1

Epidemiological considerations

Demographics

The demographic, epidemiological and electrophysiological data described in this and subsequent chapters are based on 664 patients with definite or probable amyotrophic lateral sclerosis (ALS) as defined by the El Escorial criteria (Brooks, 1994). All of the patients were examined by one of the authors (AE) between 1984 and 1996 (Table 1.1). The data are representative of typical populations of ALS patients as reported previously (Brooks, 1996). It is well established that the age-adjusted incidence of the neurodegenerative disorders (Alzheimer's disease (AD), Parkinson's disease (PD) and ALS) rises sharply with ageing and, as shown in Figure 1.1, this is true for our own data.

Gender

The overall male:female ratio of our cohort was 1.33:1. Epidemiological studies of sporadic ALS unanimously agree that the disease is more frequent in men, although the male:female ratios quoted are variable. In older patients, particularly those over 65 years, the male:female ratio begins to approach 1:1 (Chancellor *et al.*, 1993a). Based on our own data, there is a significant negative correlation between age and the male:female ratio of ALS. This is shown in Figure 1.2, and it probably reflects the greater longevity enjoyed by women. However, this benefit is limited because of an increased risk of developing ALS. In younger patients (those less than 40 years) there is a much higher frequency of ALS amongst young men (Christensen, Hojer-Pedersen and Jensen, 1990; Strong, Hudson and Alvord, 1991; Eisen *et al.*, 1993c). But, as is shown in Figure 1.2, there is a significant correlation between age and the male:female ratio of ALS, and male predominance of ALS declines with each decade.

Table 1.1. *Demographics of patients seen in the British Columbia ALS Clinic between 1984 and 1996*

	All	Men	Women
Number	664	379	285
Mean age (years) ± SD	60.6 ± 13.65	59.5 ± 13.9	61.65 ± 12.9
Minimum age (years)	14	14	17
Maximum age (years)	89	89	89
Number with spinal onset (%)	445 (67)	283 (63.6)	162 (36.4)
Number with bulbar onset (%)	219 (33)	99 (45.2)	120 (54.8)
Mean duration (years)*	3.6 ± 3.1	4.0 ± 3.8	3.2 ± 2.5

* Based on 414 patients who were followed to time of death.

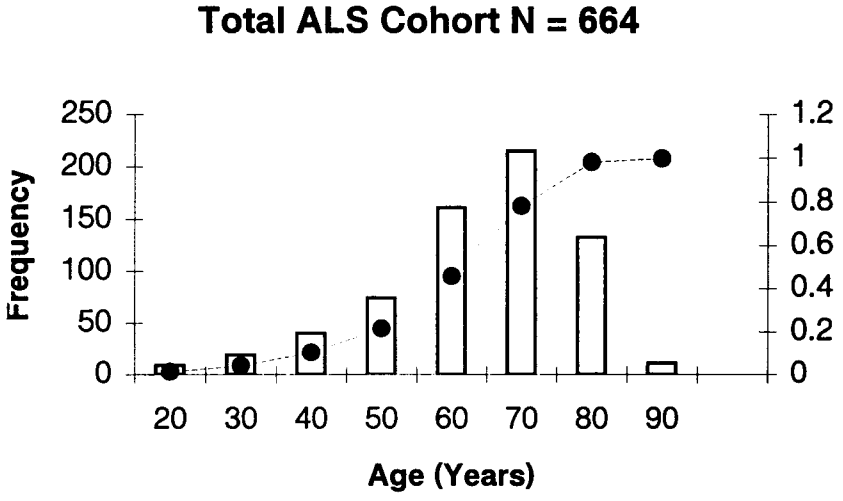

Figure 1.1. Frequency distribution by age of 664 patients with ALS. The raw data suggest that there is a decrease in frequency of ALS after about age 65 years. However, cumulative analysis, shown by the interrupted line, shows that amongst patients who do develop ALS, the frequency is highest in the elderly. Under 45 years, the chances of developing ALS are small but, as indicated, thereafter there is a steep rise in the frequency distribution curve. This might imply that the effects of neuronal ageing, which increases the risk of developing ALS, start in the fourth decade.

