteria (chapter 2) which take account of variation in clinical pattern at presentation and it is hoped that these criteria, which do have prognostic significance (chapter 6), can be applied in future studies of MND.

This thesis has examined the traditional concept of a uniform worldwide distribution of MND (chapter 2), highlighted the difficulties in comparing populations and thus might provide an impetus to further studies of MND distribution, for example in immigrant populations from developed countries or a search for clusters based on large numbers analysed using small geographical areas.

Importantly, the SMNDR has developed a novel approach to studies in MND by, for the first time in this disease, prospectively recruiting population based patients and enabling studies of incident patients during life (chapter 3). There were practical difficulties experienced, particularly in timing appropriately the involvement of patients in studies, other than simple registration, such as the case-control study, at a stage when the diagnosis was secure but that distress was not caused by approaching moribund patients. The often aggressively deteriorating course of MND also means that it is difficult to include some patients from distant regions in studies during life. However, with an informed collaborative group, it was possible to conduct this study of MND, in a relatively short space of time, on a scale which would be difficult for individual or small groups of neurologists. This important property of the SMNDR may be useful when considering treatment trials.

The measurement of incidence afforded by this study is necessary in placing in perspective the importance of a particular disease for delivery of health care and to enable charities, such as the Scottish Motor Neuron Disease Association, to promote its interests and those of its members.

Traditionally, studies of MND have relied on statistics which are not "purpose built" for this disease ie retrospectively examined morbidity and mortality data. This information is prone to error due to misdiagnosis, false positive coding and changes brought about by the periodic alterations to the International Classification of Diseases used for coding. I have been able to analyse in detail the utility of these data sources so that better use and interpretation of studies based on this informa-

tion is possible (chapter 4). However, such results must be interpreted in the light of local practices which might differ from systems employed in Scotland.

It comes as no surprise that in many patients there is no apparent cause for the disease. The case-control study (chapter 5) identified a number of factors of potential importance in the pathogenesis of MND, which clearly cannot explain the totality of MND, but which make a contribution to the weight of evidence accumulating from other epidemiological studies and may shape the approach for basic neuroscience research.

Patients expect an honest but sensitive explanation of the nature of their illness and what to expect from it[354]. I was able to provide useful prognostic data (chapter 6) based on the diagnostic classification system and so the contents of this thesis have direct clinical application for the practising neurologist who is planning patient management. I have also been able to review part of the differential diagnosis of MND as it arises in routine clinical practice (table 2-1 and appendix A).

Not included in this thesis, but mentioned in the publications list, were two laboratory based projects which were instigated or supported by the SMNDR and my work. Firstly, a study of antiganglioside antibodies in conjunction with workers in the neuroimmunological laboratory at the Institute of Neurological Sciences, Glasgow, examined the potential role of anti-GM1 antibodies and paraproteins in the pathogenesis of MND. Secondly, I collected blood from some pedigrees (appendix C) to assist in the search for a genetic marker in familial MND.

On a personal level this study has been important, not only for learning methods in observational epidemiology but for

future clinical practice. This thesis has not discussed the human suffering to which I have been witness. Motor neuron disease is a tragic affliction which combines many of the most despairing features of illness. It can affect young adults with dependents; it is an inexorably progressive terminal disease for the majority; there is loss of independence and regression to an existence which requires help with feeding, toileting, washing, and the most simple of tasks, such as relief from an itch or an uncomfortable position. It is frightening, especially when dysphagia or respiratory failure develop and many patients become lonely, bored, frustrated, angry or depressed. Despite these obstacles, I have been struck with the remarkable emotional resilience of many sufferers in the face of such terrible circumstances.

Although it is possible to read about the feeling's of sufferers[355], who vividly portray the isolation[50,356] and nihilistic approach of many doctors[357], there can be no substitute for the experience of patient contact and the lessons inherent therein. This work has taught me much that is not contained in the preceding pages, particularly about the problems and management of neurological disability and that symptomatic treatment, often relatively simple in nature, combined with human contact and support, can go a long way to easing the burden of this incurable, but not untreatable, disease.

APPENDIX A

SUMMARY OF THE CLINICAL FEATURES OF 28 PATIENTS REGISTERED WITH THE SCOTTISH MOTOR NEURON DISEASE REGISTER BUT EXCLUDED FROM THE MAIN ANALYSES

A. PATIENTS WITH CLINICAL FEATURES OF MND BUT WHO HAVE OTHER COEXISTING NEUROLOGICAL DISEASE (n=8)

HW, female age 78, SMNDR No: 7. Referral: Collaborator

Initial diagnosis: PBP/ALS

Twelve month illness to death with mixed pseudobulbar and bulbar palsy, generalised wasting and fasciculation and pathologically brisk reflexes. There was an asymmetric intention tremor in both upper limbs. NCS/EMG: compatible with MND; CT scan normal apart from prominence of the ventricals and calcification of the basal ganglia. Progressive deterioration in both motor system disease and her tremor. No autopsy.

Final diagnosis: MND with cerebellar signs. Possible multi system degeneration.

HH, male age 83, SMNDR No: 17. Referral: Collaborator

Initial diagnosis: ALS/PBP

Sustained a mild right hemisphere stroke which recovered and had a long-standing weakness of the left arm which appeared non-progressive. Then a 5 year history of difficulty walking and swallowing with nasal regurgitation of fluids. Past history of carcinoma of the colon. Examination showed dysarthria and bovine cough, deafness, but no fasciculation of the tongue. He had a dropped left shoulder with marked wasting of scapular and pectoral muscles on that side from C5 - T1. Fasciculation in deltoid and small hand muscles, normal tone throughout and normal power in the lower limbs. Absent biceps and supinator reflex, brisk triceps and preserved lower limb reflexes, absent vibration sensation at the ankle, sensation otherwise normal. NCS/EMG:

normal nerve conduction studies but motor unit potential changes in the left biceps, brachioradialis and right first dorsal interosseous (FDI). Since then a very gradual deterioration in bulbar symptoms and in limb weakness. Follow-up continues.

Final diagnosis: Uncertain, excluded because of long standing neurological signs making diagnosis uncertain.

IA, female age 56, SMNDR No: 51. Referral: Collaborator

Initial diagnosis: PBP/ALS

27 months illness to death. Presented with progressive dysphagia and dysarthria due to a mixed pseudobulbar and bulbar palsy with normal limbs apart from brisk reflexes. A CT scan, EMG and CSF were normal at this stage but CK was elevated at 307. 26 months after the onset she was anarthric and disinterested, withdrawn, inappropriately euphoric and thought to be demented, Creutzfeldt-Jakob disease was considered. She continued to deteriorate, lower motor neuron signs appeared in the upper limbs and she became breathless.

At autopsy the cerebral hemisphere showed mild to moderate global cortical atrophy with accompanying ventricular dilatation. There were no focal abnormalities identified. Sections of the frontal cortex showed focal degenerative changes in the outer layers of the grey matter with slight gliosis. The central white matter was also gliotic and showed perivascular accumulations of pigment laden macrophages. The white matter in the frontal lobe was pale consistent with a slight degree of cortical degeneration. These changes were not apparent in sections from the occipital and temporal lobes which were virtually normal in appearance and showed no spongy change. There were no Alzheimer

disease changes and no Lewy bodies identified. The medulla showed degenerative changes in the motor nuclei of the floor of the 4th ventricle confirmed by the presence of ubiquitinated inclusions in these neurones. The cerebellum was normal. The spinal cord showed a variety of degenerative changes in anterior horn cells, including chromatolysis. Some of these cells contained intensely ubiquitin-positive inclusions. Anterior roots were somewhat shrunken and there was pallor of myelin. Peripheral muscle and tongue showed denervation atrophy.

Final diagnosis: Motor neuron disease and dementia of frontal lobe type with non-specific frontal lobe degenerative changes.

HT female, age 81, SMNDR No: 78. Referral: Collaborator

Initial diagnosis: PBP

23 months illness to death. Presented with progressive dysarthria and dysphagia with choking and drooling. Past history of gastric carcinoma. Examination showed paralysis of tongue and palate with only occasional monosyllabic words possible. No wasting or fasciculation. Jaw jerk present and limb tendon reflexes brisk and symmetrical but with no motor or sensory deficit in the limbs. CT scan showed atrophic changes particularly in the posterior fossa; CSF protein mildly elevated at 0.88 g/l; NCS/EMG: widespread neurogenic abnormality. Progressive course, mental function difficult to assess in view of communication difficulties but not clearly demented. Developed wasting in both hands and quadriceps with weakness and pathologically brisk reflexes.

Autopsy showed mild cortical atrophy and ventricular dilatation with anterior spinal nerve root thinning. Microscopical

examination showed a generalised loss of nerve cells accompanied by reactive gliosis, numerous senile plaques and neurofibrillary tangles. There was pronounced loss of larger neurones in the region of the motor cortex but nerve cell loss in the bulbar nuclei was less pronounced. Numerous Lewy bodies were identified within pigmented neurones. A small focus of lymphocytic infiltration was noted within one of the fifth nerve roots, accompanied by focal demyelination but no evidence of inflammation elsewhere in the CNS or peripheral nerves. Sections of the spinal cord showed patchy loss of anterior horn cells with negative staining with ubiquitin. The gastric neoplasm showed an infiltrating moderately differentiated adenocarcinoma without lymph node metastases.

