DOCUMENTS OF THE NRPB

ELF Electromagnetic Fields and Neurodegenerative Disease

Report of an Advisory Group on Non-ionising Radiation

VOLUME 12 NO 4 2001

National Radiological Protection Board
Chilton, Didcot, Oxon OX11 0RQ

Contents

ELF ELECTROMAGNETIC FIELDS AND NEURODEGENERATIVE DISEASE

Report of an Advisory Group on Non-ionising Radiation

CHAIRMAN: SIR RICHARD DOLL

This report from the Advisory Group on Non-ionising Radiation reflects understanding and evaluation of the current scientific evidence as presented and referenced in this document.

Advisory Group on Non-ionising Radiation

CHAIRMAN

Sir Richard Doll
Imperial Cancer Research Fund Cancer Studies Unit, Oxford

MEMBERS

Professor C Blakemore
University of Oxford

Professor E H Grant
Microwave Consultants Limited, London

Professor D G Harnden
Wythenshawe Hospital, Manchester

Professor J M Harrington
Institute of Occupational Health, Birmingham

Professor T W Meade
St Bartholomew's and Royal London School of Medicine

Professor A J Swerdlow
Institute of Cancer Research, London

SECRETARIAT

Dr R D Saunders
National Radiological Protection Board, Chilton

OBSERVER

Dr H Walker
Department of Health, London

ASSESSORS

Dr A F McKinlay
National Radiological Protection Board, Chilton

Dr C R Muirhead
National Radiological Protection Board, Chilton

Dr J W Stather
National Radiological Protection Board, Chilton

CONSULTANT

Mr S G Allen
National Radiological Protection Board, Chilton

INTRODUCTION

1 There are continuing concerns about the possible health effects that may arise as a consequence of exposure to electromagnetic fields and radiations (EMFs). In relation to exposures to power frequency (extremely low frequency, ELF) electromagnetic fields, the principal concern has been the possibility that they may be implicated in the development of cancer. This has been addressed in previous reports by the Advisory Group on Non-ionising Radiation (NRPB, 1992, 1994, 2001). Research on other possible effects on health has also been carried out in recent years and a number of epidemiological studies have considered the possibility of an association between occupational exposure to ELF electromagnetic fields and the development of several neurodegenerative diseases.

2 The Advisory Group has a remit

> **'to review work on the biological effects of non-ionising radiation relevant to human health and to advise on research priorities'**

3 In developing its advice for the Board of NRPB on the possible health effects of electromagnetic fields, the Advisory Group has reviewed a number of studies that have examined associations between Alzheimer's disease, motor neuron disease and Parkinson's disease and exposure to electromagnetic fields. These diseases may be classed as neurodegenerative disease as all involve the death of neurons, although their aetiology is different (Savitz *et al*, 1998a,b). Most investigators have chosen to examine them separately and to study only one specific type of motor neuron disease in relation to electromagnetic fields, namely amyotrophic lateral sclerosis (ALS, also called Lou Gehrig's disease).

4 This report examines first the biological basis of these neurodegenerative diseases, the location of the nerve cells implicated in their development, and the pathological changes that become manifest as they develop.

5 It then reviews the relevant epidemiological studies. These have examined the possibility of a relationship with exposure to ELF electromagnetic fields, particularly as a consequence of work involving the use of electricity (eg electric power line/cable workers, welders, electricians and dressmakers).

6 Although the aetiology of these diseases is different, there is the possibility that oxidative stress may in all cases play a significant role in the death of neurons, which is a key feature in the development of each of these diseases. The evidence for oxidative stress as a common factor in their development is therefore examined.

7 The possible effects of ELF electromagnetic fields on neurodegenerative diseases have been examined in epidemiological studies, but there are very few relevant experimental investigations. Several studies have, however, examined the effect of electromagnetic fields on calcium exchange in nervous tissue and other direct effects on nerve tissue function, and the results of these studies are reviewed.

8 The balance of evidence relating these diseases to electromagnetic field exposure is then considered and recommendations made for further work.

BIOLOGICAL BASIS OF NEURODEGENERATIVE DISEASE

9 By definition, these diseases all involve the death of neurons, although the location of the cells that are most vulnerable and the many other associated pathological changes vary enormously among the three disorders.

10 There are familial forms of all three diseases, and progress has been made in identifying the genes at fault.

Alzheimer's disease

11 The defining pathological features of Alzheimer's disease (Alloul *et al*, 1998; Felician and Sandson, 1999) are the high incidence, in the cerebral cortex, of neuritic plaques, consisting of deposits of β-amyloid protein, as well as intraneuronal fibrillary tangles, which are abnormal filaments composed of hyperphosphorylated protein called tau (microtubule-associated protein). The severity of dementia correlates with the density of both tangles (Goedert and Hasegawa, 1999) and plaques (Roth *et al*, 1966). There is widespread death of neurons, especially in the amygdala, temporal, parietal and frontal association cortex and hippocampus. The large pyramidal nerve cells in layers III and V of the cortex are particularly affected (Kowall and Beal, 1991), as well as a variety of interneurons. The loss of these cells results in a reduction in the levels of the neurotransmitters somatostatin and corticotrophin-releasing factor (Davies *et al*, 1980).

12 In the affected regions, synapses become disrupted, especially those of nerve fibres from the basal forebrain, which use acetylcholine as their transmitter. The cell bodies of these fibres, in the basal forebrain, undergo degeneration (Whitehouse *et al*, 1982), leading to a reduction in the levels of acetylcholine and the activity of the enzymes choline acetyl transferase and acetyl cholinesterase (see Perry, 1986).

Familial Alzheimer's disease

13 Disorders of the genes for amyloid precursor protein (APP; on chromosome 21) as well as those for presenilin 1 and 2 (PS1 and PS2; on chromosomes 14 and 1, respectively), and apolipoprotein (apoE; chromosome 19), all heighten the risk of early-onset Alzheimer's disease (see Borchelt *et al*, 1998; Price *et al*, 1998). Transgenic methods have been used to mutate these genes in mice, some of which develop plaques similar to those in Alzheimer's disease (Borchelt *et al*, 1998). In the Alzheimer's-like disorder *familial frontotemporal dementia and parkinsonism* (FTDP-17) there is a mutation of the tau protein gene on chromosome 17, and there has been some progress in the use of transgenic methods to mimic the pathology of neurofibrillary tangles (Goedert and Hasegawa, 1999). The relationship between disorders of the tau protein and of the amyloid protein pathway is unclear (Felician and Sandson, 1999).

Parkinson's disease

14 Neuronal loss in Parkinson's disease occurs selectively in the pars compacta region of the substantia nigra, a midbrain nucleus that normally contains nearly half a million dopaminergic neurons whose axons project to the corpus striatum of the basal ganglia. There is, therefore, a dramatic loss of dopaminergic terminals in the striatum, resulting in poverty of movement and other motor symptoms (Lozano *et al*, 1998).

