

7 NEURODEGENERATIVE DISORDERS

A number of studies have examined associations between exposure to electromagnetic fields and Alzheimer's disease, motor neuron disease and Parkinson's disease. These diseases may be classed as neurodegenerative diseases as all involve the death of specific neurons. Although their aetiology seems different (Savitz, 1998; Savitz, Loomis & Tse, 1998), a part of the pathogenic mechanisms may be common. Most investigators examine these diseases separately. In relation to electromagnetic fields, amyotrophic lateral sclerosis (ALS) has been studied most often.

Radical stress, caused by the production of reactive oxygen species (ROS) and other radical species such as reactive nitrogen species (RNS), is thought to be a critical factor in the modest neuronal degeneration that occurs with ageing. It also seems important in the aetiology of Parkinson's disease and ALS and may play a part in Alzheimer's disease (Felician & Sandson, 1999). Superoxide radicals, hydrogen peroxide (H_2O_2) and hydroxyl radicals are oxygen-centered reactive species (Coyle & Puttfarcken, 1993) that have been implicated in several neurotoxic disorders (Liu et al., 1994). They are produced by many normal biochemical reactions, but their concentrations are kept in a harmless range by potent protective mechanisms (Makar et al., 1994). Increased free radical concentrations, resulting from either increased production or decreased detoxification, can cause oxidative damage to various cellular components, particularly mitochondria, ultimately leading to cell death by apoptosis (Bogdanov et al., 1998).

Several experimental investigations have examined the effect of ELF electromagnetic fields on calcium exchange in nervous tissue and other direct effects on nerve tissue function. A variety of effects of ELF exposure of potential relevance to neurodegenerative disease have previously been reported (Lacy-Hulbert, Metcalfe & Hesketh, 1998). These include small increases (Blackman et al., 1982; 1985), but also decreases (Bawin & Adey, 1976), in Ca^{2+} efflux from brain tissue, *in vivo* and *in vitro*, inhibition of outgrowth of neurites from cultured neurons (Blackman, Benane & House, 1993), and an increase in superoxide production from neutrophils (Roy et al., 1995).

It is conceivable that prolonged exposure to ELF fields could alter Ca^{2+} levels in neurons and thus induce oxidative stress through its influence on mitochondrial metabolism. On the other hand, the biological evidence, particularly concerning the response of neurons, is limited.

Neurons can be directly activated by strong electrical currents (see chapter 5, especially section 5.2.2). Some evidence, discussed in sections 5.1 and 5.2, suggests that ELF exposure might modulate ongoing electrical activity in the CNS, although studies on hormone and neurotransmitter levels have generally reported no effect or only minor influences of ELF exposure (see section 5.4.4). While these effects are unlikely to be damaging, especially in the short term, there is the possibility that prolonged exposure to ELF fields could synchronize certain neurons of high sensitivity (perhaps

especially the large motor neurons), possibly leading to voltage-activated Ca^{2+} entry, which could have a damaging effect on the neurons. There might also be an accumulation of extracellular glutamate relative to GABA (gamma-aminobutyric acid), which could have excitotoxic effects on surrounding neurons.

It is possible that even modest cellular effects of ELF fields may exacerbate pathological changes in otherwise compromised neurons. For instance, intercellular transfer of metabolites and ions via gap junctions has been shown to be affected by exposure to 0.8 mT (but not 0.05 mT) magnetic fields (Li et al., 1999).

In contrast to the effect of ELF it has been suggested that exposure to electric shocks may increase the risk for ALS (Haynal & Regli, 1964). Electric currents may damage brain tissue by disturbing the circulation. It has also been speculated that severe electric shocks cause a massive synchronized discharge of neurons, which might release sufficient glutamate to precipitate toxic changes, as outlined above (AGNIR, 2001a). No mechanism has been identified, however, that could provide a coherent explanation of the observed association between exposure to ELF or electric shocks and these neurodegenerative diseases.

7.1 Alzheimer's disease

7.1.1 Pathology

Alzheimer's disease (AD) is characterized clinically by progressive loss of memory and other cognitive abilities (e.g. language, attention). Its onset is thought to be heralded by a phase of mild cognitive impairment in which cognition is not normal but not severe enough to warrant a diagnosis of dementia. The exact duration of mild cognitive impairment is unclear, but is likely to last at least a few years. Most data on disease duration come from studies of prevalent AD which suggest that disease duration may average seven or more years, although a recent study estimated that disease duration may actually be closer to 3½ years from the onset of the manifestations of dementia. Many persons with AD also develop motor, behavioral, and affective disturbances. In particular, parkinsonian signs, hallucinations delusions, and depressive symptoms are present in half or more of persons with the disease. Data also suggest that these signs are related to increased risk of death and to rate of cognitive decline. Cholinesterase inhibitor therapy, the mainstay of symptomatic treatment, is not known to definitively affect disease course or outcomes.

Although oxidative stress may be involved in the sporadic forms of AD, the evidence is less compelling. Indices of oxidative damage are significantly increased compared with those in age-matched controls (Felician & Sandson, 1999). Inflammatory and immune responses have also been implicated, although it is difficult to know whether these are secondary to the other pathological changes. Cellular responses to increased oxidative stress

appear to be a mechanism that contributes to the varied cytopathology of AD.

Inflammation in the CNS often occurs in both Parkinson's and Alzheimer's diseases and chronic neurological disorders such as brain trauma, ischemic stroke (for a review, see Rothwell, 1997). It has long been known that the extent of inflammatory responses in the CNS is less than observed in the periphery (for review, see Lotan & Schwartz, 1994; Perry, Brown & Gordon, 1987). A cascade of inflammatory responses is orchestrated by microglia (resident macrophages) and astrocytes in the CNS.

The fact that microglia become reactive in the aging brain as the natural death of neurons occurs (Sloane et al., 1999) suggests that interactions between neurons and glia play an important role in controlling inflammatory responses in the CNS. Chang et al. (2001) showed that activation of microglia in the ageing brain was linked to the death of neurons.