Final diagnosis: MND syndrome with pathological evidence of Lewy body disease and Alzheimer disease changes (multi-system disease?).

EP, female age 57, SMNDR No: 127. Referral: Collaborator

Initial diagnosis: ALS (2 regions)

Presented with a 6 month history of slowly progressive difficulty walking and widespread limb cramps without sensory or bulbar symptoms. On examination there was a slight tremor of the head and a rest tremor in the right hand which was also present in the outstretched position. She looked a little bradykinetic. No bulbar signs, no wasting. Scanty fasciculations in the quadriceps, weakness of the entire right leg except the quadriceps, particularly affecting distal muscles and brisk reflexes throughout although the right ankle jerk depressed compared to the left. Normal sensation. EMG: compatible with a diffuse disorder of

anterior horn cell origin. In addition there was an abnormality in the right peroneal nerve, suggesting a co-existing lesion at the right fibular head. Normal myelogram, CSF and protein electrophoresis. Probably slowly worsening and appearance of bulbar symptoms.

Final diagnosis: MND with extrapyramidal disorder/Parkinsonism.

JMc, male age 61, SMNDR No: 161. Referral: Collaborator

Initial diagnosis: Multisystem atrophy

13 month illness to death. Commenced with slurred speech and clumsiness of the left side with unsteadiness of walking. Examination showed gait ataxia, dysarthria, left upper motor neuron facial weakness and striking left sided ataxia with a mild left hemiparesis and brisk reflexes with increased tone on the left. Initially thought to have a posterior fossa mass lesion lying on the left side within the cerebellum perhaps with hydrocephalus, however CT scan normal. He deteriorated with the appearance of wasting and fasciculation particularly on the left as well as his progressive pseudobulbar palsy. There was no evidence of dementia. CT and MRI were normal as were EEG, CSF, extensive blood tests and neuropsychology. EMG: typical of MND. Trial of Sinemet was unhelpful. His disease progressed inexorably and nasogastric tube feeding was considered.

Final diagnosis: Multi-system degeneration combining predominant motor system disorder, extra-pyramidal and cerebellar features.

SC, male age 66, SMNDR No: 204. Referral: SHIPS

Initial diagnosis: ALS (3 regions)

13 month illness to death. Presented with a 5 month history of dragging of the left leg with a tendency for it to give way and then a progressive deterioration in gait with wasting of both hand muscles progressing to generalised weakness but no cramps. On examination he walked with a spastic circumducted left leg, had a mild bilateral spastic paraparesis and fasciculation was plentiful over the upper arms and the right EDB. There was gross wasting of the left side of all intrinsic hand muscles, the peri-scapular and forearm muscles and both quadriceps. Sternomastoid weak, brisk asymmetric reflexes. He had a recognised, long standing pigmentary retinopathy (PR) and poor dark adaptation. Investigation revealed a high haematocrit which proved to be true polycythaemia and a marrow trephine had features consistent with, though not completely diagnostic of, primary polycythemia, he underwent venesections. CSF was normal as were biochemical tests. He had an enlarged spleen but no evidence of a hyperne-phroma. NCS/EMG: prolonged F wave latencies and slowed motor conduction in the right peroneal nerve (37 m/sec) with small compound muscle action potentials but normal sensory studies. Widespread denervation was observed affecting upper and lower limbs but the overall electrophysiological diagnosis was of a mixed axonal and demyelinating neuropathy. An electroretinogram showed a normal wave form with only mildly reduced amplitudes and therefore his PR was thought to be atypical or possibly due to the carrier state. His motor system disease progressed, no autop-sy was performed.

Final diagnosis: Uncertain, combined features of a neuono-

pathy with clear UMN signs and neuropathy (not that usually described in association with polycythemia).

SS, female age 54, SMNDR No: 333. Referral: GP mailshot

Initial diagnosis: ALS

SS's mother was almost certainly affected by MND with progressive loss of mobility, falls and difficulty swallowing and speaking. SS had an illness of 21 months to death. She presented with a one year history of behavioural and cognitive disturbance with confusion and disorientation. She became vacant and disinterested and her behaviour odd. 4 months later she was noted to be quiet and withdrawn but otherwise normal, she then developed cramps. She resigned her teacher's job and became distressed at the prospect of developing her mother's illness. She followed her relatives around to distraction, she was unable to fill in forms, had no responsibility towards money and her memory deteriorated. She was unable to place jigsaw puzzles correctly. She did not appear to understand her reading material. A year after onset she fell and broke her arm. Following this, she had difficulty in holding up her head and would support it with her hand even when standing. Her walking deteriorated. She had a few choking attacks and lost the strength in her upper arms. Her memory continued to deteriorate. She became withdrawn, stooped and crooned constantly to herself answering every question with a "No". Her back muscle lost its tone and she was unable to support her trunk. Examination showed emotional lability, cognitive disturbance, foot drop, scoliosis, bent knees, widespread fasciculation with normal tone and sensation. A neuropsychological evaluation showed that she could write quite complex words

from dictation and read alone complex passages of script. In contrast she made errors indicating named body parts and naming indicated body parts. She was easily distractable. CSF was normal, an EMG showed a widespread neurogenic disturbance with denervation potentials. Her cognitive function continued to deteriorate together with her motor system disease and she began to aspirate. At autopsy macroscopic appearances were normal. Scattered senile plaques were seen in the parahippocampal cortex, but neurofibrillary tangles were scanty. No plaques or tangles in the hippocampus or cortex samples. Pyramidal tract nerve fibre depletion in the medulla and spinal cord. Anterior horns shrunken and hyperchromatic. Ubiquitin positive cytoplasm in a few anterior horn cells.

Final diagnosis: MND with dementia and organic psychosis, although no neuropathological basis for the cognitive changes.

B. REGISTERED WITH THE SMNDR BUT DIAGNOSIS REVISED WITH FOLLOW UP OR AUTOPSY (n=15).

WC, male age 67, SMNDR No: 13. Referral: Collaborator

Initial diagnosis: PMA

Presented with a 3 year history of mild progressive asymmetric, principally proximal muscle weakness without bulbar involvement or UMN signs. CK 355 - 242. The possibility of MND was raised on NCS/EMG which showed normal nerve conduction studies apart from an absent superficial peroneal SAP and there were widespread motor unit potential abnormalities without spontaneous activity. Because of a large number of polyphasic units he proceeded to a muscle biopsy which showed features of a primary

myopathic process with inflammatory changes, focal chronic inflammation, atrophy and no fibre type grouping.

Final diagnosis: Chronic polymyositis.

AB, male age 41, SMNDR No: 25. Referral: Collaborator

Indiagnosis: ALS (2 regions).

2 year history of progressive weakness particularly in the left leg without sensory or sphincter disturbance. On examination he had fasciculations in some of the muscle groups of his upper arms but no wasting. There was a mild asymmetric spastic paraparesis with reflexes generally brisk including his jaw jerk. Cervical spine X-rays showed some narrowing of the C5, C6, C7 discs with small osteophytes in the posterior disc margins encroaching on the spinal canal. There was indentation of the contrast column at C5-6 and C6-7 with some compression of the cervical cord without evidence of nerve root impingement. CSF normal. NCS/EMG showed mild but definite LMN degeneration in a wide spread distribution, MND was thought likely, but a further EMG 9 months later showed no progression. If anything, his clinical situation improved and MRI showed mixed disc and osteophyte protrusion just touching the cord C5-6.

Final diagnosis: Cervical spondylosis causing myelopathy. Surgery is being considered.

VG,female age 74, SMNDR No: 34. Referral: GP

Initial diagnosis: ALS (3 regions)

Presented with a 2-3 year history of difficulty walking resulting in falls. Examination showed wasting of her thighs and hand muscles and loss of power in the lower limbs but no fasciculation or sensory signs. The reflexes were brisk with up going plantars. The possibility of MND was raised (Geriatric Medicine). Motor conduction studies showed mild reduction in compound muscle action potential amplitude, variable F wave latency, absent sural potentials and needle EMG occasional fibrillations and positive sharp waves in the legs with motor unit potential abnormalities principally in distal muscles. The findings were thought to suggest a chronic neuropathy but because of her brisk reflexes further investigations were undertaken and a diagnosis of normal pressure hydocephalus was made on the basis of the CT scan. Her verbal IQ was 125, performance IQ, 88. She underwent ventricular pressure monitoring and right ventricular peritoneal shunt insertion.

Final diagnosis: Chronic peripheral neuropathy of uncertain cause and normal pressure hydocephalus.

SH, male age 65, SMNDR No: 35. Referral: Collaborator

Initial diagnosis: PBP

Presented with dysarthria and dysphagia over a 6 month period. Examination showed evidence of palatal and larangeal muscle weakness. NMR scanning did not show a brain stem lesion. NCS/EMG: normal nerve conduction studies, denervation potentials in extensor digitorum brevis and widespread motor unit potential changes with increased polyphasia and impaired recruitment.

However, there was no change in these abnormalities over 2 sequential examinations. Subsequent review showed a hard swelling in the right sub-mandibular region and he was found to have some fullness in the right tonsil and tongue base and CT scanning on this occasion showed a non vascular parapharyngeal space tumour suspected to be an adenocystic carcinoma of the deep lobe of the sub-mandibular gland and his management was transferred to the ENT surgeons.

Final diagnosis: Retro-pharyngeal tumour.

