Adult onset motor neuron disease: worldwide mortality, incidence and distribution since 1950

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Abstract

This review examines the commonly held premise that, apart from the Western Pacific forms, motor neuron disease (MND), has a uniform worldwide distribution in space and time; the methodological problems in studies of MND incidence; and directions for future epidemiological research. MND is more common in men at all ages. Age-specific incidence rises steeply into the seventh decade but the incidence in the very elderly is uncertain. A rise in mortality from MND over recent decades has been demonstrated wherever this has been examined and may be real rather than due to improved case ascertainment. Comparison of incidence studies in different places is complicated by non-standardised methods of case ascertainment and diagnosis but there appear to be differences between well studied populations. In developed countries in the northern hemisphere there is a weak positive correlation between standardised, age-specific incidence and distance from the equator. There is now strong evidence for an environmental factor as the cause of the Western Pacific forms of MND. A number of clusters of sporadic MND have been reported from developed countries, but no single agent identified as responsible.

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The term MND is usually applied to a spectrum of motor system disorders which include both childhood and adult forms.^{1 2} Recent advances have been made in understanding those forms which have a genetic basis.^{3 4} Although a number of conditions have been identified which may mimic MND for the vast majority of patients with sporadic adult onset disease the cause is unknown.⁵⁻⁷

The possibility that environmental factors play a role in MND, particularly in the light of studies from the Western Pacific,⁸ is an appealing and recurring theme.⁹ This hypothesis, however, is not supported by the traditional teaching that the distribution of MND in developed countries is uniform and static.¹⁰⁻¹⁴ A recent editorial¹⁵ has challenged this view, suggesting that the distribution of MND in time and place may not be as uniform as previously believed. The tendency of many epidemiological reports to reiterate principles

expounded in the 1950s may reflect methodological or statistical difficulties in detecting true differences in the distribution of the disease within and between countries, and at different times. Clearly non-random distributions are important to identify as clues to potential environmental risks.

It has been ten years since the last review of the epidemiology of MND^{14*} and since then important additional observations have been made. A thorough reappraisal of the subject seems timely. Our aims are therefore to: 1) review all publications concerned with the mortality and incidence of adult 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 the Western Pacific forms with sporadic MND, and summarise the results of the intensive search for its cause; 5) identify standards for future epidemiological studies of MND and possible research directions.

Methods

This paper was prepared according to recent guidelines for medical reviews.^{16 17} 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 1950-65. 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,¹⁸⁻³² and incidence studies divided according to their methodology. Valid comparisons between studies can only be made if similar methodological

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Table 1a 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
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	19
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	20,21
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.	22
United States	1962–84	age/sex specific rates only	Rising rates, with substantial changes particularly amongst the elderly	23–25
Finland	1963–72	0.9	More common in women (0.87:1). Clustering in south east	26
France	1968–82	0.7–1.5	Steadily increasing rate especially for >55 years	27
United States	1968–78	0.9	Highest rates west of Mississippi	28
Scotland	1968–87	1.2–2.1	Significant rise with time.	*
Norway	1969–85	1.6–2.8(m) 1.2–1.8(f)	Substantial rises especially in men and elderly	29

Notes: Listed in ascending order of first year of data collection. Studies of individual USA states^{30–32} not included. For the USA and England and Wales notes incorporate more than one study. *R J Swingler, personal communication

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.^{33–43} 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.^{44–53} The third group were those in which incidence had been based, principally or exclusively on neurological centres, or where data were incomplete in review, or where the diagnosis was based on unverified hospital discharge statistics.^{54–63} There are a large number of clinical series of patients with MND but these were not analysed if a population denominator was unclear or unspecified.^{64–65}

Results

Mortality studies (tables 1a, 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.¹⁹ This may, however, 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 cause²⁰ while others have separated the two groups²⁵ or used rates based on wherever the diagnosis appears on the death certificate.²⁶ Comparison of rates for subgroups of MND (that is, 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.¹⁴ 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.²⁷ 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)”. 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). They may be adequate for following trends in total MND rates within countries.

Age specific mortality rates, where given, usually rise to a peak between 60 and 75 years, followed by a sharp decline, but this may simply reflect difficulties with diagnosis in the very elderly. In Sweden, for some birth cohorts followed up separately over time, the mortality increased continuously with age.²² Rates in males are consistently higher than in females, usually by about 1.5:1.

When international mortality figures were last reviewed in detail,¹⁹ a rise from 1952–60 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,²⁰ Sweden,²² USA,^{23–24} France,²⁶ Norway²⁹ and most recently, Scotland (R.J. Swingler, personal

Table 1b. A comparison of age-specific mortality rates per 100,000 between countries from table 1a from which this information can be derived.