15 The manner in which the neurons die in the substantia nigra is similar to genetically-regulated 'programmed cell death' or *apoptosis* (Burke, 1998). However, 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 (DAT) and vesicular monoamine transporter (VMAT) 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). One such toxin is N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which produces degeneration and neurological signs similar to those of Parkinson's disease in both animals and humans.

Familial Parkinson's disease

16 Recently, two defects have been associated with familial forms of Parkinson's disease – mutations of the gene for the presynaptic protein Ó-Synuclein (chromosome 4), and of the *parkin* protein gene on chromosome 6 (Lozano *et al*, 1998). As mentioned above, disorders of the tau protein gene on chromosome 17 also produce Parkinson's-like symptoms, as well as dementia (FTDP-17) (Goedert and Hasegawa, 1999).

Amyotrophic lateral sclerosis

17 Amyotrophic lateral sclerosis (ALS) is a progressive neuronal degenerative disease, sometimes considered as a clinical variant of motor neuron disease (MND). Upper and lower motor neurons (in the brain and spinal cord, respectively) die selectively. The clinical manifestations of the familial and sporadic forms of ALS are generally said to be indistinguishable (Borchelt *et al*, 1998; Rowland, 1994). In reality, each probably includes a variety of conditions. Unusual structures called inclusions are seen in neuronal cell bodies and in their processes, which are shortened. There are also neurofilamentous abnormalities, aberrant patterns of cytoskeletal antigens, atrophy of the Golgi apparatus, etc.

Familial ALS

18 About 10% of cases are familial (Brown, 1997). Mutations of the superoxide dismutase gene (SOD1) have recently been shown to occur in about 20% of autosomal dominant familial cases, implying a difficulty in coping with free radicals in the pathogenesis of the disorder. Multiple lines of transgenic mice with mutations of the SOD1 gene display pathology very similar to that of ALS (Borchelt *et al*, 1998). Transgenic mice over-expressing one of the neurofilament triplet genes also develop a motor neuronopathy, and there have been occasional reports of neurofilament gene mutations in patients with the disorder, although this seems to be rare. There is an X-linked form of motor neuron disease, known as bulbo-spinal muscular atrophy, which is associated with increased length CAG repeat sequences in the androgen receptor gene.

19 The cellular causes of the sporadic forms of ALS remain a mystery, although there is no lack of hypotheses, including glutamate-induced excitotoxicity (Dessi *et al*, 1994; Rothstein, 1995), disturbances of iron metabolism (Gerlach, 1994), and inadequate neurotrophic support (Henderson, 1995).

EPIDEMIOLOGICAL STUDIES

20 Suggestions that one or other of the three diseases might be related to working with electricity have been made periodically since amyotrophic lateral sclerosis was related to working with electricity by Haynal and Regli in Germany in 1964. At that time the suspected aetiological agent was electric shock and it is only in the last few years, since Sobel *et al* (1995) speculated that exposure to 50 or 60 Hz electromagnetic fields might be a cause of Alzheimer's disease, that interest has focused on the possible hazards of exposure to extremely low frequency fields with flux densities in the range of about 0.1 to 1.0 μT, which may be encountered at work.

Alzheimer's disease

First studies

21 Sobel *et al* (1995) reported the results of three small case-control studies of Alzheimer's disease, 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. In the case of dressmakers, seamstresses and tailors, who had not previously been regarded as having electrical occupations, the classification of medium to high exposure was confirmed by measurement of the fields produced by four industrial and two home sewing machines.

22 The first Finnish series consisted of 53 men and women with sporadic Alzheimer's disease and 70 with sporadic vascular dementia. The second was of 198 men and women admitted to a geriatric institution diagnosed as having Alzheimer's disease (sporadic and familial combined) and 299 controls selected in order from the alphabetical 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 of 136 patients admitted to the University of Southern California between 1984 and 1993 with sporadic Alzheimer's disease and 106 neuropsychologically normal individuals without any known history of dementia or memory problems in near relatives in the communities from which the Alzheimer's patients came. The results are summarised in Table 1. 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, 95% confidence interval (CI) 1.6, 5.4) by adjustment for education and social class and for age at onset, age at examination, and sex 'if their associated p-value was < 0.2'. 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 Alzheimer series and 8 out of 16 in the controls).

23 A further case-control study, based on patients attending an Alzheimer's Disease Treatment and 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 Alzheimer's disease 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). The results are also summarised in Table 1. The odds ratio for a primary occupation that caused medium or high exposure to electromagnetic fields, was 3.93 (95% CI 1.45, 10.56). Again dressmakers, seamstresses 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.

	Number of subjects with medium or high exposure/total		Odds ratio	
Study	Cases	Controls	Univariate	Adjusted
Sobel *et al* (1995)				
Finnish 1	6/53†	3/70	2.9	2.7
Finnish 2	19/198	10/299	3.1**	3.2***
University of Southern California	11/136	3/106	3.0	2.4
Sobel *et al* (1996)	39/326	8/152	2.45*	3.93**

TABLE 1 *First case-control studies of Alzheimer's disease: magnetic field exposure estimated for primary lifetime occupation*

*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$.

† Data for one patient missing.

Study	Exposure (μT)	Number of deaths*	Relative risk (95% CI)	Disease
Savitz *et al* (1998a)	Electrical occupation	256	1.2 (1.0, 1.4)	Alzheimer's
Feychting *et al* (1998)	Primary occupation ≥0.2/ < 0.12	(i) 27 (ii) 27	0.9 (0.3, 2.8) 0.8 (0.3, 2.3)	Alzheimer's
	Last occupation > 0.2/ < 0.12	(i) 29 (ii) 29	2.4 (0.8, 6.9) 2.7 (0.9, 7.8)	Alzheimer's
	Primary occupation ≥0.2/ < 0.12	(i) 41 (ii) 41	1.5 (0.6, 4.0) 1.2 (0.5, 3.2)	Dementia
	Last occupation ≥0.2/ < 0.12	(i) 44 (ii) 44	3.3 (1.3, 8.6) 3.8 (1.4, 10.2)	Dementia
Savitz *et al* (1998b)	Cumulative career	56	0.97† (0.87, 1.08)	Alzheimer's
	Cumulative 10–19 years before death	56	0.47† (0.21, 1.04)	Alzheimer's
	Cumulative ≥ 20 years before death	56	0.97† (0.87, 1.09)	Alzheimer's
Johansen and Olsen (1998b)	Any	6	0.7	Dementia
	Most highly exposed	1	0.4	Dementia

TABLE 2 *Later studies of Alzheimer's disease and dementia unspecified*

*(i) and (ii) odds ratios for same cases with two different sets of controls.

† Relative risk per μT-year cumulative exposure.

Later studies

24 The findings in four subsequent studies, which are summarised in Table 2, present a different picture. Savitz *et al* (1998a) studied men aged 20 years and over who were certified as having died from ALS, Alzheimer's disease or Parkinson's disease in the period 1985–1991 and had recorded occupations in one or other of the 25 states in the USA that coded occupational information with the death certificate. Three controls were selected from all other men dying in the same states with recorded occupations matched with each of the cases and stratified by year of death and age at death in five broad age groups. Alzheimer's disease 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 (95% CI 1.0, 1.4).