7.1.2 Epidemiology

Sobel et al. (1995) reported the results of three small case-control studies of AD, two of which had been carried out in Finland and one in the USA. Occupational histories for demented subjects were obtained from the most knowledgeable surrogates and, for non-demented controls, by direct interview. The individuals' primary lifetime occupations were classed blindly by an industrial hygienist as causing low, medium, or high (or medium to high) exposure on the basis of previous knowledge. Dressmakers, seamstresses, and tailors had not previously been classified as occupations with high EMF exposure. The classification of medium to high exposure was confirmed by measurement of the fields produced by four industrial and two home sewing machines.

The first Finnish series consisted in 53 men and women with sporadic AD and 70 with sporadic vascular dementia; the second of 198 men and women admitted to a geriatric institution diagnosed as having AD (sporadic and familial combined) and 298 controls selected in order from the alphabetic listing of patients admitted to the long stay internal medicine wards of the Koskela Hospital in 1978, excluding those with a diagnosis of dementia or mental retardation, psychosis, depression, general or brain arteriosclerosis, Parkinsonism, or multiple sclerosis. The third series consisted in 136 patients admitted to the University of Southern California between 1984 and 1993 with sporadic AD and 106 neuropsychologically normal individuals without any known history of dementia or memory problems in first degree relatives in the communities from which the Alzheimer's patients came. The results are summarized in Table 53. The odds ratio for probable medium to high exposure compared to low for the three series combined was 3.0 and was hardly altered (2.9 with 95% CI 1.6–5.4) by adjustment for education and social class and for age at onset, age at examination, and sex. [In this study the newly designated category of dressmakers, seamstresses, and tailors accounted for the greater part of the excess risk from medium to high exposure occupations (23 out of 36 individuals in the AD series and 8 out of

16 in the controls). The limitations of the study are use of different control groups in the three series, particularly patients with vascular dementia who may in fact have had AD; obtaining job histories by questionnaires; lack of validation of exposure of the study population; the measure of high exposures among seamstresses was not confirmed in a later and more extensive study in the US (Kelsh et al., 2003), dependence on proxy respondents for job histories of cases but not for some of the control.]

A further case-control study, based on patients attending an Alzheimer's Disease Treatment & Diagnostic Center in Downey, California, was reported by Sobel et al. (1996) in the following year and may be regarded as constituting a test of the hypothesis formed in the first report. Patients at the Center had been included in several previous studies and information about their primary occupation throughout life was extracted from existing forms. Comparisons were made between 326 patients with probable or definite AD and 152 control patients with cognitive impairment or dementia due to other causes, excluding vascular dementia. These were classified in 20 groups, the largest being head trauma (26) and alcohol abuse (21). These results are also summarized in Table 53. The odds ratio for a primary occupation that caused medium or high exposure to EMF, was 3.93 with 95% CI 1.45–10.56. [Again seamstresses, dressmakers, and tailors combined, in this study, with sewing factory workers and clothing cutters contributed a relatively high proportion of the cases with medium or high exposure. The odds ratios in the study were higher for men than for women, contrary to what had been observed in the previous study. The limitations of this study were that the cases included 24 patients with unclear diagnoses; the controls were not matched by age or gender to the cases and were from the same clinic, which specialized in AD; job histories were obtained by questionnaire; and the exposure of the study population was not validated. The different designs used in this study and in the three other studies of Sobel et al. lead to a diverse collection of relative risks and potential biases].

Table 53. First case-control studies of Alzheimer's disease: ELF magnetic field exposure estimated for primary lifetime occupation

Authors		No. of subjects (medium or high exposure / total)		Odds ratio	
		Cases	Controls	Univariate	Adjusted
Sobel et al., 1995	Finnish 1	6 / 53 ^a	3 / 70	2.9	2.7
	Finnish 2	19 / 198	10 / 289	3.1**	3.2***
	University S. California	11 / 136	3 / 106	3.0	2.4
Sobel et al., 1996		39 / 326	8 / 152	2.45*	3.93**

^a Data for one patient missing.

* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

The findings of subsequent studies, which are summarized in Table 54, present a different picture. Savitz, Loomis & Tse (1998) studied men aged 20 years and over who were certified as having died from amyotrophic lateral sclerosis, AD or Parkinson's disease in the period 1985–1991 and had recorded occupations in one of the 25 US states that coded occupational information on the death certificate. Three controls were selected from all other men dying in the same states matched with each of the cases and stratified by year of death and age at death in five broad age groups. AD was given as the cause of 256 deaths and the odds ratio for occupations previously defined as involving electrical work, adjusted for age, period, social class and race was 1.2 with 95% CI 1.0–1.4. [The major limitations of this study are the use of death certificates to assess outcome, particularly since AD is difficult to diagnose and is often underreported on death certificates; the small number of cases, and lack of validation in exposure assessment.]

Feychting et al. (1998) studied 77 men and women with dementia, 55 of whom were classed as having probable or possible Alzheimer's disease, diagnosed when a sample of individuals drawn from the twins registered in the Swedish Adoption/Twin Study of Ageing were screened for dementia. If both members of a twin-pair had dementia, one was randomly selected for inclusion in the study. Two groups of controls were drawn from the same original sample of twins who, on testing, were mentally intact. Death and refusal diminished the number of controls available for study and the samples were reinforced by a few additional persons from another Swedish twin study. The occupational history of both cases and controls had been recorded at a structured interview, as part of the mental testing procedure, information about demented subjects being obtained from a surrogate (mostly spouse or offspring). Each subject's primary occupation was defined as that held for the greatest number of years. The relevant information about magnetic field exposure was obtained from the records of a previous study in which work-day measurements had been made for a large number of occupations held by a sample of the population (Floderus et al., 1993; Floderus, 1996). Lack of data for some occupations and lack of occupational histories for housewives reduced the number of cases available for analysis to 41 for all dementia and 27 for Alzheimer's disease, and to 150 and 164 for the two control groups. No clear relationship with exposure from the primary occupation was seen for all dementia: the odds ratios for exposures = 0.2 μ T were 1.5 (95% CI 0.6–4.0) and 1.2 (95% CI 0.5–3.2) against the two control groups, nor for AD where the odds ratio for exposure = 0.2 μ T were respectively 0.9 (95% CI 0.3–2.8) and 0.8 (95% CI 0.3–2.3). There was, however, some evidence of a relationship with exposure from the last occupation held for both categories: the odds ratios for exposure = 0.2 μ T were for all dementias 3.3 (95% CI 1.3–8.6) and 3.8 (95% CI 1.4–10.2); and for AD 2.4 (95% CI 0.8–6.9) and 2.7 (95% CI 0.9–7.8). [It is notable that in this study the relationship with magnetic fields is stronger for all dementias than for AD, and hence stronger still for dementias other than AD, which had been used as the controls in some other studies (Sobel et al., 1995; 1996). The limitations are the small number of cases, particularly of AD; possible selection bias due to twins who

refused to be examined; potential information biases in the job histories which were obtained for cases from proxy respondents; lack of autopsy confirmation of the diagnosis of AD]