AE, female age: 83, SMNDR No: 75. Referral: Collaborator

Initial diagnosis: ALS (2 regions)

Presented with 7 month history of progressive weakness of the left hand. On examination the cranial nerves were normal, there was wasting and weakness without fasciculation of the small muscles of the left hand and the forearm extensors but no wasting or fasciculation elsewhere. Possibly slightly increased tone in the left arm and reflexes very brisk generally with a few beats of clonus at the ankles. Possible ulnar sensory loss in the left hand. NCS/EMG abnormalities were confined to the left upper limb without denervation potentials. Cervical spine X-ray showed gross spondylosis but in view of her age a cervical myelogram was not thought appropriate. With follow-up the initial suggestion of MND was thought less likely as there was no progression over 18 months.

Final diagnosis: Cervical myeloradiculopathy.

WH, male age 65, SMNDR No: 82. Referral: Collaborator

Initial diagnosis: PMA

Two month history of weakness of the left arm and wasting of the left biceps muscle without pain. Vague tingling over the left shoulder. Examination showed wasting and weakness of the left deltoid, biceps, brachoradialis and pectoralis muscle with preservation of triceps bulk and widespread fasciculation of the shoulder girdle bilaterally and involving the quadriceps. Diminished reflex at the left biceps and supinator but preserved in the triceps, no bulbar involvement or clear upper motor neurone signs. Mildly raised CK at 217. Immunoglobulins normal, EMG showed abnormalities in left deltoid biceps and triceps with motor unit potential changes and positive sharp waves. Nerve conduction studies normal. The findings were thought to suggest a C5-6 lesion. Myelogram not performed but no change with follow-up.

Final diagnosis: ?Cervical spondylotic radiculopathy.

JF, male age 78, SMNDR No: 149. Referral: Collaborator

Initial diagnosis: PMA

Presented with weakness to the extent that he was unable to open his left hand associated with some mild neck discomfort. Mode of onset was uncertain. There was some numbness over the C8 area on the left which was intermittent. There was wasting and weakness confined to the left upper limb particularly distally affecting the hypothenar and thenar eminences and wrist extension. Reflexes were depressed in the upper limbs and absent at the biceps, supinator and ankles. NCS/EMG examination showed delayed F waves, no denervation potentials and motor unit poten-

tial changes in both upper limbs and the right leg and sternomastoid. Cervical spine X-ray showed considerable degenerative changes in the lower and mid cervical spine. CSF was normal apart from a mildly elevated protein at 0.69 g/l. Follow-up over 13 months showed no clinical deterioration.

Final diagnosis: Polyradiculopathy due to cervical spondylotic disease.

JB, male age 56, SMNDR No: 150. Referral: Collaborator

Initial diagnosis: ALS (2 regions)

Presented with pain and weakness of the left upper limb, particularly the left hand. The pain had a radicular quality and there were occasional paraesthesia but these were not impressive. There was wasting of the left FDI and weakness of C8/T1 in the left hand and questionable pyramidal distribution of weakness in the remainder of the left upper limb. The reflexes were brisk throughout. There were no sensory signs. EMG examination showed motor unit potential changes confined to the left arm, myelogram with CT scanning failed to show any evidence of compression of cervical roots. However, with follow-up there was no change in his symptoms or signs.

Final diagnosis: Uncertain, non-progressive cervical lesion.

RB, male age 79, SMNDR No: 160. Referral: Collaborator

Initial diagnosis: ALS (3 regions)

Presented with an 8 month history of progressive left hand and arm weakness without pain or paraesthesia. Diabetes mellitus controlled by diet. The abnormal signs were confined to the left upper limb with marked wasting of biceps but weakness affected

all muscle groups in the same limb. The deep tendon reflexes were exaggerated throughout and there was no sensory loss. NCS/EMG: the upper limbs were normal apart from an absent ulnar sensory action potential. There was some denervation in EDB and TA and in addition motor unit potential abnormalities in all four limbs and sternomastoid. A diagnosis of MND was revised when a myelogram showed considerable spondylotic change in the cervical spine with obliteration of C6 root pockets.

Final diagnosis: Spondylotic myeloradiculopathy.

ID, male age 51, SMNDR No: 175. Referral: Collaborator

Initial diagnosis: PLS

Presented with a 2 year history of a very slowly progressive illness dominated by upper motor neuron symptoms and signs affecting all 4 limbs in an asymmetric fashion worse on the right. However, this was accompanied by wasting of the right leg of uncertain duration. There was also mild bilateral wasting and weakness at the first dorsal interosseous but no definite bulbar features. He had intermittent tingling of the hands and feet. An MRI including the cervical cord and CSF studies were normal but he did not have EMG. With follow-up he developed a left optic neuropathy but compressive causes were excluded with appropriate imaging.

Final diagnosis: Demylinating disease of undetermined cause, possibly late onset multiple sclerosis.

PC, male age 46, SMNDR No: 183. Referral: Collaborator

Initial diagnosis: ALS (2 regions)

Imprecise history of clumsiness of the hands and difficulty

walking over several months. There was a history of alcohol abuse. Distal wasting and weakness of his limbs without fasciculation. Brisk symmetrical reflexes, no sensory loss. Serum proteins and electrophoresis were normal. Neurophysiological studies showed evidence of motor unit abnormalities in muscles innervated by C8 on either side, suggesting a lesion of C8 motor roots. He had bilateral rudimentary cervical ribs, and minor degrees of root impingement at C6-7 on the left and C5-6 on the right and the cervical cord appeared marginally widened although there was no evidence of tonsilar prolapse. CSF normal. At follow-up 4 months later there had been no progression clinically or electrophysiologicaly. He developed a broncho-pneumonia and died.

At autopsy the spleen was enlarged as were the majority of the lymph nodes in the chest and abdomen. Histology showed the internal architecture replaced by masses of tumour into which there were many Reed-Sternberg-like giant cells, the appearances were those of Hodgkins or T-cell lymphoma. Detailed histological examination of the nervous system revealed extensive neuronal loss, astrocytosis and proliferation of microglia in both thalamae but outwith these areas no abnormalities in the cortex, cerebral or cerebellar hemispheres or brain stem. In the spinal cord at C8 there was no evidence of tumour either within the meninges or within the spinal cord but there was some loss of motor neurons within the ventral horn with an associated astrocytosis and hyperplasia of microglia. A sample of other spinal levels was normal, the right deltoid showed focal clustering of a small number of contracted muscle fibres suggestive of neurogenic atrophy. The right median nerve was normal and the right ulnar

nerve was normal being both well myelinated and populated by normal axons, there was no evidence of infiltration by tumour.

Final diagnosis: Motor neuronopathy associated with T-cell lymphoma.

AR male age 80, SMNDR No: 192. Referral: GP

Initial diagnsosis: PMA

Presented with unsteadiness of walking, possibly dysarthria and diminished reflexes of uncertain duration and was suspected of having MND by a consultant physician. Also sustained black-outs thought to be due to transient ischaemic attacks. No lower motor neuron signs or progression of neurological signs.

Final diagnosis: Uncertain, possible cerebrovascular disease.

JMc male, age 75, SMNDR No: 219. Referral: SHIPS

Initial diagnosis: ALS (extent?)

The diagnosis was suggested by a consultant neurologist during admission for diuretic induced hyponatraemia (sodium 118). He was noted to have wasting of the muscles of both hands with fasciculation and generally brisk reflexes but the remaining details at registration are scanty. No NCS/EMG examination. Subsequent follow-up from the GP indicated that this diagnosis had not been substantiated and there was no change in his neurological condition.

Final diagnsosis: Hand wasting of uncertain cause, hyponatraemia.

JM male age 60, SMNDR No: 240. Referral: SHIPS

Initial diagnosis: PBP

Presented with a one year history of a bulbar palsy with dysarthria and marked swallowing difficulties, mode of onset uncertain. Examination showed a mild upper motor neuron facial weakness, no tongue fasciculation and a pseudobulbar palsy. Limb reflexes were brisk without sensory disturbance. NCS/EMG showed a mild motor neuropathy with no denervation potentials. A diagnosis of MND was made (neurologist) but 10 months later there appeared to have been little change in his bulbar palsy and an isolated vascular lesion in the medulla was suspected. An MRI of the head showed multiple bilateral focal lesions concentrated around the inferior thalamus and internal capsule-basal ganglian regions. There was no change in electrophysiological appearances.

Final diagnosis: Pseudobulbar palsy due to ischaemic leucoencephalopathy.

JK, male age 73. SMNDR No: 291. Referral: GP Mailshot

Initial diagnosis: ALS (2 regions)

Presented with a 3 month history of weakness and aching in both legs without sensory symptoms. Examination showed small muscle wasting in the hand, a tremor of uncertain type and a mild spastic paraparesis. An MRI scan showed straightening of the normal cervical curvature with multiple offsets. The cord was somewhat atrophic at C3 where there was evidence of impingement and at C5-6 where impingement was associated with oedema of the cord. Nerve conduction studies showed evidence of bilateral ulnar entrapment at the elbow and an upper motor neuron pattern

in the lower limbs but no other lower motor neuron signs.

Final diagnosis: Cervical myelopathy and previous operations for tardy ulnar palsy.