25 Three other studies have been able to relate estimates of risk to quantified measures of exposure: namely, a case-control study of dementia by Feychting *et al* (1998) and two cohort studies of electricity workers.

26 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 people 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, 1996). A lack of data for some occupations and a 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, respectively, for the two control groups. No clear relationship with exposure from the primary occupation was seen either for all dementia (odds ratios for exposure of 0.2 μT or more, 1.5 and 1.2 against the two control groups) or for Alzheimer's disease (odds ratios for exposure of 0.2 μT or more, respectively 0.9 and 0.8). There was, however, some evidence of a relationship with exposure from the last occupation held for both categories (odds ratios for exposure of 0.2 μT or more, all dementias 3.3 and 3.8; Alzheimer's disease 2.4 and 2.7). It is notable that in this study the relationship with magnetic fields is stronger for all dementias than for Alzheimer's disease, and hence stronger still for dementias other than Alzheimer's disease, which had been used as the controls in some other studies (Sobel *et al*, 1995, 1996).

27 The results of the two cohort studies with measured exposures for large random samples of men with different occupations in the electricity utility industry are more compelling. The studies were designed to find out if exposure to 50 Hz magnetic fields increased the risk of leukaemia, brain cancer, and some other cancers (Johansen and Olsen, 1998a; Savitz and Loomis, 1995) but the causes of all deaths that occurred

over prolonged periods were recorded and the results can, consequently, provide unbiased tests of the hypotheses that the same fields can increase the risk of neurodegenerative disease.

28 One study covering 21 000 Danish workers followed for up to 19 years was reported by Johansen and Olsen (1998b). A later extension (Johansen, 2000) included female employees and linked occupational data to the national register of hospital patients. For senile dementia, the standardised morbidity ratio was 1.09 based on 128 cases; for presenility, which included cases specified as Alzheimer's disease, it was 0.93 based on 34 cases. For males with the highest exposures (1.0 μT or more) the ratios were 1.43 (95% CI 0.74, 2.72) and 0.92 (95% CI 0.25, 3.42). The standardised mortality ratio (SMR) for dementia (senile and presenile combined) was less than unity (0.7) for the total population based on 6 deaths and still lower for the most highly exposed group (0.4). The second study covered nearly 140 000 workers employed in five electricity utilities in the USA and followed from 1950 or 6 months after the date of hire, whichever was the later, to the end of 1988 (Savitz *et al*, 1998b). The SMR for Alzheimer's disease 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 μT-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 Alzheimer's disease, expressed as relative risk (RR) per μT-year cumulative exposure, either for career exposure or – for what might be the more relevant, as Alzheimer's disease commonly lasts for 5 to 10 years before death – for exposure 10–19 years or 20 or more years before death.

Amyotrophic lateral sclerosis

First studies

29 Trauma has long been suspected as being a cause of motor neuron disease and specifically of amyotrophic lateral sclerosis (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.

30 The results of five case–control studies are summarised in Table 3. Four studies 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 and Regli as long ago as 1964. Out of 73 patients with ALS, 9 had worked in contact with electricity against 5 out of 150 controls, giving, according to Deapen and Henderson (1986), an odds ratio of 4.1.

31 No further study was reported until 17 years later, when Kondo and 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.

TABLE 3 *First case–control studies of amyotrophic lateral sclerosis†: electrical employment and electric shocks*

Study	Exposure	Number of subjects: Cases	Number of subjects: Controls	Odds ratio
Haynal and Regli (1964)	Occupation in contact with electricity	9/73	5/150	4.1*
Kondo and Tsubaki (1981)‡				
First study	Electrical injuries	2/458 (M) 3/254 (F)	1/216 (M) 2/421 (F)	1.0
Second study	Electrical injuries	6/104 (M) 1/54 (F)	7/104 (M) 2/54 (F)	1.0
First study	Occupation: electrical work	3/458 (M)	1/216 (M)	1.4
Gawel *et al* (1983)	Struck by lightning	2/63	0/61	4.6*
	Other electric shock	13/63	5/61	4.6*
Deapen and Henderson (1986)	Occupation: electricity-related	19/518	5/518	3.8*
	Electric shock	14/518	5/518	2.8*

* $p \leq 0.05$.

† A sixth study (Gallagher and Sanders, 1987) is omitted (see paragraph 34).

‡ First study on motor neuron disease included 333 men and 178 women with ALS; second study was limited to ALS. No woman was reported with an electrical occupation in either study, nor was any man in the second study.

TABLE 4 *Later studies of amyotrophic lateral sclerosis*

Study	Exposure	Number of deaths	Relative risk (95% CI)
Savitz *et al* (1998a)	Electrical occupation	114	1.3 (1.1, 1.6)
Savitz *et al* (1998b)	Cumulative career	33	1.03† (0.90, 1.18)
	Cumulative 10–19 years before death	33	0.82† (0.40, 1.65)
	Cumulative ≥ 20 years before death	33	1.07† (0.91, 1.26)
Johansen and Olsen (1998b)	Any	14	2.0*
	≥ 1.0 μT average	4	2.8

* $p < 0.05$.

† Relative risk for μT-year cumulative exposure.

32 A small study from the UK (Gawel *et al*, 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'. In total, 13 of the patients had experienced an undefined electric shock against 5 of the controls, and 2 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 the original study by Haynal and Regli (1964).

33 The fifth, and most important, study was carried out by Deapen and 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 workmates, 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. The authors noted that electric shock was a form of trauma that had been shown to cause demyelinisation, 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'.

34 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 and 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.

35 A few years later a cohort study of over four million people who were born between 1896 and 1940, were registered in the 1960 Swedish census, and were still alive in 1970, provided information about 1067 men and 308 women with a defined 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). The occupations of the ALS subjects were compared with those of an age stratified control sample of approximately 250 people drawn from each five 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,

* The affected patients were asked to nominate two in each group and to rank them in order of their 'closeness'. Addresses of the first and second in order of closeness were obtained and the first was used as a control with the second used as an alternate if the necessary information could not be obtained from the first.

however, that – in agreement with the findings of Deapen and Henderson (1986) – 'there seemed to be an association between ALS and work with electricity' (odds ratio 1.5 for male electricity workers).

36 The results of the Davanipour *et al* (1997) study, which found that 28 patients with ALS had had, on average, more intense occupational exposure to electromagnetic fields than 32 controls, were consequently hardly surprising, although the interpretation of their findings was. 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 twelve cases and one control for only a further 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 0.999, 1.014). 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 electromagnetic 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 EMF may increase the risk of ALS'.

Later studies

37 Estimates of the risks associated with electrical work were also provided in three of the later studies described under Alzheimer's disease. These are summarised in Table 4.