	Country					
	England and Wales ²⁰		United States ²⁴		Finland ²⁷	
	Male	Female	Male	Female	Male	Female
Age Band	Age and sex specific rates:					
60–64 years	5.8	4.6	4.9	3.5	4.5	3.5
65–69 years	7.7	5.5	6.1	4.1	6.0	6.1
70–74 years	8.5	5.8	7.6	4.7	2.8	3.5
	Mortality rates (ages 60–74 years) standardised to the Scottish population:					
	7.5	5.3	6.4	4.1	4.2	4.4

Table 2a Retrospective incidence studies 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
Rochester, USA	1925–84	Mayo clinic computerised diagnostic index of Rochester residents	Y	Y	N	0.36	44	2.0 (1.4–2.7)		Updated previous study (1925–77), small but non significant increase in incidence	33,34
Israel	1959–74	National neurological disease register	Y	Y	Y	21.8	246	0.7 (0.6–0.8)		Increasing incidence in >60yrs	35,36
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)	37
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	38
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	39
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	40
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	41
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 this may be due to chance	42
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)	43

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; NW = north west; SW = south west.

communication) that mortality rates are continuing to rise with time (table 1a). In the USA overall ALS mortality increased 46% for men and 49% for women between 1977–86; the greatest increases in age specific mortality have occurred in the older age groups²⁴ but increases are also apparent in middle age groups.²³ 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 UK²⁰ or the physician/population ratio in the USA;²⁸ 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 (MRI) 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.

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 minimised) is presented in table 1b; these data are extracted from those published mortality studies in table 1a for which this was possible. Higher rates are observed in the UK compared with Finland and the USA.

Whether the incidence of MND can be studied adequately on the basis of mortality data alone is uncertain.²⁵ Although 70–90% of patients diagnosed with MND have this recorded on their death certificate,^{19 20 66 67} 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.¹⁹

Incidence studies (table 2a, b)

1) Crude rates

The best incidence studies are presented in table 2a together with the methods, crude

Table 2b. A comparison of age and sex specific incidence and age standardised incidence, 45–74 years, by country

Age band years	Country							
	Rochester* Male/Female	Israel* Male/Female	Sardinia Male/Female	Sweden 1 Male/Female	Sweden 2 Male/Female	Denmark* Male/Female	Finland Male/Female	Canada Male/Female
Age specific rate								
45–54	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
55–64	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
65–74	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 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 2a (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. 1. Varmland County, Sweden. 2. Northern Sweden. * see also figure 1.

Table 3 Syndromes which may mimic idiopathic MND

Physical factors:
Cervical spondylotic myeloradiculopathy ¹²⁷
Radiation myelopathy/plexopathy ¹²⁸
Following severe electric shock ¹²⁰
Metabolic/Endocrine disorders:
Hexosaminidase deficiency ^{129 130}
Adrenoleukodystrophy (adrenomyeloneuropathy) ¹³¹
Hyperinsulin neuropathy ¹³²
Thyrotoxicosis ¹³³ or MND precipitated by thyrotoxicosis ¹³⁴
Phosphate deficiency/hyperparathyroidism ¹³⁵
Related to malignancy or disturbed immunity:
Meningeal metastases with radiculopathy/cranial neuropathy
Multifocal neuropathy and antibodies to gangliosides ^{136 137}
MND associated with plasma cell dyscrasias ¹³⁸
Subacute motor neuropathy ALS?, with lymphoma ¹³⁹
Other paraneoplastic? ^{140 142}
Foramen magnum tumours ¹⁴³
Infections:
Post-polio syndrome ^{144 145}
Human immunodeficiency virus; mononeuritis/myelopathy ^{146 147}
Syphilitic amyotrophic meningomyelitis ^{148 149}
Cysticercosis ¹⁵⁰
HTLV-I ¹⁵¹
Toxins/Drugs:
Cranial irradiation and intrathecal chemotherapy ¹⁵²
Lead, ¹⁵³ mercury, ¹⁵⁴ manganese, ^{155 156} aluminium ¹⁵⁷
Lathyrus sativus: Neurolathyrism (Africa/Asia) ¹⁵⁸
Domoic acid (algae ingestion from mussels) ¹⁵⁹
Pesticide exposure (pyrethrin and chlordane based) ¹⁶⁰
Amitriptyline overdose? ¹⁶¹
Following anaphylactic reactions? ¹⁶²
Vascular:
Rheumatoid arthritis with arteritis and neuropathy ¹⁶³
Ischaemia of the anterior horns of the spinal cord ¹⁶⁴
Bilateral cerebral ischaemia (bulbar palsy)
Other primarily neurological diseases or MND associated with other disease:
Benign fasciculations and cramps ¹⁶⁵
Syringomyelia ¹⁶⁶
Cyst of the conus medullaris ¹⁶⁷
Amyotrophy in multisystem disease ^{168 170}
MND with dementia of various types ¹⁷¹
Monomelic atrophy ¹⁷²
X-linked bulbospinal atrophy ¹⁷³