The results of the two cohort studies with measured exposures for large random samples of men with different occupations in the electricity utility industry provide unbiased tests of the hypotheses that the fields can increase the risk of neurodegenerative disease. The studies were designed to find out if exposure to 50Hz magnetic fields increased the risk of leukaemia, brain cancer, and some other cancers (Johansen & Olsen, 1998b; Savitz & Loomis, 1995) but the causes of all deaths that occurred over prolonged periods were recorded and the results can provide relevant information. Such a test, however, is limited since these are mortality studies which are limited in investigating causes such as Alzheimer's which might not be reported consistently on the death certificate.

One study covering 21 000 Danish workers followed for up to 19 years was reported by Johansen & Olsen (1998a). The standardized mortality ratio (SMR) for dementia (senile and presenile combined) was less than unity (0.7) for the total population based on six deaths and still lower for the most highly exposed group (0.4). [As specified previously, the use of death certificates for diagnosis of AD is a major limitation, as is the absence of validation of exposure in the study population].

The second study covered nearly 140 000 workers employed in five US utilities and followed from 1950 or 6 months after the date of hire, whichever was the later, to the end of 1988 (Savitz, Checkoway & Loomis D.P., 1998). The SMR for AD was 1.0, based on 24 deaths. Information was also obtained on the frequency with which the disease was referred to on the death certificates as a contributory cause and the 56 deaths for which it was mentioned as an underlying or contributory cause were related to the individuals' estimated cumulative exposure in terms of μ T-years: that is, the time weighted average exposure multiplied by the number of years exposed. This provides no evidence of any association between exposure and death from AD, expressed as relative risk (RR) per μ T-year cumulative exposure, either for career exposure or, for what might be the more relevant, as AD commonly lasts for 5 to 10 years before death, for exposure 10–19 years or 20 or more years before death. [Again, the use of death certificates for diagnosis of AD is a major limitation].

Recently Li, Sung & Wu (2002) reported that among 2198 elderly individuals aged 65 years or over, there was no increased risk of cognitive impairment due higher levels of exposure to power frequency EMFs from a previous occupation, higher residential exposure or both and therefore little support for a link between cognitive impairment and ELF exposure.

Feychting and colleagues (2003) identified all men and women included in the 1980 Swedish census who were working in 1970 or 1980 and alive on January 1, 1981 and followed them until December 31, 1995. All deaths with neurodegenerative disease listed were identified, although AD

and vascular dementia were not separate categories until January 1, 1987, thus the follow-up for these started from that date. Information on subjects' occupational and socioeconomic status (SES) came from census data.

To estimate EMF exposure over the working lifetime, Feychting et al. used Floderus's 1996 job-exposure matrix, which includes some sample occupational 50-Hz magnetic field measurements for the 100 most common jobs held by Swedish men. They also analyzed occupations with the highest estimated EMF exposure in the matrix, plus a group of "electrical occupations" reported earlier by others (Sobel and Savitz) as being associated with higher AD and ALS risk. They calculated person-years of exposure and created groups based on 1st (below 0.11 μT) and 3rd quartiles (0.11 to 0.19 μT), the 90th percentile (0.19 to 0.29 μT) and the 95th percentile ($> 0.5 \mu\text{T}$). All risk estimates were adjusted for age and SES.

A total of 2 649 300 men and 2 163 346 women were included. Overall, AD was not associated with magnetic field exposure of 0.3 μT or above in men or women. A modest increased risk of AD in men with exposure of 0.5 μT and above in 1970, with a "slightly higher" risk estimate in 1980. Stronger associations were found among men when analyses were limited to mortality before age 75, and even stronger when follow-up was limited to 10 years after the 1980 census. The highest risk ratio (RR) of 3.4 (95% CI 1.6–7.0) was reported for men exposed to 0.5 μT or above in 1980. [The limitations include lack of a complete work history and the reliance on the job-exposure matrix developed for a different study, use of death certificates and reliance on census data for occupation and SES].

Another investigation in Sweden, by Håkansson et al. (2003) evaluated the relationship between occupational 50-Hz magnetic field exposure and mortality from AD, ALS, Parkinson's and multiple sclerosis. This population overlapped with a previous study, but focused on highly exposed group of workers (resistance welders) with some exposures in the millitesla range. First, 40 types of occupation where resistance welding could be part of the job description during the study period 1985 to 1994 were identified. Income tax records were used to identify subjects employed at any of the selected work places. A total of 537 692 men and 180 529 women were identified and about 10% of eligible subjects, 53 049 men and 18 478 women, for whom either occupation or exposure data were missing were excluded.

The census data from 1980, 1985 and 1990, which included occupation codes and some job descriptions, were used to identify resistance welders. These 1697 subjects formed the highest exposure group for the analyses. For assignment to other exposure categories, the same Floderus's 1996 job-exposure matrix, plus some additional "exposure information" from a 1993 Swedish study for some rare occupations were used. Further, Håkansson et al. added three other occupations employing mostly women – "domestic service", "computer operator" and "other needlework" – not included in the matrix. They assigned domestic workers to a low exposure category and computer operators and needleworkers to a high exposure category. As the authors note, overall this cohort was "comparatively young"

with a median age of 35. Causes of death were ascertained from the Swedish national death certificate registry. For workers who moved from a higher exposure level job to a lower one during the study period, the higher level was used for analysis. If information on a subject was lacking for a given census period, the earlier data was used.

Håkansson et al. (2003) report elevated relative risk for AD among exposed men and women, with increasing risk with increasing exposure. Exposure-response analysis yielded an RR of 3.2 for each increase of 1 μ T. The risk estimate for men and women in the highest exposure category was 4.64 (95% CI 1.40–11.66), but based on only eight cases. [Results rely on small numbers. No effect is seen if only primary cause of death (without contributing cause) is used. Potential confounding from welders' exposure to metals might be present].