38 In the proportional mortality study by Savitz *et al* (1998a), electrical work, as previously defined, was recorded slightly more often for the 114 men with ALS 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 Johansen and Olsen (1998b) cohort study of Danish electricity workers recorded only 14 deaths from ALS, but the SMR (2.0) was, nevertheless, statistically significant and was higher (2.8), although no longer significant, for men with the highest average exposure (0.1 μT or more). The later extension to morbidity data (Johansen, 2000) found 15 cases and gave a standardised morbidity ratio of 1.57, which was not statistically significant. 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. The cohort study by Savitz *et al* (1998b), of electricity utility workers in the USA, 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, either as the underlying or as 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 of 1.03). In contrast to 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 of 1.07).

Parkinsonism

39 Occupation has been considered as a possible cause of Parkinson's disease in several studies, but according to Savitz *et al* (1998a) 'only Wechsler *et al* (1991) provided data on a sufficiently broad array of jobs to speculate about EMF exposure'. Savitz *et al* (1998a) noted that 3 of 19 affected men in the Wechsler *et al* study were welders against 0 out of 9 controls and that 2 other affected men had worked as electricians or electrical engineers. In their own study, however, they found very little evidence of an increased risk in electrical workers, the odds ratio derived from the occupations of 168 men dying from Parkinson's disease and 1614 controls being 1.1 (95% CI 0.9, 1.2).

40 In the Danish cohort study, the SMR for Parkinsonism was 0.8 based on 14 deaths and even lower for the more heavily exposed men (0.5). The later extension to mobidity data (Johansen, 2000) recorded 68 cases and gave a standardised morbidity ratio of 0.87 and a still lower ratio of 0.64 for men exposed to the highest levels (1 μT or more). In the American study, positive relationships were observed with both cumulative career exposure and exposure more than 20 years before death, neither of which was, however, statistically significant (relative risks of 1.03 per μT-year, 95% CI 0.90, 1.18, and 1.07 per μT-year, 95% CI 0.91, 1.26).

BIOLOGICAL STUDIES OF NEURODEGENERATIVE DISEASE

41 While the common factor in these diseases is the death of neurons, the particular forms of cellular pathology and the specific cell types at risk differ in each condition. While other factors may contribute to the variety of cellular changes, oxidative stress may occur in all three types of disease.

Oxidative stress as a common factor

42 Oxidative stress is thought to be a critical factor in the modest neuronal degeneration that occurs with normal ageing, and it also seems important in the aetiology of Parkinson's disease and ALS. It may play a part in Alzheimer's disease (Felician and Sandson, 1999).

43 During normal metabolism, oxygen is reduced to H_2O in mitochondria. This involves the sequential addition of four electrons, producing three intermediate reactive oxygen species (ROS). These are the superoxide anion radical ($O_2\bullet-$), hydrogen peroxide (H_2O_2) and the hydroxyl radical ($OH\bullet$). A relatively small fraction of the electron flow (less than 5%) leaks from the respiratory chain at physiological oxygen concentrations. However, even this is significant in the brain because of its high oxygen consumption (20% of total body oxygen). Moreover, the rate of leakage of ROS from the respiratory chain increases considerably when mitochondria are exposed to elevated concentrations of sodium or calcium (Dykens, 1994).

44 Neurons contain a variety of anti-oxidant mechanisms. In particular the several isoforms of superoxide dismutase (SOD) catalyse the dismutation of $O_2\bullet-$ to H_2O_2, which is detoxified by catalase or glutathione peroxidase (Facchinetti *et al*, 1998). However, these protective systems can be overwhelmed by the production of ROS during excitotoxic shock. This occurs as a result of exposure to excess glutamate, which is released from injured neurons (eg in regions affected by stroke). The glutamate acts on NMDA and non-NMDA receptors, causing both Ca^{2+} and Na^+ entry.

45 The polyunsaturated fatty acids of cell membranes are particularly vulnerable to oxidation by ROS, leading to leakage of ions across the membrane (see Figure 1). The membrane proteins involved in ion homeostasis, including N-methyl-D-aspartate receptor channels, are also impaired. This leads to a further influx of Ca^{2+}, which, as well as leading to further elevation of ROS, damages cellular components such as proteins, DNA and lipids, and can precipitate apoptotic cell death. Increased Ca^{2+} can also lead to the production of the phosphorylating enzyme protein kinase C, which is implicated in tau and amyloid metabolism (Facchinetti *et al*, 1998; Felician and Sandson, 1999).

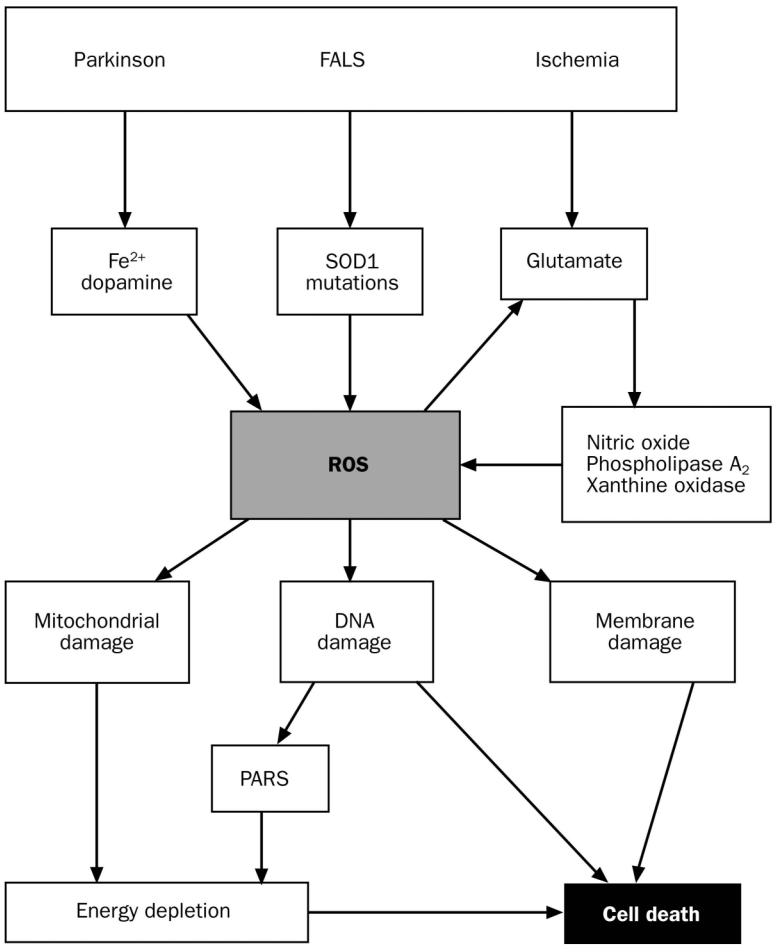

FIGURE 1
Hypothetical model showing how increased ROS formation might induce a cascade of events leading to cell death (from Facchinetti et al, 1998)

Decreased ROS scavenging (familial amyotrophic lateral sclerosis or FALS), increased ROS formation (Parkinson's disease), or increased extracellular glutamate (ischemia) can cause oxidative stress leading to membrane and DNA damage and energy depletion. Prolonged glutamate receptors stimulation can lead to prolonged elevation in intracellular calcium and activation of different enzymatic sources of ROS. At the same time, ROS enhance glutamate release. Therefore, different pathological conditions can converge toward oxidative stress, rendering a common mechanism for neurodegeneration.

