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The Epidemiology of Primary Degenerative Dementia and Related Neurological Disorders

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Summary. Observation of cytopathological similarities between the changes of Alzheimer-type dementia, Parkinson's disease and motor neuron disease, as well as of some degree of clinical association between these conditions, has led to the suggestion that all three belong to a common class of degenerative neurological disorders, each of which as a rule first becomes manifest when age-related neuronal attrition is superimposed on subclinical damage caused by environmental noxae earlier in life. The importance of this model lies in its potential relevance to prevention. The epidemiological data reviewed here suggest that, while the three disease groups are all strongly linked with ageing, there may be major differences between their patterns of occurrence in populations, which make it doubtful if the same environmental pathogens are responsible in each instance. The most plausible unifying hypothesis at present is that the predisposing neuronal damage can be caused by a number of widely distributed metallic neurotoxins, each of which has a tendency to pick out specific areas or cell groups within the CNS and thus to give rise to distinct though overlapping clinical syndromes. The evidence bearing on this and other causal hypotheses is, however, still tenuous because of the scarcity of empirical data. Population-based case-control and cohort studies are called for, as part of a co-ordinated research endeavour.

Key words: Epidemiology – Dementia – Parkinsonism – Motor neuron disease

Introduction

The primary dementias of late life have traditionally been neglected both in psychiatric and in neurological research. A more active concern with their aetiology has in the past been discouraged by uncertainty in distinguishing between dementia as a pathological condition, "senility" and normal ageing processes, as well as by a longstanding belief that the mental decline in affected persons is pre-ordained and inevitable, its onset being triggered by a biological clock whose timing is genetically determined. Thus, Gowers [37] included late-life mental failure due to cerebral atrophy as one form of "neuronic abiotrophy", a term which implied that the innate viability of the central nervous system, or some parts of it, may be more limited than that of other organ systems even in the absence of external pathogenic agents.

If Gower's concept of abiotrophy did not tend to encourage causal research, it was nonetheless valuable in bringing the primary dementias into perspective as part of a larger category of late-life degenerative disorders of the central nervous system, together with Parkinson's disease (PD) and the group now usually referred to as motor neuron disease (MND), which includes amyotrophic lateral sclerosis (ALS), progressive muscular atrophy and progressive bulbar palsy. His suggestion that these clinically disparate conditions share a common type of pathogenesis has attracted renewed attention in recent years, partly because of the improved differentiation of dementia of Alzheimer type (DAT) from other forms, partly due to the emergence in the United States and some other countries of a new discipline of neuroepidemiology [66], whose practitioners recognize in this disease a major subject for research. Additional impetus has come from studies of areas in the Western Pacific, where clinical syndromes combining features of these three diagnostic categories were found to be endemic and highly prevalent [64].

Against this background, Calne and his co-workers [15] in Vancouver have postulated that DAT, PD and MND all arise as a result of environmentally determined damage to localized centres in the central nervous system, which may be caused much earlier in life but usually remains subclinical until the effects of age-related neuronal attrition supervene and a clinical threshold is crossed. This challenging hypothesis is based on the occurrence of co-morbidity in affected patients, associations found between specific environmental noxae and a number of neurodegenerative diseases, and the prolonged latency period that can elapse between exposure to a pathogen and the onset of illness. Calne has argued

that differences in cell pathology observed by conventional microscopy may have led to false conclusions. The newer histological techniques suggest that a general type of neuronal decay, characterized by the deposition of cytoskeletal débris, is so typical of all three diagnostic groups that they might collectively be termed "cytoskeletal disorders" [13].

The shift of focus thus signalized, from a primarily genetic to a primarily environmental causal model, has profound implications for future research. If the causes of the predisposing subclinical damage in earlier life can be identified, prevention may become a realistic goal. The arguments so far adduced in favour of this model are, however, far from conclusive. The neuropathological evidence rests largely on the overlapping of different forms of cytoskeletal destruction, whose hallmarks are the neurofibrillary tangles, amyloid plaques and granulovacuolar bodies of DAT, the Lewy bodies of PD and the Bunina bodies and spheroids of MND [15]. In addition, clinical evidence of the co-existence of dementia and parkinsonism, and the association of both with MND, which has continued to accumulate since the review by Hudson [48], points to some degree of causal association. But to reach firmer conclusions, the relative distributions of the three diagnostic groups must be studied in unselected elderly populations. Precisely at this crucial point, the research data are sparse and fragmentary and the vital epidemiological links in the chain of evidence missing. The aim of the present paper is to review this fragmentary material and to gauge how far it supports an unifying hypothesis.