C.DIAGNOSIS UNCERTAIN OR FAILS TO FULFIL THE SMNDR CRITERIA FOR CLINICALLY DEFINITE OR PROBABLE MND (n=5)

WS, female age 44, SMNDR No: 53. Referral: Collaborator

Initial diagnosis: ALS (2 regions)

Presented with a 10 month history of weakness of the left arm and pains around the elbow. Aware of occasional fasciculation in the intrinsic muscles of the left hand and a tendacy to drop objects. Some neck discomfort. Examination showed fasciculation of the intrinsic muscles as well as the forearm muscles and wasting of the intrinsic muscles of the left hand with a more widespread weakness of pectorals, rhomboids, triceps and intrinsic musculature. Triceps jerk absent, limb reflexes otherwise brisk and plantars equivocal. NCS/EMG: normal nerve conduction studies and possible fasciculation potentials in the lower limbs as well as the affected limb. Myelogram and CSF normal. The patient was informed of the diagnosis of probable MND but her situation remained entirely stable with follow-up.

Final diagnosis: Monomelic MND, non progressive.

LB, female age 57, SMNDR No: 66. Referral: Collaborator

Initial diagnosis: ALS (2 regions)

Four month history of progressive weakness of the left ankle leading to a foot drop. Examination showed normal cranial nerves, brisk upper limb reflexes and an asymmetric spastic

paraparesis worse on the left without sensory abnormalities. Fasciculation was observed in the left quadriceps on one examination. Lumbar radiculogram (Orthopaedic service) and then a total myelogram did not show a compressive lesion. Routine blood tests, B12 and folate, CT scan, EMG normal. Mildly raised CSF protein (0.53 g/l) but no oligoclonal bands, VER's normal. At review her signs were stable, she complained of cramp but on this occasion no fasciculation was evident.

Final diagnosis: Spastic paraparesis, cause uncertain, follow up continues.

JB, female age 67, SMNDR No: 071. Referral: Collaborator

Initial diagnosis: PLS

Presented with a 2½ year history of progressive dysarthria and gait difficulty due to pseudobulbar palsy and asymmetric spastic quadraparesis without definite LMN or sensory signs. CSF (including immunological studies), MRI, EMG normal. Excluded on the basis of a history of a previous episode of possible transverse myelitis 15 years previously and abnormal visual evoked responses, although diagnosis is unclear and follow up continues.

Final diagnosis: Uncertain, possible PLS, possible multiple sclerosis.

WS, male age 69, SMNDR No: 188. Referral: Collaborator

Initial diagnosis: ALS

Presented with an 18 month history of stiffness and weakness of the left leg. A little weakness in the left hand. No other abnormalities apart from a slight hesitancy of urine. No cramp. Examination showed normal cranial nerves, C8-T1 weakness in the

hands but no upper limb fasciculation. Wasting of the left quadriceps and fasciculation in several lower limb muscles with bilateral increase in leg tone and a mild spastic paraparesis. Normal upper limb reflexes. Mild vibration sense impairment at the toes. NCS/EMG: delayed F waves in both upper and lower limbs, absent sural SAP and some motor unit potential changes affecting the left lower limb only. Normal CT scan, myelogram and CSF. Follow-up 6 months later showed no definite change.

Final diagnosis: Possibly arrested MND, follow up continues.

RI, male age 66, SMNDR No: 344. Referral collaborator

Initial diagnosis: PBP

Presented with slurring of speech which seemed to be progressive but since a tentative diagnosis of MND in 8/89 remained largely static. Signs rather equivocal with clumsy tongue but normal facial jerks and no lower motor neuron involvement or limb signs. Thrombocythemia of uncertain cause. Awaiting MRI.

Final diagnosis: Brainstem lesion not yet diagnosed ?arrested MND, follow up continues.

APPENDIX B

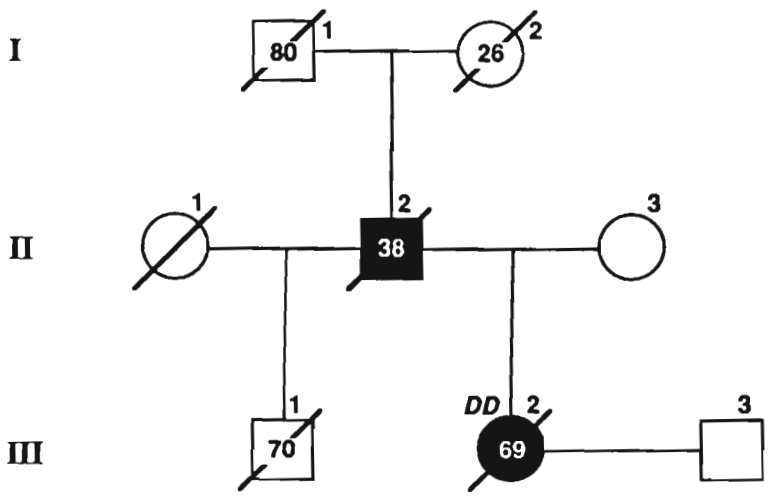
DETAILS OF FAMILY MEMBERS IN PEDIGRESS WHERE A GENETIC CAUSE FOR MOTOR NEURON DISEASE SEEMS LIKELY. (n=11).

Key to pedigrees

In all pedigrees a circle indicates a female, square a male. Shading indicates affected with MND. A diagonal line indicates a deceased individual and age at death is included (where known). If unshaded, cause of death was not MND.

The proband on the SMNDR is indicated by initials. No family has more than one member on the SMNDR at this stage. b= born.

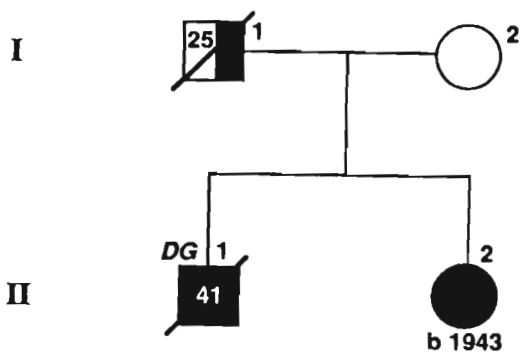
Roman numerals are used for separate generations and individuals numbered from right to left for reference below the family tree. The source of information is included.



DD, female age 67, SMNDR No: 60

2.2: ALS with bulbar involvement as for proband. Duration 17 months (death certificate and family history).

3.2: (DD): SMNDR. 26 month illness. ALS with bulbar involvement.



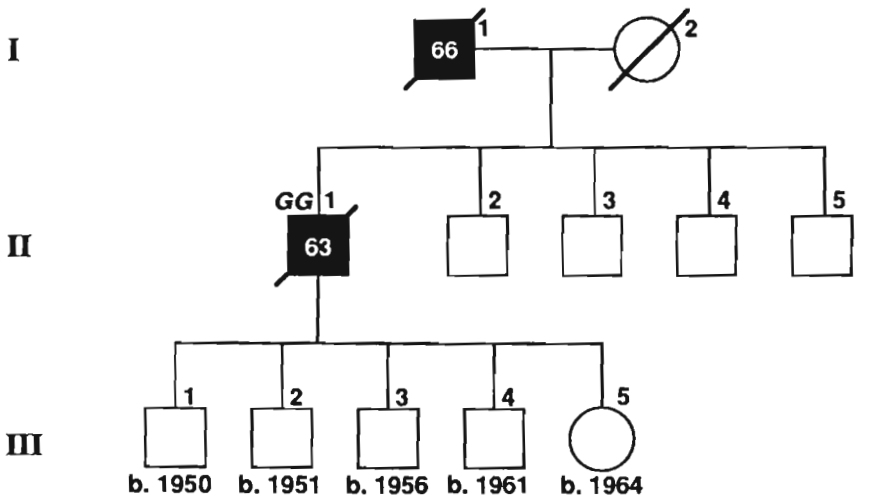
DG, male age 41, SMNDR No: 68

1.1: Progressive wasting disorder affecting the left arm but not elsewhere. Died 6 months later with pneumonia which was certified cause of death (history from family).

2.1: (DG) SMNDR. Rapid (<12 months) illness to death. Typical ALS and PBP.

2.2: Typical ALS with PBP (neurologist's report to SMNDR).

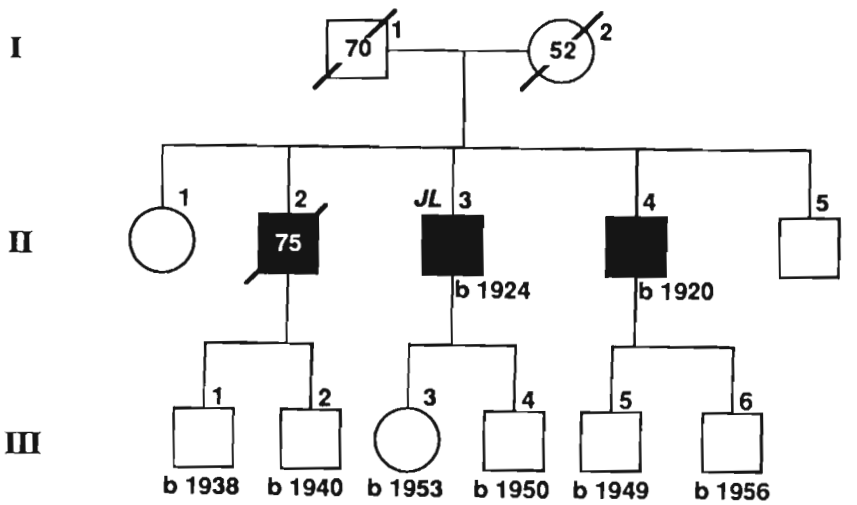
Details of earlier generation uncertain, birth and death certificates of parents not in Register House (Edinburgh), may have died in England.