The most recent study (Qiu et al., 2004) is also from Sweden (Stockholm). It evaluates lifetime occupational exposures to magnetic field and Alzheimer's in a community cohort of individuals 75 years and older. This cohort was dementia-free at the beginning of the follow-up (1987–89) and was followed to 1994–96. Information on occupational history was obtained from a proxy, exposure to magnetic fields was based on the already mentioned job-exposure matrix and some supplementary information focusing on women. Of 931 individuals 202 were diagnosed with AD based on a structured interview, a clinical examination and psychological assessment. For the deceased subjects the diagnosis was made by the examination of medical records by two physicians. Adjustment was made for numerous potential confounders. Increased risk was seen for men in both medium lifetime average occupational exposure (RR = 1.7; 95% CI 0.6–4.5) and high exposure (RR = 2.0; 95% CI 0.7–5.5), but these elevations were not statistically significant and the broad confidence intervals indicate a high level of uncertainty. The risk was slightly higher but less consistent when adjustments for many potential confounders were made. No risk was evident for women. [Limitations include exposure assessment including information on jobs held and relevance of the job-exposure matrix used especially for women.]

When evaluated across all the studies, there is only very limited evidence of an association between estimated ELF exposure and disease risk. This is mainly confined to the first two studies (Sobel et al., 1995; 1996) and it is not clearly confirmed by the later studies (Feychting et al., 1998; Feychting et al., 2003; Qiu et al., 2004; Savitz, Checkoway & Loomis, 1998; Savitz, Loomis & Tse, 1998). The exception might be a study by Håkansson et al. (2003). The two studies that show excess (Sobel et al., 1995; 1996) may have been affected by selection bias. Because the study populations are undefined, there is no way to determine the extent to which the controls are representative with respect to exposure of the population from which the cases originated. The Håkansson et al. results depend on the use of a contributing cause. Use of mortality information for the evaluation of AD is particularly problematic, because this diagnosis is often not reported as an under-

Table 54. Later studies of Alzheimer's disease and dementia unspecified

Authors	Exposure (μT)	No. of deaths	Relative risk (95% CI)	Disease
Savitz, Loomis & Tse, 1998	Electrical occupation	256	1.2 (1.0–1.4)	AD
Feychting et al., 1998	Primary occupation 0.2 / < 0.12	(i) 27 ^a	0.9 (0.3–2.8)	AD
		(ii) 27	0.8 (0.3–2.3)	
	Last occupation 0.2 / < 0.12	(i) 29	2.4 (0.8–6.9)	AD
		(ii) 29	2.7 (0.9–7.8)	
	Primary occupation 0.2 / < 0.12	(i) 41	1.5 (0.6–4.0)	Dementia
		(ii) 41	1.2 (0.5–3.2)	
	Last occupation 0.2 / < 0.12	(i) 44	3.3 (1.3–8.6)	Dementia
		(ii) 44	3.8 (1.4–10.2)	
Savitz, Checkoway & Loomis, 1998	Cumulative career	56	0.97 (0.87–1.08) ^b	AD
	Cumulative 10–19 y before death	56	0.47 (0.21–1.04) ^b	AD
	Cumulative 20 y before death	56	0.97 (0.87–1.09) ^b	AD
Johansen & Olsen, 1998a	Any	6	0.7	Dementia
	Most highly exposed	1	0.4	Dementia
Feychting et al., 2003	Occupation in 1970 (males)			AD
	Reference (< 0.11)	178		
	3rd quartile (0.12–0.19)	696	1.0 (0.9–1.2)	
	90th percentile (0.20–0.29)	239	1.1 (0.9–1.3)	
	95th percentile (> 0.5)	90	1.3 (1.0–1.7)	
Håkansson et al., 2003	Occupational exposure (males & females)			AD
	Reference (< 0.16)	7		
	Medium (0.16–0.25)	17	1.3 (0.5–3.2)	
	High (0.25–0.53)	8	2.2 (0.6–6.3)	
	Very high (> 0.53)	8	4.0 (1.4–11.7)	
Qiu et al., 2004	Lifetime average occupational exposure (males & females)			AD
	Reference (< 0.15)	69		
	Medium (0.16–0.18)	64	1.2 (0.9–1.7)	
	High (> 0.18)	69	1.1 (0.7–1.5)	

^a (i) & (ii) odds ratios for same cases with two different sets of controls.

^b Relative risk per μT -year cumulative exposure.

lying cause and is underrepresented as a contributing cause as well. Note that, overall, the studies that did not rely on the death certificates for diagnosis appear to be more positive. This should be considered in the interpretation and development of future studies.

7.2 Amyotrophic lateral sclerosis

7.2.1 Pathology

Amyotrophic lateral sclerosis (ALS) is characterized clinically by progressive motor dysfunction, including painless muscle wasting and spasticity. Most data on disease duration come from clinic samples which suggest that disease duration may average only two to three years. Signs of the disease depend greatly on where the symptoms begin. Brainstem (bulbar) dysfunction may be the first sign in persons presenting with dysphagia or dysarthria. Alternatively, persons may present with painless wasting and weakness of a limb, or one side of the body. Persons with ALS may develop cognitive and autonomic dysfunction. In particular, a frontal lobe dementia and hypotension may develop. Some data suggest that these signs portend a more malignant course of disease. As the disease progresses, pulmonary function and dysphagia result in the need for artificial respiratory support and the insertion of feeding devices to maintain life. Pathologically, the hallmarks of the disease are degeneration of anterior horn cells, ubiquitinated inclusions, hardening (sclerosis) of the white matter in the brain and spinal cord, and degeneration of other motor nuclei. Evidence of degeneration and regeneration in muscle is thought to be secondary to the loss of anterior horn cells. About 10% of ALS cases are familial (Brown, 1997).

Trauma has long been suspected as being a cause of motor neuron disease and specifically of ALS. No clear evidence that it was a cause has, however, ever been obtained, partly, perhaps, because of variation in the reports of the type, location, and timing of the trauma in relation to the onset of the disease and partly because of the probability that the many positive findings were affected by recall bias, patients with the disease being more motivated to recall traumatic events than their corresponding controls.