Parkinson's disease

46 Mitochondrial dysfunction, exogenous toxins and the intracellular accumulation of their metabolites, viral infections, excitotoxicity, inadequate trophic support and immune dysfunction are all implicated in the aetiology of Parkinson's disease (see Figure 2; Lozano *et al*, 1998). The final common path of many of these factors may be oxidative stress. This may be the principal causal factor in dopaminergic cell degeneration in the common sporadic form of Parkinson's disease (Jenner, 1998).

47 Animal studies certainly suggest a specific role for ROS in Parkinson's disease. The toxin MPTP, which selectively destroys dopaminergic neurons and hence mimics the disease, is much less damaging in transgenic mice overexpressing SOD (Przedborski *et al*, 1992).

Amyotrophic lateral sclerosis

48 It is generally thought that motor neuron degeneration is an expression of a diverse range of abnormal cell biological processes. There are a number of known pathways for neuronal damage, including the effects of nitric oxide (released by glia and neurons when highly active: see Snyder and Bredt, 1992), as well as free radicals and superoxides (generated by microglia), which can trigger oxidative cascades (Gerlach, 1994).

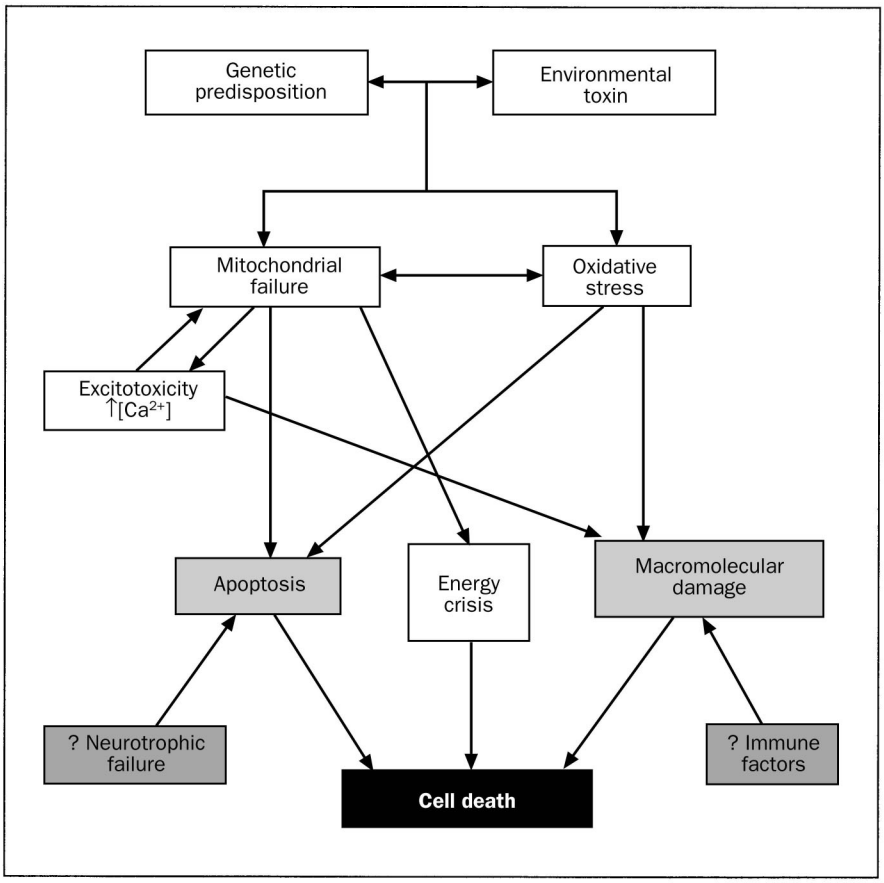

FIGURE 2 *Proposed pathophysiology of dopaminergic cell death in the substantia nigra of patients with Parkinson's disease (from Lozano et al, 1998)*

49 SOD1, which is mutated in familial ALS and may be dysfunctional in the sporadic form, is thought to be particularly important in the aetiology of these forms of motor neuron disease. SOD1 is a member of a family of metalloenzymes that act as scavengers of free radicals by catalysing the formation of H_2O_2 through the dismutation of $\bullet O_2$. The mutations of SOD in familial ALS appear to interfere with the protective effects of the enzyme. Transgenic mice expressing mutant human SOD1 develop a syndrome very similar to ALS (Ripps *et al*, 1995).

Alzheimer's disease

50 Although the evidence is less compelling, oxidative stress may be involved in the sporadic forms of Alzheimer's disease. Indices of oxidative damage are significantly increased compared with those in age-matched controls (Felician and 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.

BIOLOGICAL STUDIES OF THE EFFECTS OF ELECTROMAGNETIC FIELDS ON NEURONS

51 The suggestion that neurodegenerative diseases, particularly ALS, are related to occupational exposure to electromagnetic fields (see, for example, Davanipour *et al*, 1997) has not yet stimulated specific biological research. However, a variety of effects of electromagnetic field exposure on biological systems have previously been reported (Lacy-Hulbert *et al*, 1998). Those of potential relevance to neurodegenerative disease include small increases (Blackman *et al*, 1982, 1985), but also decreases (Bawin and Adey, 1976), in Ca^{2+} efflux from brain tissue, *in vivo* and *in vitro*, inhibition of outgrowth of neurites from cultured neurons (Blackman *et al*, 1993), and an increase in superoxide production from neutrophils (Roy *et al*, 1995).

52 Barbier *et al* (1996) reported a sustained increase (roughly a doubling) of intracellular Ca^{2+} in rat pituitary cells (lactotrophs) exposed to 50 Hz sinusoidal fields of 50 μT for 30 minutes or 3 hours. They presented some evidence that this is due to influx from extracellular fluid via voltage-dependent Ca^{2+} channels. Walleczek (1994) has also reported an increase in Ca^{2+} influx into human lymphocytes (the Jurkat T-cell line) on exposure to 'moderate-strength' magnetic fields (50/60 Hz; magnetic flux density of 1–10 mT), but only when the cells have low initial influx.

53 Thus, it is conceivable that prolonged exposure to mains frequency electromagnetic fields from electrical machinery could alter Ca^{2+} levels in neurons and thus induce oxidative stress through its influence on mitochondrial metabolism. However, the biological evidence, particularly concerning the response of neurons, is thin. Moreover, as Lacy-Hulbert *et al* (1998) concluded in their extensive review of the literature 'no EMF-induced response has yet been replicated in independent laboratories'.