GG, male age 60, SMNDR No: 50

1.1: Five year history of progressive paralysis of all limbs. No bulbar symptoms. Confined to bed for final 6-12 months, died with pneumonia (history from family, death certificates of previous generation not in Register House, Edinburgh).

2.1: (GG) SMNDR. 14 month illness. ALS PBP, autopsy (appendix C): typical pathological findings of MND.



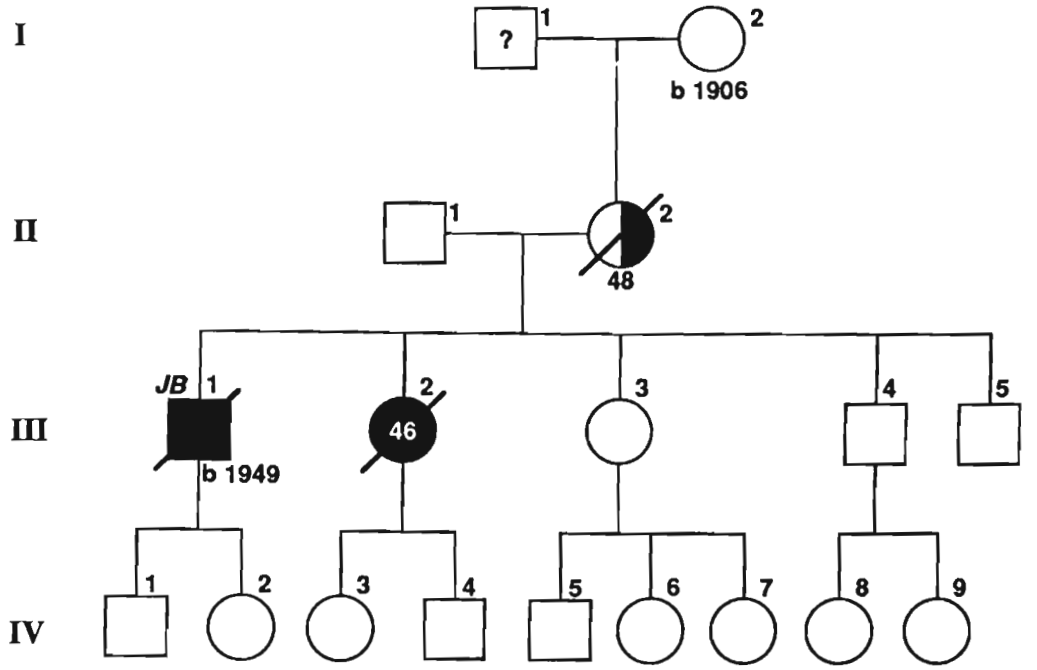
JL, male age 69, SMNDR No: 279
(Bulbospinal neuronopathy/Kennedy syndrome)

1:2: Carrier? Details of her two brothers unknown.

2.2: Long duration of "motor neuron disease", similar illness to proband (history from family).

2.3: (JL) SMNDR. 12 year history of progressive generalised muscular atrophy, facial weakness, bulbar paralysis, gynaecomastia (seen in person 1991).

2.4: 23 year history of generalised progressive muscular atrophy, involving face and bulbar muscles. Striking shoulder girdle involvement (seen in person 1990).



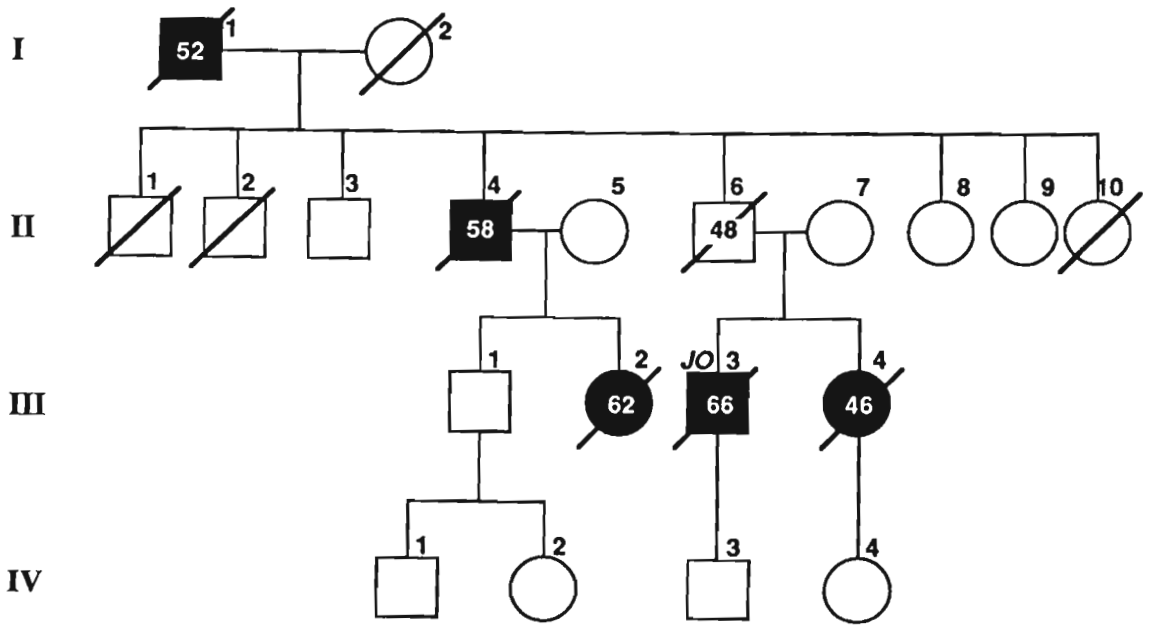
JB, male age 41, SMNDR No: 122

2.2: "Dystrophica myotonica" (death certificate). Illegitimate, father unkown, mother alive.

3.1: (JB) SMNDR. Rapidly progressive muscular atrophy with breathlessness (seen in person 11/90).

3.2: Died after 3 year illness of progressive muscular atrophy with bulbar and respiratory involvement (seen in person 3/91)

4.1-4.9: All children are younger than 25 years.



JO, male age 66, SMNDR No: 2

1.1: Bulbar paralysis (death certificate). Rcords of parents cannot be traced.

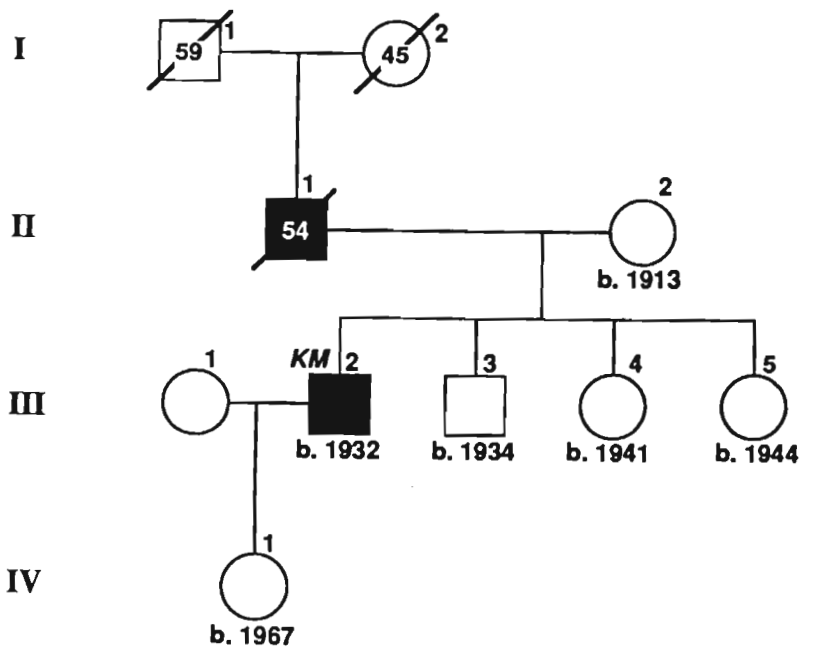
2.4: Progressive generalised weakness of muscles (died in the USA, age uncertain, history from family).

2.6: Died at sea in world war II.

3.2: One year history of progressive muscular atrophy with respiratory and bulbar symptoms. Autopsy: spinal cord anterior horn cell loss and pallor of anterior and dorsal roots. Myelophages in posterior column nucleii. Neurogenic atrophy of muscle. (Medical records).

3.3: (JO) SMNDR. 11 month history of ALS. Autopsy: Anterior root atrophy, spinal cord anterior horn cell loss and posterior column myelophages. Astrocytic gliosis some perivascular lymphocytic cuffs.

3.4: <12 month history of progressive muscular weakness of all limbs. Some parasthesiae. Autospy: Hypoglossal nuclei neuron loss, anterior horn cell loss. Neurogenic atrophy of muscles. Some posterior root ganglia cell loss (medical records).