7.2.2 Epidemiology

The results of five case-control studies examining possible etiology of electric shocks and ALS are summarized in Table 55. Four of them specifically noted the prevalence of electric shocks or injuries and four the proportion of people employed in defined electrical occupations. The first study, which gave rise to the hypothesis, was reported from Germany by Haynal & Regli as long ago as 1964. Nine out of 73 patients with ALS had worked in contact with electricity against five out of 150 controls, giving, according to Deapen & Henderson (1986) an odds ratio of 4.1.

No further study was reported until seventeen years later, when Kondo & Tsubaki (1981) described two studies in Japan, one of which involved a substantial number of cases. Both were essentially negative. In the first, information was obtained by personal interview from the spouses of

458 men and 254 women whose deaths were attributed to motor neuron disease, most of whom had ALS (333 men and 178 women) and the findings were compared with those obtained from 216 of the widowers and 421 of the widows, who were used as controls. In the second study, 104 men and 54 women with ALS were interviewed and the findings compared with those in a similarly sized control group matched for sex, age within 5 years, and area of residence, about half of whom were “normal”, the others being patients in the same hospitals with relatively mild neurological disease. Very few subjects in either group reported “electrical injuries”, that is injuries that resulted in burns, persistent pain, or loss of consciousness, very few were employed in electrical work, and the relative risks were close to unity.

A small study from the UK (Gawel, Zaiwalla & Rose, 1983) reported the findings in response to a questionnaire given to 63 patients with motor neuron disease and 61 undefined controls whose “age and sex distribution was not statistically significant different”. Thirteen of the patients had experienced an undefined electric shock against five of the controls and two of the patients had been struck by lightning (one stating that he had been flung to the ground) against none of the controls. The difference between the combined results was statistically significant, but is difficult to interpret in the absence of a clearer description of the method of enquiry. The odds ratio for the combined exposures (4.6) was similar to that of 4.1 for “working in contact with electricity” in Haynal & Regli's (1964) original study.

The fifth, and most important, study was carried out by Deapen & Henderson (1986) in conjunction with the Amyotrophic Lateral Sclerosis Society of America. Histories were obtained from 518 patients with the disease and from a control group of the same size matched for sex and age within 5 years, drawn from individuals nominated by the patients as work-mates, neighbours, and other social acquaintances. Information was obtained *inter alia* about the individual's occupation 3 years before the date of diagnosis of the disease (or the corresponding period in the case of the controls) and the occurrence more than 3 years previously of electric shocks severe enough to cause unconsciousness. Odds ratios of 3.8 and 2.8 were calculated respectively for employment in one or other of 19 previously defined electrical occupations and for the occurrence of severe electric shocks. Both were statistically significant. Deapen & Henderson (1986) noted that electric shock was a form of trauma that had been shown to cause demyelination, reactive gliosis, and neuronal death in experimental animals, but that previous studies had provided inconsistent results and they were unable to draw any conclusions from their findings, the significance of which they considered to be “not clear”. [Limitations of the Deapen & Henderson's study are that the exposure to EMF was assessed from job titles based on responses to the questionnaire; failure to report the criteria for control selection and the potential recall bias inherent in using occupational histories and reports of electric shock].

A further study of 135 patients with ALS whose disease began under 45 years of age and 85 control patients with multiple sclerosis, is of

limited value. Eight of the ALS patients were noted to have experienced electric shocks before the onset of the disease, severe enough “in some cases” to throw the subject to the ground (Gallagher & Sanders, 1987) but the severity of the shocks in the other cases is not defined and no reference is made to the occurrence (or non-occurrence) of shocks in the controls. Cruz et al. (1999) assessed the association between ALS and several risk factors including electrical shocks. They found a positive association for a familial history of ALS but found no association for electrical shocks.

A cohort study of over 4 million people who were born between 1896 and 1940, were registered in the 1960 Swedish census, and were still alive in 1970 was examined. About 1067 men and 308 women with a known occupation who died between 1970 and 1983 and had ALS given as either the underlying cause or a contributory cause of death on their death certificates (Gunnarsson et al., 1991) were identified. The occupations of the ALS subjects were compared with those of an age-stratified control sample of approximately 250 persons drawn from each 5 year birth cohort from 1896–1900 to 1936–1940. Occupations were classified in 90 groups (54 for men and 36 for women) and significant excesses of ALS were observed for only two (male office workers and male farm workers). It was noted, however, that, in agreement with Deapen & Henderson's (1986) findings “there seemed to be an association between ALS and work with electricity” (OR = 1.5 for male electricity workers). [This study can be viewed only as hypothesis generating].

In 1997 Davanipour et al. found that 28 patients with ALS had had, on average, more intense occupational exposure to ELF fields than 32 controls. In their study, the controls were relatives of the patients and selected to be of similar age and, if possible, of the same gender. Unfortunately the requirements were too stringent and they obtained the two controls intended (one blood and one non-blood relative) for 12 cases and only one control for the remaining eight. Detailed occupational histories were obtained and exposure to ELF electromagnetic fields was classed for each job held in one of five categories, from low to high, and exposure indices were calculated taking into account the numbers of years worked in each job. The odds ratio per unit value of the exposure index (which ranged from 3 to 383) was positive (1.006) but not quite statistically significant (95% CI 0.99–1.01). Gender made little difference to the results and the odds ratio cited is one for all subjects irrespective of sex. Davanipour et al. (1997) considered that recent findings had made the concept that ELF fields were an aetiological factor in the development of ALS more plausible and that, despite the defects of the control group, their findings indicated that “long term occupational exposure to ELF may increase the risk of ALS.” [The study is limited by the small sample size and potential control selection bias].

Table 55. Case-control studies of amyotrophic lateral sclerosis before 1997: electrical employment and electric shocks^a

Authors	Exposure	No. of subjects		Odds ratio
		Cases	Controls	
Haynal & Regli, 1964	Occupation in contact with electricity	9 / 73	5 / 150	4.1*
Kondo & Tsubaki, 1981 first study ^b	Electric injuries	2 / 458 (M) 3 / 254 (F)	1 / 216 (M) 2 / 421 (F)	1.0
Kondo & Tsubaki, 1981 second study		6 / 104 (M) 1 / 54 (F)	7 / 104 (M) 2 / 54 (F)	1.0
Kondo & Tsubaki, 1981 first study	Occupation electric work	3 / 458 (M)	1 / 216 (M)	1.4
Gawel, Zaiwalla & Rose, 1983	Struck by lightning	2 / 63	0 / 61	4.6*
	Other electric shock	13 / 63	5 / 61	
Deapen & Henderson, 1986	Occupation electricity related	19 / 518	5 / 518	3.8*
	Electric shock	14 / 518	5 / 518	

^a A sixth study (Gallagher & Sanders, 1987) is omitted (see text).