Note: A differential diagnosis of the idiopathic anterior horn cell disorders is not included.

incidence with calculated 95% confidence intervals,⁶⁸ 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 2a compared with all other studies (difference = 0.64/100 000/year 95% CI 0.15–1.13) and when studies in table 2a were compared with those which relied on single hospital case ascertainment (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,³⁶ based on a comprehensive survey of Jews as part of a national neurological disease register, and in Sardinia,³⁷ which used five separate sources of case finding. The claim of a low incidence in Mexico⁴⁶ 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 1950.¹⁸ 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,³⁴ show a steady rise to a peak, usually between 60 and 75 years with a sharp decline after this (fig 1). 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 difference⁴⁵ or even a female predominance.²⁷ Incidence rates with time, although reported as increasing, are unreliable in studies with small numbers.³⁴ In Israel this increase was considered to be due to causes other than improved case ascertainment.³⁵

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^{34 35 40} are plotted in the figure 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 2b), the differences between populations are also apparent. When age stan-

Figure 1 Age specific incidence of adult onset MND (male and female) in three countries selected from table 2a to show the range.

Figure 2 Correlation of age standardised incidence of MND with mean degrees north latitude (studies from table 2b).

dardised rates (over 45–74 years) for males and females combined from those studies in table 2a (excluding NW England where insufficient data for this calculation are provided) are plotted against their degrees north latitude (fig 2), there is a positive correlation (p value for the slope 0.05). The cause of this relationship is uncertain.

3) Clusters

There are reports of conjugal^{69 70} and other nonconsanguineous clusters of MND outside the Western Pacific, with rates much higher than would be expected by chance. Examples include people who work^{71 72} or live^{73–75} in close proximity; play in the same sports team;⁷⁶ have been war evacuees;⁷⁷ share an environmental peculiarity such as high soil selenium;⁷⁸ or a common occupational exposure such as leather⁷⁹ or textile⁸⁰ workers. Toxins from freshly caught fish were implicated in a cluster in Wisconsin.⁸¹ In one example,⁷⁴ all those affected were of Ashkenazi Jewish extraction. 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.^{44 82} Other studies show a significant⁸³ or non-significant^{20 27 28 43} uneven distribution but most studies that have examined distribution within a population have demonstrated geographical uniformity. It may be difficult to know whether small clusters are purely due to chance, particularly when the overall population incidence is not known.⁸⁴ A recent publication from north west England⁴² 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.⁸⁵ 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 little support for viral infection from laboratory studies.⁸⁶ Although late neurological deterioration after poliomyelitis may resemble MND,⁸⁷ the relationship between previous poliomyelitis and sporadic MND remains a matter of debate. Table 3 gives a list of other syndromes which may mimic idiopathic MND.

4) Western Pacific forms of MND

The Western Pacific clusters are found in: 1) Guam, the southernmost and largest of the Mariana islands, where the Chamorro Indians are affected;^{88–90} 2) the Kii peninsula of Japan¹⁴ and 3) the Auyu and Jakai people of West New Guinea.⁹¹ 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. The pathology of both 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^{92 93} in MND/ALS. This difference suggests that the sporadic and Western Pacific forms of MND may have a different aetiology. Discovery of the cause of these high incidence foci might have widespread repercussions for the understanding of sporadic MND.

The evidence for an environmental cause, or at least a genetically determined host response to an exogenous factor,^{82 94–96} is now very strong. The disease is confined to a particular area of the Mariana islands despite a shared original migration pattern;⁹⁷ there is no evidence for Mendelian inheritance⁹⁴ and the disease is of no higher incidence in offspring of affected than non affected Guamanians. The incidence of MND/ALS on Guam has declined by at least 50% from rates that were 50–100 times greater than developed countries in 1950–69^{98–101} although the accuracy of some reports has recently been questioned.¹⁰² Age of onset may be increasing.⁹³ MND does not develop among those who have had a brief exposure to the implicated environment¹⁰³ and the latency for the development of MND, as judged by studies of Chamorro migrants to the USA, is long^{104 105} implying that an early exposure may be crucial, or any proposed environmental factor must be slow acting, or the ageing factor is interacting with an earlier environmental agent. Attempts to transmit the disease have failed.¹⁰⁶