Others have made the same observation (Chancellor *et al.*, 1993a). Of our total patient population 46 (7 per cent) were aged 75 years or older when the diagnosis of ALS was made, and 28 of these were women, so that midway through the seventh decade of life the male : female ratio in favour

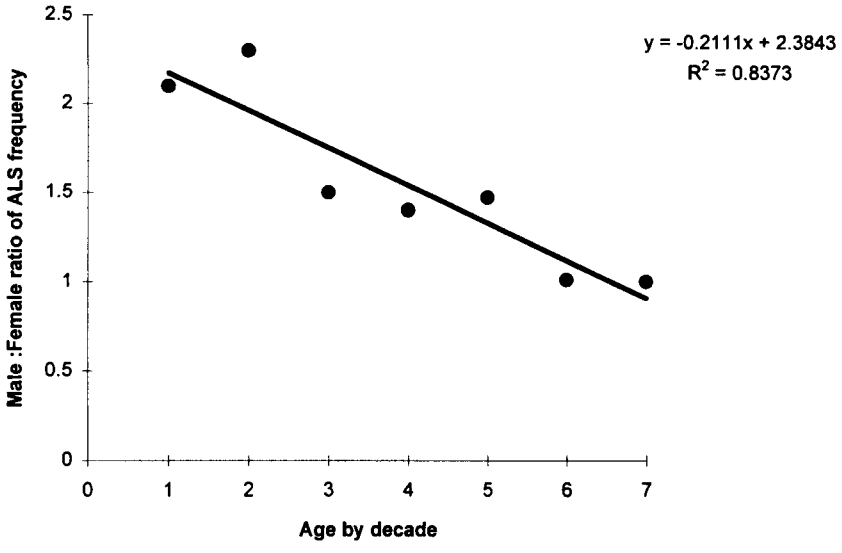

Figure 1.2. Relationship between age (x-axis) shown by decade and male:female ratio of ALS (y-axis). There is a linear decline in the ratio which in the young favours men, but by age 70 years there is an equal chance for men and women to develop ALS. In the old old (greater than 85 years) the frequency of ALS is higher in women.

of men had reversed (M:F = 0.6:1). The higher incidence of ALS in younger men is not readily explained. It may partly relate to the rate of decline in the serum concentrations of the neurosteroid dehydroepiandrosterone (DHEA). Serum concentrations of DHEAS, the sulphate of DHEA, normally declines with age. As shown in Figure 1.3, men with ALS have much lower age-predicted serum DHEAS concentrations than do women (Eisen, Pearmain and Stewart, 1995). Figure 1.3 shows the individual DHEAS concentrations expressed as a percentage of age-predicted normal values. We have measured serum DHEAS in 56 men and 35 women with ALS. In 63.2 per cent of men and 30.6 per cent of women, the DHEAS serum concentrations were below age-predicted values. This gives a male:female ratio of abnormal concentrations of about 2:1, which is similar to the usually quoted men:women ratio for ALS. The finding suggests that the greater frequency of lowered DHEAS concentrations in men plays a role in their greater risk of developing ALS. How this may happen is not known, but DHEA is discussed as a possible therapy for ALS in Chapter 7.