^b First study was on motor neuron disease, included 333 men and 178 women with ALS; second study limited to ALS. No woman was reported with an electric work occupation in either study, neither was any man in the second study.

* $p \leq 0.05$

Estimates of the risks associated with electric work were also provided in five of the later studies described under Alzheimer's disease. These are summarized in Table 56.

In the Savitz, Loomis & Tse (1998) proportional mortality study, electrical work, as previously defined, was recorded slightly more often for the 114 men with amyotrophic lateral sclerosis than for the 1614 controls, giving an odds ratio of 1.3 adjusted for age, period, social class, and race, which was statistically significant (95% CI 1.1–1.6). [The diagnosis of ALS from death certificates in this study was based on ICD9, which groups ALS with other motor neuron diseases. Other limitations of this study include the fact that only one occupation was taken from death certificates and the absence of data on important confounders, such as familial neurodegenerative diseases or exposure to electric shocks].

Johansen & Olsen's (1998a) cohort study of Danish electricity workers recorded only 14 deaths from ALS, but the SMR (2.0; 95% CI 1.1–3.4) was, nevertheless, statistically significant and was higher, though no longer significant, for men with the highest average exposure of $= 0.1 \mu\text{T}$ (SMR = 2.8; 95% CI 0.8–7.3). In this population the mortality from electricity accidents was 18 times the national average (based on 10 deaths) and 31 times that expected in the group with the highest average exposure.

In a study of the morbidity from neurodegenerative diseases and other disorders of the central nervous system, data on the entire Danish cohort ($n = 30\ 631$) were linked to the population-based National Register of Patients, which records more than 99% of all hospital discharges for somatic diseases (Danish National Board of Health, 1981). Data on all 30 631 employees were linked to the Register for follow-up for central nervous system diseases between 1 January 1978 or the date of first employment, whichever came last, and the date of death, emigration or 31 December 1993, whichever came first. Medical records were obtained for cases of ALS and other motor neuron diseases to verify the diagnosis and to obtain information on episodes of electric shocks or other occupational exposure before development of the disease. Men had an increased risk for all motor neuron diseases combined (SIR = 1.89; 95% CI = 1.16–2.93), based on 20 cases, which was confined to the 15 men with a diagnosis of ALS (SIR = 1.72; 95% CI 0.96–2.83). They also had an increased risk for other motor neuron diseases (SIR = 2.75; 95% CI 0.88–6.41) and for demyelinating diseases, with four cases observed (SIR = 1.90; 95% CI = 0.51–4.86) (Johansen, 2000).

The Savitz, Checkoway & Loomis (1998) cohort study of US utility workers recorded 28 deaths from ALS giving an SMR of 0.8. When, however, all the 33 deaths in which ALS was mentioned on the death certificate as either the underlying or a contributory cause of death, were related to the individuals' estimated cumulative exposure in terms of μT -years, that is the time-weighted average exposure multiplied by the number of years exposed, a positive but non-significant association was observed (relative risk per μT -year = 1.03; 95% CI 0.90–1.18). Unlike Alzheimer's disease, ALS progresses rapidly over 1 or 2 years and this may be the most relevant association. Should, however, any effect of exposure have a long latent period, it is notable that the only positive relationship for a specific period was that for 20 or more years in the past (relative risk per μT -year = 1.07; 95% CI 0.91–1.26). [Limitations of this study are the modest number of ALS cases, diagnosis from death certificates, and the absence of the data on electric shocks or the family's disease history].

In a previously described study, Feychting et al. (2003) found no increased risk for ALS in any of their analyses, including occupations having the highest EMF exposure. They also analyzed the "electrician" category separately because this job reports the largest number of electric shock accidents in Sweden. When looking at risk for men only by job title alone, Feychting et al. observed an increased risk (statistically significant) of ALS among welders based on 24 cases, and a slightly elevated risk among radio and television assemblers (seven cases) and telephone and telegraph installers/repairmen (six cases), but these were not statistically significant. No risk was observed for electricians.

For ALS Håkansson et al. (2003) report the statistically significant risk estimate RR = 2.2 (95% CI 1.0–4.7) for both men and women in the very high exposure group (based on 13 cases). Additionally, they report an exposure-response relationship with an RR of 1.5 for an increase of 1 μT .

Table 56. Later studies of amyotrophic lateral sclerosis

Authors	Exposure	No. of deaths	Relative risk (95% CI)
Savitz, Loomis & Tse, 1998	Electrical occupation	114	1.3 (1.1–1.6)
Savitz, Checkoway & Loomis, 1998	Cumulative, career	33	1.03 (0.90–1.18) ^a
	Cumulative, 10–19 y before death	33	0.82 (0.40–1.65) ^a
	Cumulative, 20 y before death	33	1.07 (0.91–1.26) ^a
Johansen & Olsen, 1998a	Any	14	2.0 (1.1–3.4)*
	1.0 μ T average	4	2.8 (0.8–7.3)
Feychting et al., 2003	Occupation in 1970 (males)		
	reference group < 0.11 μ T	227	
	3rd quartile 0.12–0.19 μ T	723	0.9 (0.7–1.0)
	90 th percentile 0.20–0.29 μ T	210	0.8 (0.7–1.0)
	95 th percentile > 0.5 μ T	70	0.8 (0.6–1.0)
Håkansson et al., 2003	Occupational exposure (males & females)		
	reference < 0.16 μ T	15	
	medium 0.16–0.25 μ T	52	1.6 (0.9–2.8)
	high 0.25–0.53 μ T	17	1.9 (1.0–4.0)
	very high > 0.530 μ T	13	2.1 (1.0–4.7)

^a Relative risk for μ T-year cumulative exposure.