The putative environmental cause is unknown. If the incidence is declining then this coincides with adoption of a lifestyle closer to Western standards and suggests that environmental 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.¹⁰⁷ A degenerative motor system disease with similarities to MND has been produced in primates by feeding the cycad derived toxin—BMAA (α -amino- β -methyl-aminopropionic acid)^{108 109} but motor neuron pathology can also be induced by other experimental methods.¹¹⁰ Doses required for these experiments are high but washing the seeds, as is the custom, removes all but minute traces of BMAA,¹¹¹ probably to such low levels that toxicity is unlikely.¹¹² Gadjusek and others suggest an alternative mechanism.^{102 113 114} 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.¹¹⁵ The interested reader is referred elsewhere for details of this extensive debate.¹¹⁶

Conclusions

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. 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 a rising trend 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. 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. There may, however, 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;⁴² prospectively designed studies; and attention to life events and environmental exposures which may be remote from the development of MND.

Criteria for the ideal MND incidence study

From this review we believe 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.¹¹⁷ The terms used by authors under the rubric of MND often vary in their meaning. ALS, PBP and PMA, the usually accepted principal clinical subtypes in adults, are almost certainly varieties of a single disease with the common pathological feature of anterior horn cell loss and variable pyramidal tract involvement. The distribution of pathological changes does not necessarily correlate with clinical features even in well studied cases.^{118 119} Some authors even separate MND and ALS as different disorders.¹²⁰ There is increasing evidence, with the widespread use of MRI, that primary lateral sclerosis (PLS), a numerically small group, and much debated entity, is part of the spectrum of MND but with exclusively upper motor neuron signs.^{121 122} The term ALS, favoured in North America, generally refers to MND with upper and lower motor neuron signs with or without bulbar features, although ALS literally implies disease caused by sclerosis of *spinal* lateral tracts and anterior horns. A practical consensus statement for clinical and epidemiological studies is required which deals with the problems of defining the clinical limits of MND, reducing interobserver error in the interpretation of physical signs (for example when is a retained reflex in a wasted corresponding myotome an upper motor neuron 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 brief, we believe definite cases should exhibit a *combination* of lower motor neuron signs (clinically or by electromyography), and upper motor neuron signs, not due to longstanding neurological disease, which involve the brainstem and one or more spinal regions (cervical, thoracic, lumbosacral). In addition there should be a progressively deteriorating course and no abnormal sensory *signs* (including visual abnormalities); sphincteric disturbance; Parkinsonism; dementia and causes of MND mimic syndromes which might be confused with idiopathic disease (table 3). Bulbar

involvement removes the possibility of multiple level spinal spondylotic disease, the most commonly confused entity. Probable MND (spinal ALS, PBP, PMA and PLS) should be included in the calculation of incidence but defined separately.

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, we agree with others¹²³ that studies from specialised centres^{124 125} are likely to be biased in favour of younger patients. The elderly, in whom age specific rates are high, but the 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, hospital discharge data; primary care physicians and 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. Misleading rates for an open ended upper age band may be the result of changes in population age structure rather than true changes in disease incidence. Information should therefore 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 although we are now attempting such a study in Scotland.¹²⁶

* A further review has been published since the preparation of this manuscript (Kurtze JF. Risk factors in amyotrophic lateral sclerosis. *Adv Neurol* 1991;56:245-70).

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Neurological stamp

Edmund Halley (1656-1742)

Edmund Halley, best known for his contributions to astronomy and particularly the calculation of the orbit of a comet, later named after him, was one of the first medical statisticians. In 1693, more than a century after the first modern life insurance policy (1583) was issued in England, he created a true actuarial table when he published the mortality tables for the city of Breslau, "to ascertain the prices of annuities upon lives." This was one of the first attempts to relate mortality and age in a population and influenced the further development of such tables in life insurance.

He was a friend of Isaac Newton and discussed with him the law of force under which planets move in elliptical orbits with the sun in one focus. As a result he persuaded Newton to prepare and publish his masterpiece *Principia*, which Halley himself financed. A man of remarkable versatility, working to the threshold of extreme old age he also wrote poetry, propounded a theory to account for changes in the earth's magnetism, was the first to use the barometer to measure heights, made important contributions to gunnery and ballistics, improved the diving bell and gave a critical discussion of the time and landing of Julius Caesar in Britain.

This stamp of the British Antarctic Territory was one of many issued in 1986 commemorating the appearance of Halley's Comet. (Stanley Gibbons 147, Scott 129).

L F HAAS