54 An intriguing avenue of investigation is the effect of alternating magnetic fields on chemical reactions (Hamilton *et al*, 1988) – the 'radical pair mechanism' or 'magneto-kinetic effect', and, in particular, the 'low field effect' (McLaughlan *et al*, 1999). This occurs at modest field strength (0.1 mT), when alternating fields (at low audio to microwave frequency) are superimposed on static fields. Under some conditions, the yield of free radicals produced by chemical reactions is increased, and this might influence the activity of enzymes and other biological molecules. Eichwald and

Walleczek (1998), for example, suggest that this mechanism may account for changes in Ca^{2+} influx into cells. Whether this phenomenon ever occurs in living cells, *in vivo*, under realistic conditions of electromagnetic field exposure is unknown. A recent study by Gamble *et al* (1999) failed to detect any increase in oxyradical damage to protein in Syrian hamster dermal cells exposed for 60 hours to a 50 Hz electromagnetic field (100 μT). However, this subject deserves further investigation.

55 It is possible that even modest cellular effects of electromagnetic 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, 1996).

56 Of course, neurons can be directly activated by strong electric currents. Indeed, the threshold for rats to detect an electric field (in behavioural experiments) is only 8 kV m^{-1} at 50 Hz (Stell *et al*, 1993), and this is probably mediated by a direct effect on sensory nerves rather than through induced movement of hairs or whiskers. However, studies on hormone and neurotransmitter levels have generally reported no effect or only minor influences of electromagnetic field exposure (Sienkiewicz *et al*, 1991; Wolfe and Portier 1998).

57 Jaffe *et al* (1980) exposed rats *in vivo* chronically to electric fields of 65 kV m^{-1} (60 Hz). They found that synaptic excitability was subsequently elevated in neurons of the excised superior cervical ganglion. A number of studies have reported that the electroencephalogram (EEG) and the firing of impulses by cortical neurons can be modified by electric and magnetic fields, although the effects were more prominent at frequencies below 30 Hz (see, for example, Gavalas *et al*, 1970; Blackwell, 1986; Dowman *et al*, 1989). While these effects are unlikely to be directly dangerous, especially in the short term, there is the possibility that prolonged exposure to electromagnetic fields could synchronise certain neurons of high sensitivity (perhaps especially the large motor neurons), perhaps 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, which could have excitotoxic effects on surrounding neurons.

58 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, synchronised 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 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 *et al*, 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 ROS.

DISCUSSION*

59 Of the three neurodegenerative diseases that have been considered, Parkinson's disease has received the least attention. No study has provided clear evidence of an association with above average exposure to extremely low frequency electromagnetic fields and, in the absence of laboratory evidence to the contrary, it seems unlikely that such fields help to cause the disease.

60 The evidence relating to Alzheimer's disease is more difficult to assess. It is not much more extensive, but the initial report 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 classing groups of garment workers in the heavily exposed groups that had not previously been so classed. 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 death certificates in the USA. 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 any 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 any 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 numbers of cases were, however, small and the idea that exposure to 50–60 Hz electromagnetic fields increase the risk of Alzheimer's disease is neither proven nor excluded.

61 Much more evidence is available for amyotrophic lateral sclerosis (ALS). Eight reports† of the relationship between electrical work or the experience of electric shocks have been published since the original suggestion was made that electric shocks might increase the risk of the disease (Tables 3 and 4). Two early studies from Japan, where the prevalence of electrical work (as recorded in the medical history) and of electric 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 USA) the prevalence was significantly raised. In summary, the epidemiological evidence suggests that employment in electrical occupations may increase the risk of ALS, possibly, however, as a result of the increased risk of receiving an electric shock rather than from the increased exposure to electromagnetic fields.

---

* In this review, no account has been taken of the Schulte *et al* (1996) study of the proportional mortality attributed to Parkinsonism, Alzheimer's disease, and motor neuron disease. Schulte *et al* utilised the death certificate data that were subsequently analysed by Savitz *et al* (1998a) with the addition of the deaths for which neurodegenerative disease was given as a contributory cause. Schulte *et al* found clusters of all the three diseases of interest associated with occupations involving electrical work among many others, but the clusters are not obvious and seem to have been defined subjectively and the data as presented are unhelpful.

† The report by Gallagher and Sanders (1987) is omitted for the reasons given in paragraph 34.

62 A review by Ahlbom (2001) reached similar conclusions about Alzheimer's disease and ALS, although perhaps not quite so dismissive of an effect on the risk of the former.

63 Quantitatively, the flow of electricity through the brain is likely to be substantially greater from the use of electroconvulsive therapy for the treatment of psychiatric conditions than from even severe electric shocks received occupationally or from non-fatal strikes by lightning, but 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 1 death in 500 adults.

CONCLUSIONS

64 There is no good ground for thinking that exposure to extremely low frequency electromagnetic fields can cause Parkinson's disease and only very weak evidence to suggest that it could cause Alzheimer's disease. The evidence that people employed in electrical occupations have an increased risk of developing amyotrophic lateral sclerosis is substantially stronger, but this could be because they run an increased risk of having an electric shock rather than any effect of long-term exposure to the fields *per se*.

RECOMMENDATIONS

65 Case-control studies of Alzheimer's disease, in which information about past occupations has been obtained from surrogates, are an inefficient means of testing for small relative risks. A possibility that electromagnetic fields might contribute to the aetiology of the disease should be kept in mind when causes for Alzheimer's are being sought and information about deaths from or with Alzheimer's should be obtained in any further cohorts of electrical workers. The current evidence does not, however, justify undertaking further investigations specifically for the purpose of testing for a relationship with electromagnetic fields.

66 Case-control studies are, however, appropriate for investigating the aetiology of amyoptrophic lateral sclerosis and, in view of the rarity of the disease, are generally preferred to cohort studies. A large-scale case-control study might, therefore, be profitably undertaken in which special enquiries were made about:

(a) employment in electrical occupations, with special reference to the occurrence of severe electric shocks,
(b) medical treatment with electroconvulsive therapy that could be confirmed from hospital records,
(c) exposure to transcranial magnetic stimulation (Walsh and Cowey, 1998), a technique for magnetic induction of neuronal activity in small brain volumes, which is used both experimentally and clinically.

67 More work is needed to explore the effects of electromagnetic fields on neurons and glial cells. In particular, the effects of both brief explicit shock and prolonged exposure to electromagnetic fields on intracellular Ca^{2+}, superoxide dismutase (SOD) activity and enzyme function in neurons deserve particular attention.

REFERENCES

Ahlbom A (2001). Neurodegenerative diseases, suicide and depressive symptoms in relation to EMF. *Bioelectromagnetics*, **5**(Suppl), S132–43.

Alloul K, Saurio L, Kennedy W, Laurier C, Tessier G, Novosel S and Contandriopoulos A (1998). Alzheimer's disease: a review of the disease, its epidemiology and economic impact. *Arch Gerontol Geriat*, **27**, 189–221.