* $p < 0.05$

Most of these studies do not allow examination of possible confounding from electric shock. It is conceivable that exposure to electric shocks increases ALS risk and, also, clearly work in the utility industry carries a risk of experiencing electric shocks. Some of the reviewed studies did report analyses that indeed linked electric shocks to ALS (Deapen & Henderson, 1986; Gunnarsson et al., 1992; Johansen & Olsen, 1998a), but none of the studies provided an analysis in which the relation between EMF and ALS was studied with control for electric shocks. A crude calculation can be made from the data provided by Deapen and Hendersen, and this seems to indicate the EMF association holds up even after control for electric shock experience.

There is no obvious biological explanation for the epidemiological evidence for a link between severe electric shocks and ALS. However, it is

possible that the massive, synchronized discharge of neurons (especially the large motor neurons) might release sufficient glutamate to precipitate excitotoxic changes. It might also trigger more subtle and persistent changes in the excitability of neurons. In many parts of the brain a tetanic burst of impulses arriving at a synapse can lead to a prolonged increase in the efficacy of that synapse and neighbouring synapses in activating the post-synaptic cell (a phenomenon called Long-Term Potentiation or LTP). In many situations, LTP appears to involve activation of the N-methyl-D-aspartate (NMDA) receptor by glutamate. The ionic channel of the NMDA receptor is blocked by intracellular Mg^{2+} at normal intracellular potentials, but this block is released if the cell is substantially depolarised by a preceding burst of impulses. Any impulse that follows a burst will then cause Ca^{2+} influx through the NMDA receptor channel, and this is thought to trigger reactions that lead to an increase in the effectiveness of the synapse, which can last for months (Kandel, Schwartz & Jessell, 1991). If severe electric shocks do produce LTP, the increased excitability of cells might produce cumulative pathological changes, perhaps involving Ca^{2+} influx through voltage-activated channels or increased metabolic demand, with spillover of reactive oxygen species.

The pathogenetic mechanisms leading to the selective loss of certain populations of dopaminergic neurons are not clear. It has been suggested that the dopamine transporter and vesicular monoamine transporter proteins, which are heavily expressed in the dopaminergic neurons of the substantia nigra, might act as portals of entry for toxins that are structurally related to monoamines (Speciale et al., 1998; Uhl, 1998).

7.3 Parkinson's disease, Multiple Sclerosis

7.3.1 Pathology

Parkinson's disease is characterized clinically by progressive motor dysfunction, including bradykinesia, gait disturbance, rigidity, and tremor. Most data on disease duration come from clinical samples which suggest that disease duration may average seven or more years. Many persons with Parkinson's disease develop cognitive, behavioral, and autonomic signs: visible or measureable indications of changes in responses controlled by the autonomic nervous system, such as skin colour, sweating, pupil diameter and blood pressure. In particular, dementia, hallucinations, delusions, and hypotension develop in many persons with the disease. While the behavioral disturbances and autonomic signs are worsened by the dopaminergic agents commonly prescribed to treat the disease, these agents improve quality of life and probably prolong life. Some data suggest that behavioral disturbances and autonomic signs portend a more malignant course of disease. Pathologically, an important hallmark of the disease is degeneration of the substantia nigra (e.g. neuronal loss) .

7.3.2 Epidemiology

Occupation has been considered as a possible cause of Parkinson's disease in several studies. The study by Wechsler et al. (1991) included jobs likely to involve relatively high exposures to EMF and reported three of 19 affected men were welders against zero out of nine controls and that two other affected men had worked as electricians or electrical engineers. However, Savitz, Loomis & Tse (1998) found very little evidence of an increased risk in electrical workers. Overall the odds ratio derived from the occupations of 168 men dying from Parkinson's disease and 1614 controls was 1.1 (95% CI 0.9–1.2).

In the Danish cohort study (Johansen & Olsen, 1998a), the SMR for Parkinsonism was 0.8, based on 14 deaths and even lower for the more heavily exposed men (0.5). In the US study by Savitz, Loomis & Tse (1998), positive relationships were observed with both cumulative cancer exposure and exposure more than 20 years before death, neither of which were, however, statistically significant (relative risks 1.03 per μT -year, 95% CI 0.90–1.18, and 1.07 per μT -year, 95% CI 0.91–1.26). Noonan et al. (2002) reported a positive association with an OR of 1.5 for the highest exposure category for Parkinson disease and magnetic field exposure in electrical workers.

Feychting et al. (2003) found no increased risk for vascular dementia, senile dementia, pre-senile dementia, Parkinson's disease, multiple sclerosis or epilepsy for either men or women. Håkansson et al. (2003) also found no increased risk for Parkinson's disease or multiple sclerosis (MS) and they observed a decreased RR for epilepsy.

In one Danish study (Johansen et al., 1999) of the risk for MS, data on the entire cohort ($n = 31\,990$) were linked to the files of the Danish Multiple Sclerosis Registry, which was founded in January 1948 as a nationwide program to register all cases of MS in Denmark. All cases of suspected or verified MS are currently notified to the Register from all 22 Danish neurological departments and the two rehabilitation centers of the Danish Multiple Sclerosis Society. Only verified cases of MS were included in the present study. Overall, 32 cases of MS were diagnosed, as compared with 23.7 expected from national incidence rates, to yield a standardized incidence ratio of 1.35 (95% CI 0.92–1.91).

7.4 Discussion

Of the four neurodegenerative diseases that have been considered, Parkinson's disease and MS have received the least attention in epidemiology. No study has provided clear evidence of an association with above-average exposure to extremely low frequency EMFs and, in the absence of laboratory evidence to the contrary, it seems unlikely that such fields are involved in the disease.

The evidence relating to Alzheimer's disease is more difficult to assess. The initial reports that gave rise to the idea suggested that the increased risk could be substantial (Sobel et al., 1995). Despite the fact that the initial

report was based on the combined results of three independent studies, it should be regarded only as hypothesis forming, as the greater risk was largely the result of classifying groups of garment workers in the heavily exposed groups that had not previously been so classified. The finding was quickly confirmed (by some of the authors of the original report) in another case-control study and was weakly supported by the proportional mortality ratio of causes of death as recorded on US death certificates. It was not supported, however, by the three studies that could provide quantified estimates of people's exposures. One, a case-control study, that did not show risk associated with the individual's primary occupation, did show a substantial and statistically significant risk with the last recorded occupation, which would have been the association recorded in the death certificate study. Neither of the cohort studies, however, provided evidence of a risk with increasing exposure nor, in the one study that provided the information, any excess mortality in power plant workers as a group. The three more recent studies have provided a mixed evidence as well: one providing a limited evidence for males in the highest exposure group, another (overlapping) study focusing on the resistance welders showed an effect, and a third one showing an effect in males, but not in females. In conclusion, there is only inadequate evidence to suggest that 50/60 Hz fields could cause Alzheimer's disease.