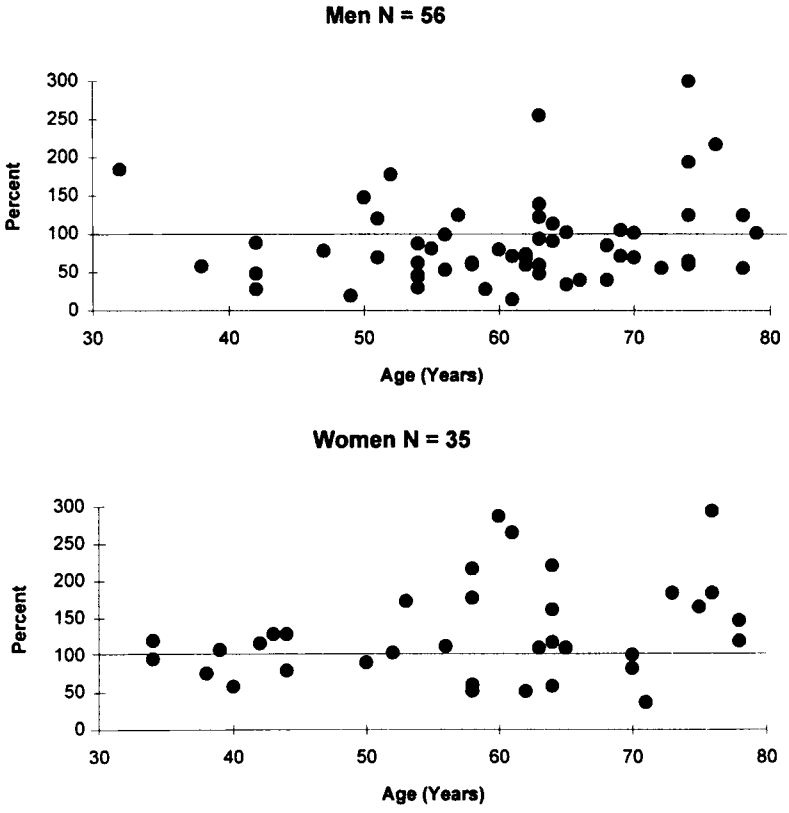

Figure 1.3. Scatterplot relating dehydroepiandrosterone sulphate (DHEAS) serum concentrations (ml/l) and patient's age. The values are expressed as a percentage of normal for the age. This is indicated by the solid line at 100 per cent. The serum DHEAS is frequently reduced in men (top scatterplot) but in only about a third of women.

Age

The frequency distribution of age of ALS onset for all patients is shown in Figure 1.4. The same figure also shows the frequency distribution for men and women separately. The peak incidence for men occurred over a 15-year period between 55 and 70 years but for women there was a more steadily increasing incidence starting at about 50 years of age and reaching a peak at about 70 years. The gender difference can be explained by the larger number of younger men with ALS and the greater mean life-span of women. There are very few firm data regarding ALS in the elderly (aged 75

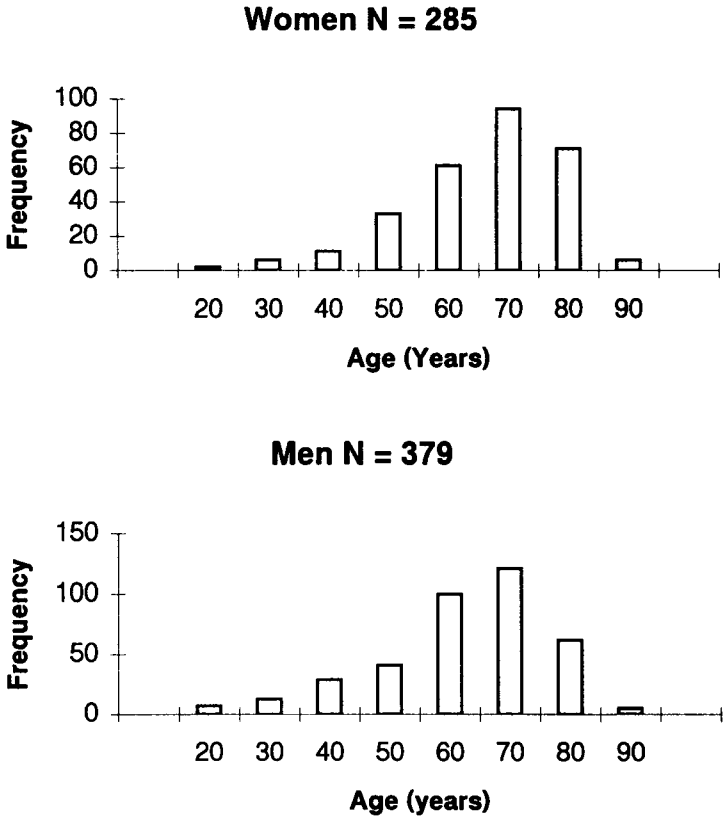

Figure 1.4. Histograms showing the frequency distribution by age for women and men with ALS. Overall, the peak age at which ALS developed in our cohort was 65–70 years. For women there is a steady rise in the frequency up to this age. For men the age range at which ALS develops is spread over the sixth and seventh decades.

years and over), but the apparent decrease in the incidence of ALS after age 70 years probably reflects a rapidly rising mortality rate after this age from other diseases that compete with the probability of developing ALS. Also, progressive loss of strength and difficulty in walking in elderly subjects who are frequently frail may be easily discarded as simply being due to 'old age' and the possibility of ALS is overlooked. This too would erroneously lower incidence of the disease in the elderly.