Barbier E, Duffy B and Veyret B (1996). Stimulation of Ca^{2+} influx in rat pituitary cells under exposure to a 50 Hz magnetic field. *Bioelectromagnetics*, **17**, 303–11.

Bawin S M and Adey W R (1976). Sensitivity of calcium binding in cerebral tissue to weak environmental fields oscillating at low frequency. *Proc Natl Acad Sci USA*, **73**, 1999–2003.

Blackman C F, Benane S G, Kinney L S, House D E and Joines W T (1982). Effects of ELF fields on calcium ion efflux from brain tissue *in vitro*. *Radiat Res*, **92**, 510–20.

Blackman C F, Benane S G, Rabinowitz J R, House D E and Joines W T (1985). A role for the magnetic field in the radiation induced efflux of calcium ions from brain tissue *in vitro*. *Bioelectromagnetics*, **8**, 215–27.

Blackman C F, Benane S G and House D E (1993). Evidence for direct effect of magnetic fields on neurite outgrowth. *FASEB J*, **7**, 801–6.

Blackwell R P (1986). Effects of extremely-low-frequency electric fields on neuronal activity in rat brain. *Bioelectromagnetics*, **7**, 425 (1986).

Borchelt D R, Wong P C, Sisodia S S and Price D L (1998). Transgenic mouse models of Alzheimer's disease and amyotrophic lateral sclerosis. *Brain Pathol*, **8**, 735–57.

Brown RH Jr (1997). Amyotrophic lateral sclerosis. Insights from genetics. *Arch Neurol*, **54**, 1246–50.

Burke R E (1998). Programmed cell death and Parkinson's disease. *Mov Disord*, **13**(suppl 1), 17–23.

Davanipour Z, Sobel E, Bowman J D, Qian Z and Will A D (1997). Amyotrophic lateral sclerosis and occupational exposure to electromagnetic fields. *Bioelectromagnetics*, **18**, 25–35.

Davies P, Katzman R and Terry R D (1980). Reduced somatostatin-like immunoreactivity in cerebral cortex from cases of Alzheimer disease and Alzheimer senile dementia. *Nature*, **288**, 279–80.

Deapen D M and Henderson B E (1986). A case–control study of amyotrophic lateral sclerosis. *Am J Epidemiol*, **123**, 790–99 (1986).

Dessi F, Charriaut-Marlangue C and Ben-Ari Y (1994). Glutamate induced neuronal death in cerebellar culture is mediated by two distinct components: a sodium-chloride component and a calcium component. *Brain Res*, **650**, 49–55.

Dowman R, Wolpaw J R, Seegal R F and Satya-Murti S (1989). Chronic exposure of primates to 60-Hz electric and magnetic fields: III. Neurophysiological effects. *Bioelectromagnetics*, **10**, 303.

Dykens J A (1994). Isolated cerebral and cerebellar mitochondria produce free radicals when exposed to elevated Ca^{2+} and Na^{+}: implications for neurodegeneration. *J Neurochem*, **63**, 584–91.

Eichwald C and Walleczek J (1998). Magnetic field perturbations as a tool for controlling enzyme-regulated and oscillatory biochemical reactions. *Biophys Chem*, **74**, 209–24.

Facchinetti F, Dawson V L and Dawson T M (1998). Free radicals as mediators of neuronal injury. *Cell Mol Neurobiol*, **18**, 667–82.

Felician O and Sandson T A (1999). The neurobiology and pharmacotherapy of Alzheimer's disease. *J Neuropsychiatry*, **11**, 19–31.

Feychting M, Pedersen N L, Svedberg P, Floderus B and Gatz M (1998). Dementia and occupational exposure to magnetic fields. *Scand J Work Environ Health*, **24**, 46–53.

Floderus B, Persson T, Stenlund C, Wennberg A, Öst A and Knave B (1993). Occupational exposure to electromagnetic fields in relation to leukaemia and brain tumours: a case–control study in Sweden. *Cancer Causes Control*, **4**, 465–76.

Floderus B, Persson T and Stenlund C (1996). Magnetic field exposures in the workplace: reference distribution and exposures in occupational groups. *Int J Occup Environ Health*, **2**, 226–38.

Gallagher J P and Sanders M (1987). Trauma and amyotrophic lateral sclerosis: a report of 78 cases. *Acta Neurol Scand*, **75**, 145–50.

Gamble S C, Arrand J E, Newbold R, Sutherland I and Wolff H (1999). The biological consequences of exposure of mammalian cells to low frequency electromagnetic fields. IN Proceedings EMF Biological Research Trust Workshop on Biological Interactions of Low-frequency Fields, London, January 1999.

Gavalas R J, Walter D O, Hamer J and Adey W R (1970). Effect of low-level, low-frequency electric fields on EEG and behavior in *Macaca nemestrina*. *Brain Res*, **18**, 491.

Gawel M, Zaiwalla Z and Rose C F (1983). Antecedent events in motor neuron disease. *J Neurol Neurosurg Psychiatry*, **46**, 1041–3.

Gerlach M (1994). Altered brain metabolism of iron as a cause of neurodegenerative disease. *J Neurochem*, **63**, 793–807.

Goedert M and Hasegawa M (1999). The tauopathies: toward an experimental animal model. *Am J Pathol*, **154**, 1–6.

Gunnarsson L-G, Lindberg G, Söderfeldt B and Axelson O (1991). Amyotrophic lateral sclerosis in Sweden in relation to occupation. *Acta Neurol Scand*, **83**, 394–8.

Hamilton C A, Hewitt J P and McLaughlan K A (1988). High resolution studies of the effects of magnetic fields on chemical reactions. *Mol Phys*, **65**, 423–38.

Haynal A and Regli F (1964). Zusammenhang der amyotrophischen lateralsclerose mit gehäufter elektrotraumata. *Confinia Neurologica*, **24**, 189–98.

Henderson C E (1995). Neurotrophic factors as therapeutic agents in amyotrophic lateral sclerosis. Potential and pitfalls. *Adv Neurol*, **68**, 235–40.

Jaffe R A, Laszewski B L, Carr D B and Phillips R D (1980). Chronic exposure to a 60 Hz electric field: effects on synaptic transmission and peripheral nerve function in the rat. *Bioelectromagnetics*, **1**, 131–47.

Jenner P (1998). Oxidative mechanisms in nigral cell death in Parkinson's disease. *Mov Disord*, **13**(suppl 1), 24–34.

Johansen C (2000). Exposure to electromagnetic fields and risk of central nervous system disease in utility workers. *Epidemiology*, **11**(5), 539–43.

Johansen C and Olsen J H (1998a). Risk of cancer among Danish utility workers – a nationwide cohort study. *Am J Epidemiol*, **147**, 548–55.

Johansen C and Olsen J H (1998b). Mortality from amyotrophic lateral sclerosis, other chronic disorders, and electric shocks among utility workers. *Am J Epidemiol*, **148**, 362–8.