More evidence is available for ALS. Eight reports of the relationship between electrical work or the experience of electrical shocks have been published since the original suggestion was made that electric shocks might increase the risk of the disease. Two early studies from Japan, where the prevalence of electrical work (as recorded in the medical history) and of electrical shock was low, failed to provide any support for the hypothesis. The others all provided some support. In three, including one of the two cohort studies with measured exposure, the excess associated with exposure was statistically significant. Electric shocks were recorded only in four early reports, in two of which (one from the UK and one from the US) the prevalence was significantly raised. The two most recent and overlapping studies from Sweden focusing on magnetic field exposure and electric shock are inconsistent, with one showing no effect and the other indicting a relative risk of about 2 in the two highest exposure categories. The epidemiological evidence suggests that employment in electrical occupations may increase the risk of ALS, however, separating the increased risk due to receiving an electric shock from the increased exposure to EMFs is difficult.

In considering a possible causal relationship between neurodegenerative disease and the electrical environment, the relevant exposure has been assumed to be some aspect (e.g. time weighted average, number of exposures above some critical level, etc.) of ELF magnetic fields, contact currents and/or electrical shock¹. "Contact current" is defined here as an electrical current that

1. There are other environmental exposures that can cause electrical effects in the human body, such as the environmental electric field. Except in special circumstances such as near high voltage transmission lines, however, the effect of this source is usually smaller than either of the other two sources.

passes through the body between two points when they are in “contact” with an external electrical system. An electrical shock occurs as “a reflex response to the passage of current through the body” and thus is the result of contact currents large enough to be perceived. Although it is clear from these definitions that contact current and electrical shock are closely related, it may appear that the ELF magnetic field is a distinctly different exposure because ambient magnetic fields, with specific exceptions (e.g. MRI machines) are not nearly large enough to produce neural stimulation. This is not entirely correct. In fact, there are several important connections between the two that should be understood before the possible effects of one exposure can be separated from those of the other.

The first connection is that each exposure can be responsible for inducing an electric field and a corresponding electric current density within the human body. Biophysicists consider *the induced electric field* as the metric most relevant for evaluating biological interactions from EMF or contact current exposure¹. Thus, a biological effect due to an electric field in the body may be caused by exposure to an ELF magnetic field, a contact current or some other aspect of the electrical environment that can cause an electric field in the body. What might allow one to discern the origin of the effect is recognition that the distribution of the magnitude and orientation within the body of the electric field induced by an ELF magnetic field and that due to a contact current can be significantly different.

It is well known that a time varying ELF magnetic field in the body can cause electric fields and currents to be induced in the body via Faraday’s law. This induced electric field is limited by the size of the body and the magnitude of the magnetic field. In fact, it is generally well recognized that the electric fields induced by typical environmental 50/60-Hertz magnetic fields are usually thought to be too small to cause biological effects. Contact currents with commonly experienced amplitudes, on the other hand, have been estimated to produce electric fields in the body that are orders of magnitude larger than induced electric fields from typical levels of ambient magnetic fields. Further, the electric field produced by a magnetic field is larger near the periphery of the body while the electric field produced by contact currents is larger in the path between contact points and hence often in the limbs and the body’s interior. These differences in amplitude and spatial distribution within the body may be suggestive of a cause and effect relationship with diseases that have their origin in specific parts of the body. For these reasons, contact currents and the related electrical shocks are important exposures and should be considered when conducting studies of possible health outcomes due to the electrical environment.

The second connection between the ELF magnetic field and contact currents is the fact that environmental magnetic fields may induce voltages

1. Several other mechanisms have been proposed by which ELF magnetic fields might directly interact with the body. However, they are either thought to be implausible or unlikely at environmental field levels.

in electrical systems that in turn cause current, i.e. contact current, in a human body that is in contact with this system. In addition, conducted currents on residential grounding systems may be related to nearby ELF magnetic fields. When either is the case, the amplitudes of the ELF magnetic field and the contact current are related.

The identification of which of these two exposures (if either) is associated with a health outcome, is a very important question. Properly configured studies should be designed to identify the specific exposure responsible for a specific biological effect.

The measurement of magnetic fields is a well-established enterprise. The measurement of electrical contact current and or shock current, however, is not as well advanced. It would require either that the current entering the body during normal life or work be measured or that the circuit contacted by the body be characterized by a simple equivalent circuit. It is only recently that an instrument for measuring the currents entering the body has been developed and it has not been extensively tested. Measurements that lead to a simple equivalent for a circuit that can be contacted by a human, however, have been made. In either case, methodology to allow evaluation of “contact current” exposure should be tested further. If acceptable, it should be used in further studies of the relationship between the electrical environment and neurodegenerative diseases.

Quantitatively, the flow of electricity through the brain is likely to be substantially greater from the use of electro-convulsive therapy for the treatment of psychiatric conditions than from even severe electric shock received occupationally or from non-fatal strikes by lightning. However, no large, long-term study of patients has been reported in sufficient detail to permit the detection of (say) a five-fold risk of a disease that normally causes about one death in 100 adults.

7.5 Conclusions

It has been hypothesized that exposure to ELF fields is associated with several neurodegenerative diseases. For Parkinson’s disease and multiple sclerosis the number of studies has been small and there is no evidence for an association with these diseases. For Alzheimer’s disease and amyotrophic lateral sclerosis (ALS) more studies have been published. Some of these reports suggest that people employed in electrical occupations have an increased risk of ALS. So far no biological mechanism has been established which can explain this association, although it could have arisen because of confounders related to electrical occupations such as electric shocks. Overall, the evidence for the association between ELF exposure and ALS is considered inadequate.

The few studies investigating the association between ELF exposure and Alzheimer’s disease are inconsistent. However, the higher quality studies that focused on Alzheimer morbidity rather than mortality do not indicate an association. Altogether, the evidence for an association between ELF exposure and Alzheimer’s disease is inadequate.