ALS commencing under the age of 40–45 years is well recognized but unusual. The incidence of young sporadic ALS may be increasing, but present data are insufficient to make a firm statement on this point. Eighty-three of our patients (52 men and 31 women) were aged 45 years

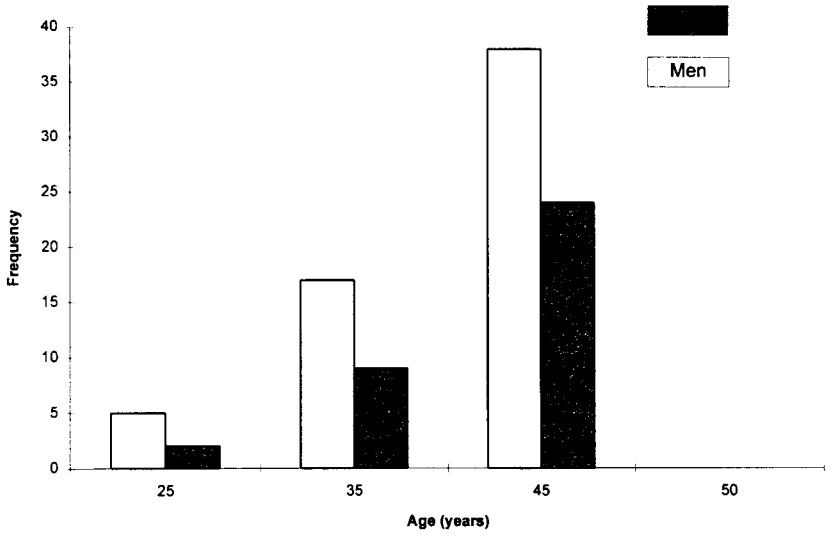

Figure 1.5. Young-onset ALS. This is defined as an onset at, or less than, 45 years of age. As shown in the bar chart, the frequency of young-onset disease in men is much greater than in women.

or younger (Fig. 1.5). Why young men develop ALS so much more frequently than young women is not known. Most young-onset disease turns out to be typical sporadic ALS, but lower motoneuron features often predominate for many months. During this period there are several disorders, mimicking ALS, which are commoner in younger patients. Progressive muscular atrophy (PMA), Kennedy's syndrome (X-linked progressive bulbar spinal muscular atrophy) and Ben Hamida syndrome, better known as juvenile ALS, need to be considered. Ben Hamida syndrome is inherited as an autosomal recessive trait and progresses very slowly. However, a specific genetic defect has not been identified and it is probably better to refer to these disorders as Ben Hamida variants (Ben Hamida, Hentati and Ben Hamida, 1990). They seem to be largely restricted to Tunisia, Turkey and possibly other mid-Eastern countries which border the Mediterranean Sea. Three clinical subgroups have been identified. Group 1 is characterized by upper limb amyotrophy and spastic paraplegia, combining upper and lower motoneuron deficits. There may also be bulbar involvement. This group most closely resembles classic sporadic ALS. Group 2 combines hereditary spastic paraplegia with peroneal atrophy. Group 3 is essentially primary lateral sclerosis with minimal lower motoneuron features involving the hand or peroneal

musculature. These and other disorders that resemble ALS are discussed further in Chapter 2.