Kandel E R, Schwartz J H and Jessell T M (1991). *Principles of Neural Science* (3rd ed). East Norwalk CT, Appleton & Lange, Chapter 65, pp 1009–31 (1991).

Kondo K and Tsubaki T (1981). Case–control studies of motor neurone disease. Association with mechanical injuries. *Ann Neurol*, **38**, 220–26.

Kowall N W and Beal M F (1991). Glutamate-, glutaminase-, and taurine-immunoreactive neurons develop neurofibrillary tangles in Alzheimer's disease. *Ann Neurol*, **29**, 162–7.

Lacy-Hulbert A, Metcalfe J C and Hesketh R (1998). Biological responses to magnetic fields. *FASEB J*, **12**, 395–420.

Li C M *et al* (1996). Effects of extremely low magnetic fields at differing intensity on gap junction communication. IN 1996 Bioelectromagnetics Conference Transactions.

Lozano A M, Lang A E, Hutchison W D and Dostrovsky J O (1998). New developments in understanding the etiology of Parkinson's disease and in its treatment. *Current Opin Biol*, **8**, 783–90.

McLaughlan K A, Brocklehurst B and Hore P J (1999). Magnetic field effects on radical reactions. IN Proceedings EMF Biological Research Trust Workshop on Biological Interactions of Low-frequency Fields, London, January 1999.

NRPB (1992). Electromagnetic fields and the risk of cancer. Report of an Advisory Group on Non-ionising Radiation. *Doc NRPB*, **3**(1), 1–138.

NRPB (1994). Electromagnetic fields and the risk of cancer. Supplementary report by the Advisory Group on Non-ionising Radiation (12 April 1994). *Doc NRPB*, **5**(2), 77–81.

NRPB (2001). ELF Electromagnetic fields and the risk of cancer. Report of an Advisory Group on Non-ionising Radiation. *Doc NRPB*, **12**(1), 1–179.

Perry E K (1986). The cholinergic hypothesis – ten years on. *Br Med Bull*, **42**, 63–9.

Price D L, Tanzi RE, Borchelt D R and Sisodia S S (1998). Alzheimer's disease: genetic studies and transgenic models. *Ann Rev Genet*, **32**, 461–93.

Przedborski S, Kostic V, Jackson-Lewis R *et al* (1992). Transgenic mice with increased Cu/Zn-superoxide dismutase activity are resistant to N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced dopaminergic neurotoxicity. *J Neurosci*, **12**, 1658–67.

Ripps M E, Huntley G W, Hof P R, Morrison J H and Gordon J W (1995). Transgenic mice expressing an altered murine superoxide dismutase gene provide an animal model for amyotrophic lateral sclerosis. *Proc Natl Acad Sci USA*, **92**, 689–93.

Roth M, Tomlinson B E and Blassed G (1966). Correlation for scores between dementia and counts of 'senile plaques' in cerebral grey matter of elderly subjects. *Nature*, **209**, 109–10.

Rothstein J D (1995). Excitotoxic mechanisms in the pathogenesis of ALS. *Adv Neurol*, **68**, 7 (and other papers in this issue).

Rowland L P (1994). Natural history and clinical features of amyotrophic lateral sclerosis and related motor neuron diseases. IN *Neurodegenerative Diseases* (D B Calne, Ed). Philadelphia, WB Saunders, pp 507–21.

Roy S, Noda Y, Eckert V *et al* (1995). The phorbol 12-myristate 13-acetate (PMA)-induced oxidative burst in rat peritoneal neutrophils is increased by a 0.1 mT (60 Hz) magnetic-field. *FEBS Lett*, **376**, 164–6.

Savitz D A and Loomis D P (1995). Magnetic field exposure in relation to leukaemia and brain cancer mortality among electric utility workers. *Am J Epidemiol*, **141**, 123–34.

Savitz D A, Loomis D P and Tse C J (1998a). Electric occupations and neurodegenerative disease: analysis of US mortality data. *Arch Environ Health*, **53**, 71–4.

Savitz D A, Checkoway H and Loomis D P (1998b). Magnetic field exposure and neurodegenerative disease among electric utility workers. *Epidemiology*, **9**, 398–404.

Sienkiewicz Z J, Saunders R D and Kowalczuk C I (1991). Biological effects of exposure to non-ionising electromagnetic fields and radiation: II. Extremely low frequency electrical and magnetic fields. Chilton, NRPB-R239.

Schulte P A, Burnett C A, Boeniger M F and Johnson J (1996). Neurodegenerative diseases: occupational occurrence and potential risk factors, 1982 through 1991. *Am J Publ Health*, **86**, 1281–8.

Sobel E, Davanipour Z, Sulkava R, Erkinjunnti T, Wikstrom J, Henderson V W, Bowman J U D and Lee P-J (1995). Occupations with exposure to electromagnetic fields: a possible risk factor for Alzheimer's disease. *Am J Epidemiol*, **142**, 515–24.

Sobel E, Dunn M, Davanipour Z, Qian Z and Chui H C (1996). Elevated risk of Alzheimer's disease among workers with likely electromagnetic fields exposure. *Neurology*, **47**, 1477–81.

Snyder S and Bredt D (1992). Biological roles of nitric oxide. *Sci Am*, May 1992.

Speciale SG, Liang CL, Sonsalla PK, Edwards RH and German DC (1998). The neurotoxin 1-methyl-4-phenyl-pyridinium is sequestered within neurons that contain the vesicular monoamine transporter. *Neuroscience*, **84**, 1177–85.

Stell M, Sheppard A R and Adey W R (1993). The effect of moving air on detection of a 60 Hz electric field. *Bioelectromagnetics*, **14**, 67–78.

Uhl G R (1998). Hypothesis: the role of dopaminergic transporters in selective vulnerability of cells in Parkinson's disease. *Ann Neurol*, **43**, 555–60.

Walleczek J, Killoran P L and Adey W R (1994). 60-Hz magnetic field effects on Ca^{2+} (Mn^{2+}) influx in human Jurkat T-cells: strict dependency on cell state. IN Abstracts, 16th Annual Meeting of the Bioelectromagnetics Society, Copenhagen, June 1994, p 76.

Walsh V and Cowey A. Magnetic stimulation studies of visual cognition. *Trend Cognit Sci*, **2**(3), 103–10 (1998).

Wechsler LS, Checkoway H, Franklin G M and Costa L G (1991). A pilot study of occupational and environmental risk factors for Parkinson's disease. *Neurotoxicology*, **12**, 387–92.

Whitehouse P J, Price D L, Struble R G, Clark A W, Coyle J T and DeLong M R (1982). Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. *Science*, **215**, 1237–9.

Wolfe MS and Portier CJ (Eds) (1998). Assessment of health effects from exposure to power-line frequency electric and magnetic fields. *NIEHS Working Group Report, 1998*. Bethesda MD, National Institute of Environmental Health Sciences, NIH Publication No. 98-3981.