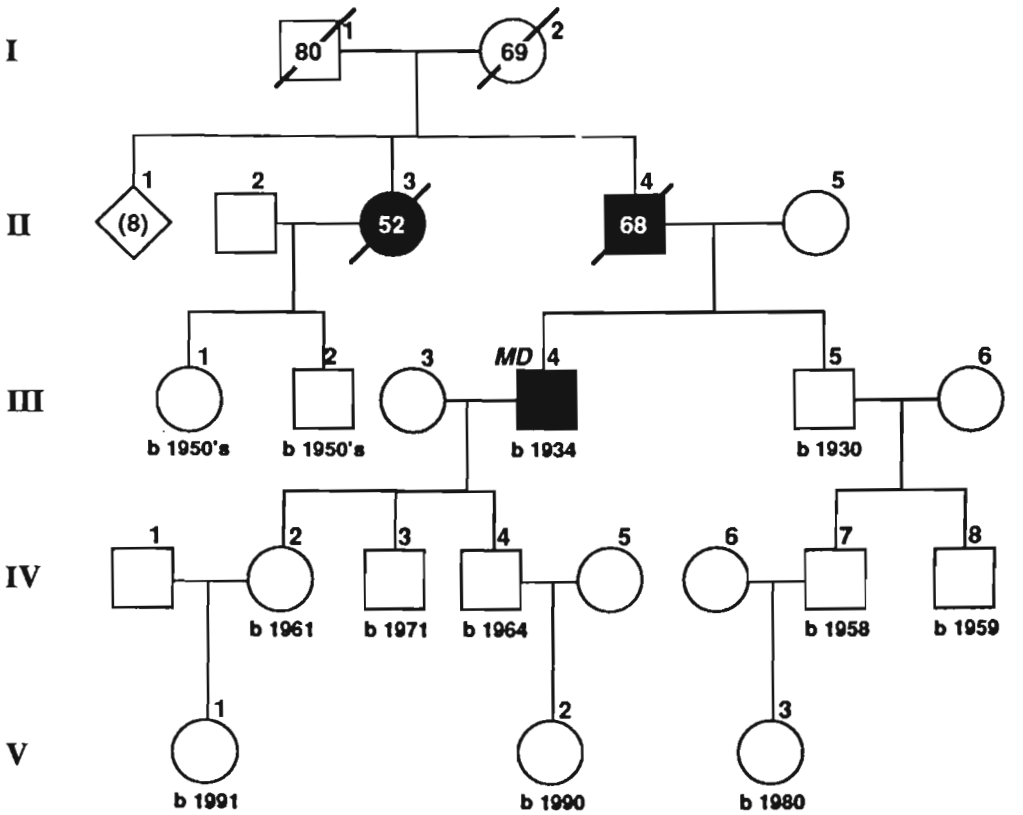


KM, male age 57, SMNDR No: 62

1.2: Died of pulmonary tuberculosis.

2.1: Died of illness suggesting a progressive bulbar paralysis (proband's description).

3.2: (KM) SMNDR. Slowly progressive wasting and weakness of limbs. Principally arms. PMA.



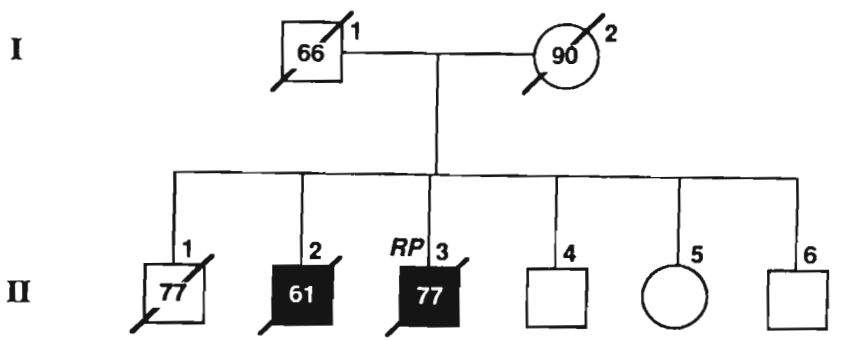
MD, male age 56, SMNDR No: 283

1.2: Died of heart disease, mother not affected, father no record (death certificate).

2.2: Died in Canada of a neurological illness which involved definite wasting and weakness of muscles but details scanty (history from family member).

2.3: Seven year history of wasting and weakness of the limbs, becoming wheelchair bound, speech disturbance in terminal phase only. Proband reports this illness closely resembled his own.

3.1: (MD) SMNDR. Illness began 3/87, diagnosis 11/90. Inexorably progressive, asymmetric, generalised wasting and weakness with fasciculation. Useless right arm, droopy head, bilateral foot drop, needs assistance for most activities. PMA (Seen in person 3/92).



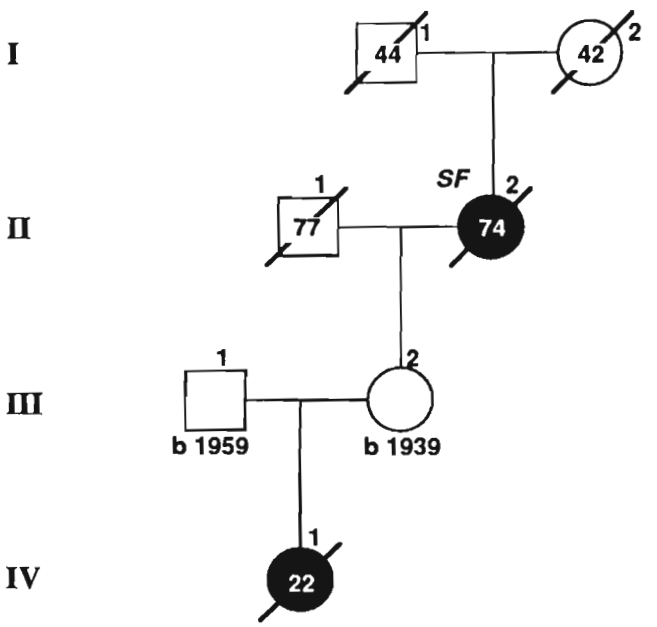
RP, male age 76, SMNDR No: 84

2.1: Parkinsonism and dementia (history from family).

2.2: Motor neuron disease (death certificate).

2.3: (RP) SMNDR. 14 month illness. ALS with PBP.

RP's father was illegitimate, therefore no information on proband's paternal grandfather. MND not included on death certificates of proband's maternal grandparents.

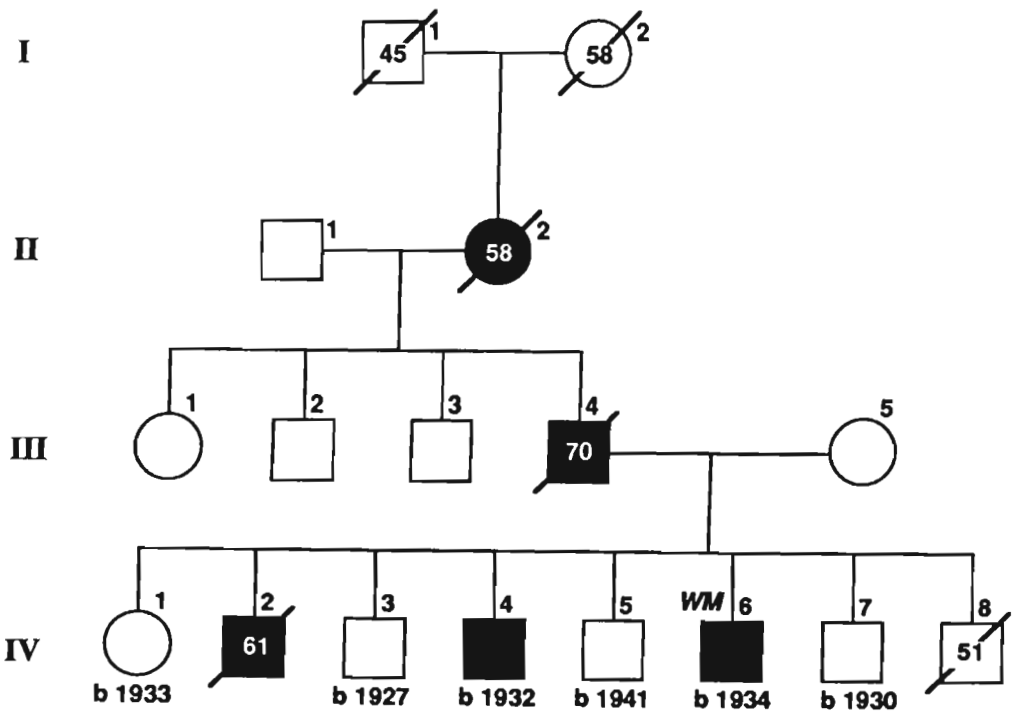


SF, female age 74, SMNDR No: 314

1.2: "Lupus of the face and nose and exhaustion" but no mention of MND (Death certificate).

2.2: (SF) SMNDR. Typical PBP/ALS.

4.1: Juvenile MND with pathological confirmation (access to detailed report denied by pathologist).



WM male age 56, SMNDR No: 307

2.2: Spastic paraplegia (death certificate) and creeping paralysis (history from family).

3.4: Wasted legs, wheel chair dependent, died of pneumonia (history from family).

4.2: Died 12 months after diagnosis of MND. Generalised muscle weakness, respiratory distress and upper motor neuron signs (ALS). (Discussion with GP).

4.4: 10 year history of a progressive muscular atrophy (neurologist's diagnosis).

4.6: (WM) SMNDR. Five year history, now fully dependent for all activities. Progressive muscular atrophy begining in the shoulders and later mild bulbar involvement (seen in person 11/91).

APPENDIX C

SUMMARY OF THE PATHOLOGICAL FEATURES OF THOSE PATIENTS INCLUDED IN THE MAIN ANALYSES WHO UNDERWENT AUTOPSY (N=15)

JO, male age 66, SMNDR No: 002.