Increasing mortality

The incidence of a disease refers to the number of new cases in a population over a given time, which for ALS is usually expressed as the number of new cases per 100 000 population per year. Globally, the incidence of ALS varies from about 0.3 to over 2 per 100 000 population. Incidence rates are used to establish the prevalence of ALS, which is defined as the total number of patients per 100 000 population. The prevalence of ALS varies from about 2.5 to 4.5 times that of its incidence (a low of 0.75–9 per 100 000 population). Prevalance rates are more variable than incidence rates because they are dependent upon disease duration, which varies with the level of care and other factors. For example, survival is likely to be prolonged by early implementation of bimodal passive airway pressure (BIPAP) and percutaneous endoscopically placed gastrostomy (PEG) (Hopkins, Tatarian and Pianta, 1996; Kasarskis and Neville, 1996). Prevalence will be increased in the future as 'palliative' therapies such as riluzole are developed (Brooks, 1996). Mortality rates are defined as the number of deaths annually per 100 000 population, and these are increasing for ALS as the population ages (Lillienfeld *et al.*, 1989; Kurtzke, 1991; Chancellor and Warlow, 1992; Briani *et al.*, 1996; Brooks, 1996). There is a close association between increased life expectancy and increasing mortality from ALS (Neilson *et al.*, 1993; Brooks, 1996). Life expectancy has risen, and continues to rise. It has been estimated that by the year 2021, deaths from ALS will have increased by approximately 20 per cent (Neilson *et al.*, 1993). By the year 2000, the USA will have over 5 million people who are 85 years and older and more than 10 million people who are over the age of 65 years. Based upon available data from 18 different countries, between 1951 to 1958, the mean worldwide age-adjusted death rate from ALS was 0.76 ± 0.28 per 100 000 population. For the years 1966–1971, this had doubled to 1.37 ± 0.41 per 100 000 population ($p < 0.0001$). Between 1985 and 1992, the worldwide mortality from ALS exceeded 2 per 100 000 population and within the last five years is approaching 3 per 100 000 (Brooks, 1996).

Incidence rates have also shown similar significant increases. Before 1975, the incidence rate of ALS per 100 000 population was 0.99 ± 0.41, since when it has steadily risen to 1.3 ± 0.63 ($p < 0.01$). Mortality rates

from ALS are a reasonable approximation of its incidence, and increasing mortality rates from ALS have been interpreted to indicate that there has been an increase in the incidence of ALS (Chancellor *et al.*, 1993b; Neilson *et al.*, 1993). The accuracy of mortality data is dependent on the vagaries of death certificates and definition of disease. As a group of disorders becomes better clarified so that they can be separated into definitive entities, the International Classification of Diseases (ICD) also changes. Prior to 1969, ALS was not separated from other sporadic or familial motoneuron diseases (MND). However, non-ALS MND patients comprise only a small fraction of the total number of MND cases so that their inclusion is unlikely to have significantly biased the results. If anything, the incidence would have been overestimated. Recent evidence, from the UK, indicates that the diagnostic accuracy of ALS based upon death certificates has a positive predictive value of 90 per cent, with a false-negative rate of 6 per cent (Chancellor *et al.*, 1993b). Similar studies regarding the diagnostic accurracy of ALS based on death certificates need to be done in North America to confirm the same high predictive value in that and other continents. On the other hand, coded hospital discharge data are inaccurate for ascertaining a diagnosis of ALS and in their present form cannot be used reliably to measure disease incidence. Possible explanations for the recent increase in the incidence of ALS are (1) better case ascertainment, (2) improved diagnosis, (3) increasing longevity, and (4) survival of a susceptible subpopulation who survived other potentially fatal diseases earlier in life, and who are now at risk for developing ALS.

It is unlikely that improved diagnosis or better case ascertainment can fully explain the increased incidence of ALS in the developed countries, but this may be a factor in underdeveloped countries. Although most non-neurologists may only see one or two cases of ALS during their careers, few patients with ALS in developed countries fail to reach the attention of a neurologist during the course of their disease. The diagnosis remains dependent upon a clinical constellation, and this has not substantially changed since Charcot's time. The El Escorial diagnostic criteria are detailed in Chapter 2 and should help exclude diseases mimicking ALS that could falsely increase the recorded disease incidence (Brooks, 1994).

Laboratory aids other than electromyography have not helped in the confirmation of ALS. Improved diagnostic imaging has been helpful in revealing structural lesions in patients who appear to have ALS. These diagnostic techniques would tend to decrease the apparent incidence of ALS.

Geographic distribution

The incidence rates of ALS vary in different places. Although these figures are confounded by non-standardized case ascertainment and diagnosis, they suggest a correlation between age-specific incidence of ALS and distance from the Equator (Chancellor and Warlow, 1992). If one excludes areas within the South Pacific in which there are high, albeit declining, incidences of ALS, it is widely believed that the incidence of ALS throughout the rest of the world is uniform and the reported variations are thought to reflect inaccuracies in ascertainment. However, Chancellor and Warlow (1992) reviewed the incidence rates for ALS from nine surveys which were judged to have nearly complete case ascertainment. The crude annual incidence rates ranged from a low of 0.6 per 100 000 to a high of 2.6 per 100 000. When the incidence rates were standardized to the Scottish population, the differences were statistically significant, suggesting a true geographic variation. Other studies have also shown there to be a relationship between the incidence of ALS and latitude (Eisen and Calne, 1992; McGuire *et al.*, 1996; Brooks, 1996). Like multiple sclerosis, there is a significant positive correlation between incidence of ALS and latitude degrees north ($p < 0.001$) (Fig. 1.6). These data might imply a transmittable agent which is more readily expressed in northern climates. It could also be that populations living in northern latitudes have a lifestyle that renders them more susceptible to a toxin(s) which may be of importance in developing ALS. The issue of geographic variation in ALS incidence is worthy of further investigation. If such a relationship can be firmly established, it would support an environmental role in ALS, or a role of different geographic racial groups, some with a greater abundance of susceptibility genes for ALS.

Disease duration, prognosis and life expectancy

A question that is frequently asked by newly diagnosed ALS patients and their families concerns the length of their expected survival. Because ALS has such a variable progression, this question is difficult to answer for any given individual when initially seen. Disability scores, which include manual muscle testing as well as computerized measures of isometric muscle strength (Tufts Quantitative Neuromuscular Exam, TQNE), can be used to assess the rate of disease progression. These assessments indicate that over much of its course the clinical decline of ALS is linear and it is possible to predict an individual's rate of progression by

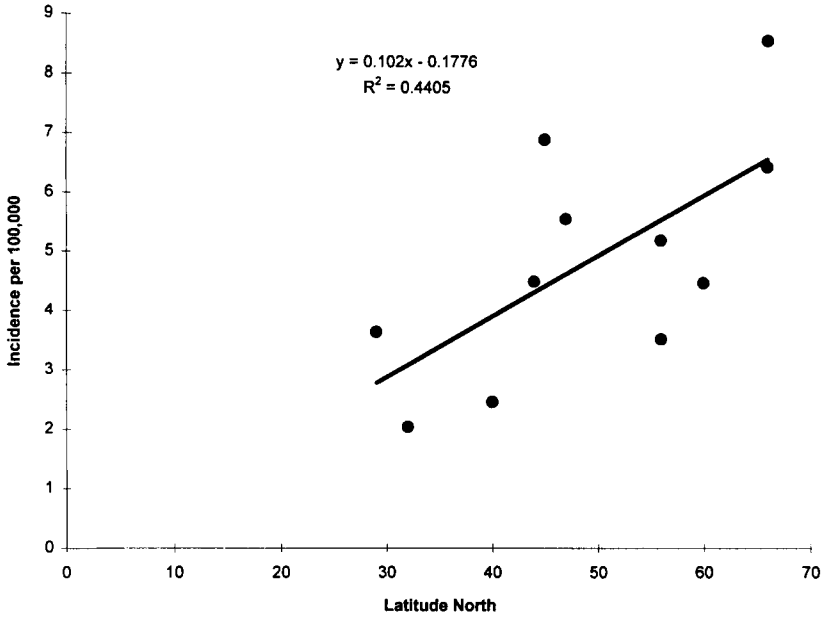

Figure 1.6. Relationship between the incidence of ALS per 100 000 population and the latitude in degrees north. The data are derived from epidemiological studies in the literature that were considered to have near-complete ascertainment. The incidence of ALS is significantly higher in northern climes. The relationship is given by:

$$\text{incidence} = \text{latitude} \times 0.102 - 0.1776 \; (r^2 = 0.4404, \; p < 0.001).$$

calculation of the regression slope obtained from data points using TQNE and other scales. However, to construct and calculate the slope of the regression line which is used to determine the length of survival of an individual, two or more data points must be acquired over several months. This does not allow one to comment on an individual's anticipated survival at the first visit. Appel and colleagues (1987) developed a quantitative measure of clinical function, the Appel Rating Scale. This is based upon the patient's swallowing ability, speech, respiratory function and muscle strength and function. For a given patient, this score has been shown to increase linearly with time, but the rate of progression varies twenty-fold between different patients. However, a change in the score of the Appel Rating Scale of greater than 22 points over 6 months is predictive of death within a year. Jablecki, Berry and Leach (1989) have devised a simple composite predictive score based upon the patient's age