Diagnosis: ALS (Familial)

Macroscopic appearance: Anterior root atrophy in the spinal cord.

Microscopic appearance: Cerebral hemispheres normal and hypoglossal nucleus normal. Striking depletion of anterior horn cells and pale roots. Myelophages present most obviously in the dorsal column nuclei.

ES, female age 72, SMNDR No: 023.

Diagnosis: PBP/ALS

Macroscopic appearance: Thin cauda equina but otherwise normal.

Microscopic appearance: Neuronal depletion in the anterior horns of the spinal cord, degenerative changes in surviving neurons. Associated increase of astrocytes and microglial cells, no ubiquinated inclusions identified. Myelin pallor unequal on either side in the crossed and uncrossed pyramidal tracts. Mild pallor in the medullary pyramids and depletion of neurons in the hypoglossal nuclei accompanied by gliosis.

GG, male age:60, SMNDR No: 050.

Diagnosis: ALS/PBP (familial)

Macroscopic appearance: Parietal atrophy. Mild ventricular dilatation otherwise normal.

Microscopic appearance: Cortex normal; pallor of the central white matter; flea bite infarcts; focal atrophy of the folia in the cerebellum. Cortico-spinal tract myelin depletion and accu-

mulation of myelinophages. Demyelination of the anterior roots of the spinal cord with tract degeneration and myelin loss in the lateral and anterior cortico-spinal tracts. Depletion of anterior horn cell neurons, occasional ubiquitin-positive inclusions. Severe degeneration of anterior roots of the cauda-equina. Denervation atrophy of peripheral muscles. Terminal bronchopneumonia.

MG, female age 62 years, SMNDR No: 067.

Diagnosis: ALS/PBP

Macroscopic appearance: Small pons and flattened pyramids, shrunken anterior roots of the spinal cord and all regions, particularly at the cauda equina.

Microscopic examination: Cortex and hemispheres normal. Swollen neurons and depleted Nissl substance in the floor of the fourth ventrical. Demyelination of the pyramids, depletion of anterior horn cells in the spinal cord, poorly myelinated cortico-spinal tracts and shrunken anterior spinal roots. At the cauda equina the anterior roots contrasted markedly with the posterior roots showing loss of myelin and increased collagenisation. Hashimoto's disease in the thyroid, microadenoma of the pituitary, terminal bronchopneumonia.

AH, female age 69, SMNDR No: 081.

Diagnosis: ALS/PBP

Macroscopic appearance: Normal brain, cerebellum and brain stem. Obvious atrophy of ventral roots of cervical region in the cauda equina.

Microscopic examination: Loss of neurons in the ventral horn

and the cervical and lumbar regions, no obvious abnormality in myelination. Carcinoma of the sigmoid colon.

IB, female age 67, SMNDR No: 094.

Diagnosis: ALS/PBP

Macroscopic appearance: Slight general cortical atrophy, dilated ventricles, brain stem and cerebellum normal. Shrinkage of the anterior spinal roots in the cervical region and to a lesser extent in the cauda equina.

Microscopic examination: Normal cortex. Focal abnormalities of the neurons in the floor of the fourth ventricle and the presence of myelinophages in cortico-spinal tract on both sides at various levels in the brainstem. Myelin loss in the cortico-spinal tracts and the pyramids. Depletion of Purkinje cells in the cerebellum. Anterior horn cells of the spinal cord focally swollen and loss of Nissl substance. Demyelination of the corti-co-spinal tracts and the cauda equina. Denervation atrophy in muscle.

TM, male, age 80, SMNDR No: 096.

Diagnosis: PBP/ALS

Samples of the nervous system deteriorated during transport-ing and examination not possible.

JM, male age 77, SMNDR No: 107.

Diagnosis: ALS/PBP

Macroscopic appearance: Moderate degree of cortical atrophy.

Microscopic appearance: Pyramids reduced in size with loss of myelinated axons. Depletion of motor cells from the hypoglos-

sal nuclei and occasional cytoplasmic inclusions on ubiquitin immunocytochemistry. Pallor of myelin in the spinal cord pyramidal tracts and anterior horn cell population reduced. Peripheral nerves showed large axonal loss and secondary demyelination. Focal group atrophy in muscle.

CO', female age 75, SMNDR No:176.

Diagnosis: PBP/ALS

Macroscopic appearance: Cauda equina atrophy.

Microscopic appearance: Loss of neurones in the hypoglossal nuclei and demylination in the lateral and anterior white columns but spinal cord structure well maintained.

MR, female age 67, SMNDR No: 200.

Diagnosis: ALS/PBP

Macroscopic appearance: Gaping central sulcus, otherwise normal.

Microscopic appearance: Typical spinal cord changes with loss of neurons in the central horn and pallor of myelin staining in the lateral and ventral columns, loss of neurons in the hypoglossal nuclei, established neurogenic atrophy of muscle.

SC, female age 74, SMNDR No: 205.

Diagnosis: ALS/PBP.

Macroscopic appearance: No external abnormality of the brain or spinal cord.

Microscopic appearance: Marked neuronal loss in the hypoglossal nuclei and some ventral horns in the spinal cord. Shrinkage of the ventral nerve groups. Pallor of staining of

lateral and ventral white columns. Atrophy of ventral nerve roots and the spinal cord and cauda equina.

PT, male age 66, SMNDR No: 218.

Diagnosis: ALS

Macroscopic appearance: Normal.

Microscopic appearance: Depletion of anterior horn cell neurons particularly in the lumbo-sacral region with associated increase of neuroglial cells. Pyramidal tract normal. Brain stem normal. Neurogenic atrophy without inflammation in muscle.

MC, female age 66, SMNDR No: 232.

Diagnosis: PBP/ALS

Macroscopic appearance: Normal apart from an uncomplicated one centimetre vascular malformation in the cerebellum.

Microscopic appearance: Mild spongiosis of the outermost layers of the cerebral cortex unaccompanied by plaques, neurofibrillary tangles or inflammation. Depletion of hypoglossal neurons, meylinophages in the cortico-spinal tract. Widespread degeneration and atrophy of skeletal muscles fibres including sternomastoid, tongue and quadriceps.

IP, male age 74, SMNDR No: 256.

Diagnosis: ALS/PBP

Awaiting report from the Procurator Fiscal, Glasgow. Unavailable as of 15.5.91.

AF, male age 69, SMNDR No: 290.

Diagnosis: ALS/PBP

Macroscopic appearance: Slight to moderate symmetrical dilation of the ventricular system and atrophy of the ventral roots particularly in the cauda equina.

Microscopic appearance: Loss of motor neurons in all spinal segments examined. Partial atrophy of the nuclei of the lower cranial nerves, particularly glosso-pharyngeal and hypoglossal. Clusters of microglial cells within the fifth nerve nuclei. Dennervation atrophy of muscle with normal peripheral (median,femoral) nerve.

APPENDIX D

QUESTIONNAIRE USED IN THE CASE-CONTROL STUDY

Contents

1. Patient Details

CCS Identification number:
(odd numbers=case, even numbers=corresponding control

Register Study No:

Name:

Address:

Telephone No:

General Pratitioner's name, address and telephone number:

Neurologist or physician:

Patient's date of birth (day/month/year):

Age:

Sex:

Date of Interview (day/month/year):

Throughout coding 1 for yes, 2 for no, 3 for can't recall.

2. Clinical features

History

When did your symptoms relating to MND begin? (month/year)

Total duration of symptoms relating to MND (months)

First Symptom

1. Muscle cramps,
2. Muscle twitching,
3. Hand weakness or wasting or difficulty writing,
4. Other UL weakness or wasting,
5. Footdrop,
6. Other LL weakness or wasting or difficulty walking,
7. Difficulty swallowing,
8. Difficulty speaking,
9. Other (e.g. pain, sweating - specify)

Present Symptoms (code as above)

Signs at visit

UMN bulbar signs
LMN bulbar signs
UMN signs (arms)
UMN signs (legs)
LMN signs (arms)
LMN signs (legs)
SMNDR Classification:

Examine eye movement/ocular mobility(analysis not in this thesis)

1. Voluntary or saccadic movements (horizontal and vertical)
Restricted excursion
Inability to maintain eccentric gaze
Slow saccades
Hypometric saccades
Prolonged reaction time

2. Smooth Pursuit (horizontal and vertical)
Restricted excursion
Saccadic pursuit

3. Convergence

4. Optokinetic nyastagmus.
Failure to generate slow phase velocities

5. Suppression of vestibulo-ocualar reflex.
Failure to suppress

Date of Diagnosis of MND (from records)

3. Past medical history

(Record response from patient and later as from GP Notes)
Have you ever suffered from:

Angina or a heart attack?
(central chest pain related to exertion, relieved by rest and/or resulting in admission with a diagnosis of angina or MI)

Strokes or TIAs?
(Sudden onset of a focal neurological/ocular CNS disturbance with no other explanation at follow up)

Leg Claudication?
(Pain in the calf or buttock related to exertion and relieved by rest with absent foot pulses)

Hypertension
(High BP requiring treatment, record BP before diagnosis of MND in GP's notes)

Previous Infections

Measles	Yes/No/Can't remember
	If Yes, how old?
Chickenpox	Yes/No/Can't remember
	If Yes, how old?
Scarlet fever	Yes/No/Can't remember
	If Yes, how old?
Diptheria	Yes/No/Can't remember
	If Yes, how old?
Mumps	Yes/No/Can't remember
	If Yes, how old?
Glandular fever	Yes/No/Can't remember
	If Yes, how old?
Poliomyelitis	Yes/No/Can't remember
	If Yes, how old?

Did any of your family ever have polio?
Yes/No/Can't remember

If yes, were you living in the same house as them? Yes/No/Can't remember

If yes, how old were you at the time?
Record details of person

Have you received polio vaccination?

4. Trauma prior to MND

Recording the same information from the patient and the GP records.

Date GP records began

How many fractures have you had? (number)

How old? (age of first, age of last)

Date of most recent fracture

Details of fracture

Location of most recent fracture?
1=UL, 2=LL, 3=Head, 4=Spine, 5=Ribs

Have you ever sustained another injury requiring medical consultation, including severe electric shocks? (n)

How old were you?

Date of most recent injury

Details of injury

Location of most recent injury (code as above)

Have you had a tonsillectomy?

Have you ever had a blood transfusion?

Have you ever had an operation requiring a GA?

List all prior to onset of MND (excl. tonsillectomy)

Operation Age (not coded)

Date of onset of MND

5. Toxin exposure

If response yes, specify details

Have you ever worked in extraction of minerals or ores, manufacture of metals?

Have you worked with lead as part of your occupation?

Have you ever had an occupation with known exposure to solvents or chemicals (eg shoemakers, tanners, house painters, rubber product makers, compositors, typesetters, laundry worker, petrol station attendants)?

Have you ever been exposed to pesticides or herbicides, domestic or commercial?

Have you ever been a POW?

Smoking (Roll your own - 1oz=28 cigarettes)
Current smoker?
If Yes, n per day
Ex smoker?
When stopped (age)
Max n/day when smoking

Are you vegetarian?

Do you keep or have you kept (for 2 or more seasons) a vegetable garden?

Do you eat garlic?

Do you eat cabbage, cauliflower or sprouts: 1 > 3/week
2 1-3/week
3 < 1/week

6. Family history

Has anyone in your family had MND? Yes=1, No=2
Details:

Has anyone in your family had any neurological disorder including PD or ATD?
Yes=1, No=2

Draw a family tree for families with MND/PD/ATD

For deceased relatives:

1=Full name 2=Date of birth 3=Year of death
4=Town of residence at death 5=Cause of death if known

7. Educational and occupational history

How old were you when you left school?

Did you obtain any qualifications after the age of 18?

What were your 4 principal jobs (begin with most recent)
Code according to OPCS 1980,1-16, include Military Service.

Occupation	Address	Dates

What is the main occupation of your wife/husband?

What was the main occupation of your father when you were born?

Code patient's and father's social class (OPCS 1980)

1	Professional	(1)
2	Intermediate occupations	(2)
3N	Skilled occupations - non manual	(3)
3M	Skilled occupations - manual	(4)
4	Partly skilled	(5)
5	Unskilled	(6)

01. Professional & related supporting management, senior national & local government managers
02. Professional and related in education, welfare and health
03. Literary, artistic, sports
04. Professional and related in science, engineering technology and similar fields
05. Managerial
06. Clerical
07. Selling
08. Security
09. Catering, cleaning, hairdressing, personal service
10. Farming, fishing and related
11. Material processing, making and repairing (excluding metal and electrical)
12. Processing, making, repairing (metal and electrical)
13. Painting, repetative assembling, product inspecting, packaging and related
14. Construction, mining and related not identified elsewhere
15. Transport operating, materials moving and storing
16. Misc. including labourers and unskilled

8. Residential history

(Each house of more that 1 year residence)

House Number (1-6)

Where was the 1st house you lived in after you were born?

Address:

Was this your residence when you developed MND?
(equivalent for controls)

1=Large town 2=Small town 3=Village 4=Isolated house

During which years? From/To

Did the house have a garden? Yes/No/Can't remember

Did the house have a separate bathroom? Yes/No/Can't remember

Did the house have a running hot water system? Yes/No/Can't remember

Did the house have a flush lavatory? Yes/No/Can't remember

How many bedrooms did the house have?

Who lived in the house?
(include anyone staying for more than 6 months)

Total adults:
Total children (under 18):
Total number of rooms:

Pet Exposure

Did dogs sleep in the house?
Did cats sleep in the house?

Did you have regular contact with farm animals?

APPENDIX E

THE SCOTTISH MOTOR NEURON DISEASE REGISTER: INFORMATION FOR MEDICAL PRACTITIONERS

Copy of the information sent to General Practionioners upon registration of a patient with the Scottish Motor Neuron Disease Register.

What is the Scottish MND register?

A national register of patients with motor neuron disease is being co-ordinated from the Department of Clinical Neurosciences, Western General Hospital, Edinburgh, with financial support from the Scottish Motor Neurone Disease Association. All the consultant neurologists and clinical neurophysiologists in Scotland are collaborating. The register has been approved by the hospital ethical committee and the Data Protection Officer for the Lothian Health Board. We are ascertaining cases from all of the consultant neurologists and clinical neurophysiologists in Scotland. Additional information is being obtained from the membership lists of the Scottish Motor Neurone Disease Association and computerised records of Hospital discharges and deaths held by the Common Services Agency and the Registrar General for Scotland.

Why do we need a Scottish Register?

There are no really good epidemiological studies of motor neuron disease, most series consisting only of a hundred or so patients. What we want to do is establish prospectively a register of all the cases presenting to medical attention in Scotland, which will be about 70 a year. Scotland is an ideal place to do this since it is geographically well defined, very few patients in Scotland are unlikely to get health care outside

the country, and the number of cases coming to attention every year is reasonable. As the years go by, we will therefore, progressively build up an impressive series of patients. We are registering the patients and then asking if we could have a photocopy of the relevant medical summary. This allows us to classify the nature of the motor neuron disease. Also, we are contacting the patients' general practitioners so that we can find out some simple follow up information and when the patient dies. From these very simple data we can look at incidence, geographical clustering, and natural history.

How will the register be constructed?

Unlike many other surveys in which everyone is sent a questionnaire at exactly the same time, the Register will have to be built on a 'rolling' basis so that doctors will be asked for information as their patients are registered, and subsequent requests for help will follow at regular intervals from that initial contact. We realise that the progression of the condition may mean that this could be problematic, although we believe that we have to work this way to ensure that the information we obtain is properly gathered and organised for research use.

Two separate, but related, computing systems are being used one which will assist the administration of the Co-ordinating Centre in Edinburgh by charting contacts with those aiding the Unit's work, and the other on which the main research information will be held. These systems will be modified and developed as necessary to enable smooth operation of the work of the Co-ordinating Centre.

Who should be registered?

Because we wish to study the natural history of the disease we are trying to register patients as soon as possible, even when the diagnosis is only suspected. It will then be possible, at a later date, to reclassify patients after collating information from all sources to produce a register of patients that conform to more rigorous diagnostic criteria. We have registered patients since January 1989 and if this rate of ascertainment continues it seems likely that incidence will be equal to or higher than we predicted (50-100 patients /year).

Will the patients be informed that they are registered?

If patients submit a request for disclosure of information held on computer the Data Protection Officer will inform us. We have discussed this legal issue with the Data Protection Officer of the Lothian Health Board whose interpretation of the law is that the release of such information is *at the discretion of the consultant responsible for the care of the patient and may be witheld if it is likely to be damaging*. There is no legal obligation to tell people that they are on a computerised register. However we would not object if patients were told by the referring doctor that simple data about them are being collected in Edinburgh so that we can learn more about the disease (whether they are told the diagnosis precisely at this stage is entirely up to the referring doctor).

Self-referred patients, or those contacted through the SMNDA, will be asked to give written consent for their participation (if necessary through a proxy), and for obtaining confirmation of their medical diagnosis. Data on patients will be com-

pletely confidential, both under the terms of the Data Protection Act and following normal medical conventions. Patients will be continuously recruited to the register, but can withdraw from the register at any time.

Who will be contacted?

At present there are no plans for approaching patients directly but a case-control study of environmental factors antecedent to the development of motor neuron disease is planned and contact will be made under a seperate cover concerning this. We hope to set up a system of systematic blood collection as part of a study of the genetic contribution to sporadic motor neuron disease in conjunction with the MRC Human Genetics Unit at the Western General Hospital, Edinburgh. Details of this will be posted at a later date after registration.

How will patients be followed up?

We intend to follow the patients' progress by writing to their general practitioners in the first instance. Because we do not want to produce too much paper work for those registering cases; any one GP is extraordinarily unlikely to have more than one case at a time so that any extra work for him/her is minimal.

Collaboration with other Clinical and Medical Research

The Register is also intended to be a research resource for clinicians and scientists who may wish to pursue projects in relation to motor neuron disease, subject to satisfactory scientific and ethical criteria being fulfilled.

How to obtain more information.

We hope that you will be reassured that this project is scientifically and ethically sound. If you personally have any worries about registering patients would you please let us know as soon as possible. Further information about the project is available on request (see below) and we plan to send regular newsletters to doctors who have registered patients.

For further information write to:

Professor CP Warlow, Dr AM Chancellor or Mrs Hazel Fraser,
Scottish Motor Neurone Disease Register,
Neurosciences Trials Unit
Department of Clinical Neurosciences,
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Crewe Road,
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