The Epidemiology of Dementia, with Special Reference to DAT

Dementia has been defined [87] as a syndrome due to disease of the brain, usually chronic or progressive, in which there is impairment of higher cortical functions, including memory, abstract thinking, orientation, comprehension, calculation, learning capacity, language and judgement. These impairments are commonly accompanied, and sometimes preceded, by deterioration in emotional control, social behaviour and motivation. In DAT, the neuropathological changes are thought to commence in the hippocampus and possibly other parts of the limbic system, and to spread thence to the neocortex [4]. The clinical diagnosis is favoured by a history of insidious onset and gradual, progressive course, in the absence of focal neurological signs or other evidence that the mental decline is secondary to a specific disease. The fact that DAT is still partly a diagnosis of exclusion is a serious handicap in studying its associations with cerebrovascular and other forms of neurological disease.

Prevalence and Incidence Studies of Dementia

Mortality statistics are of very limited value as indicators of the frequency of DAT in populations. Martyn and Pippard [70], noting that fewer than one-quarter of persons diagnosed during life as demented had this condition coded as the underlying cause of death and, moreover, that the diagnosis was recorded most often for institutional residents, concluded that in the United Kingdom death-certificate data are unlikely to be useful in examining either geographical variation or time trends in frequency. In fact, mortality data have yielded some intriguing associations with environmental variables (see below), but the findings of such studies can be no more than suggestive.

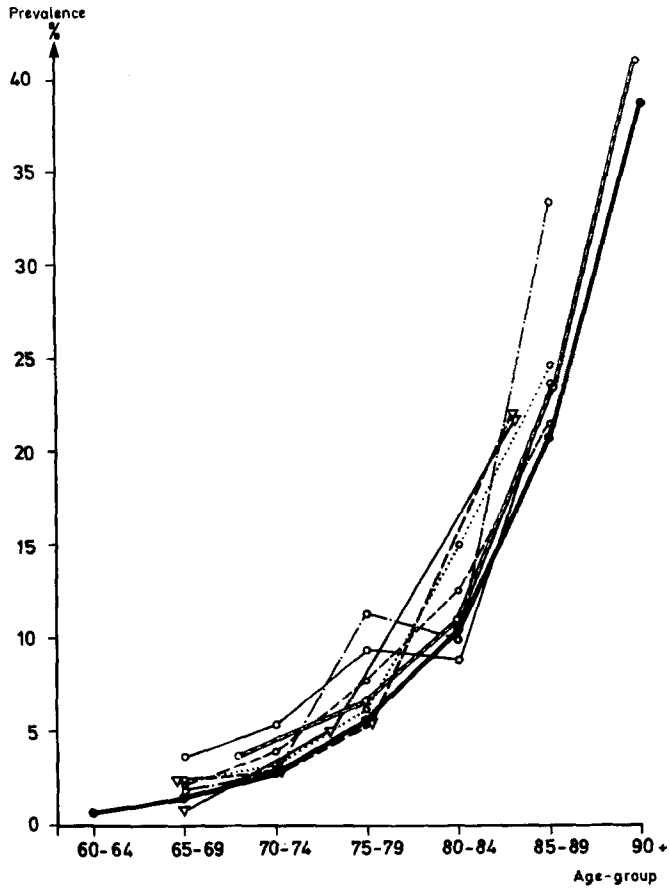

Fig. 1. Age-group-related prevalence ratios for dementia (moderate and severe grades) from population-based field studies. ▽——▽ "Lundby", Sweden [41]; ○——○ New York State, USA [76]; ○----○ Samsø Is., Denmark [77]; ▽----▽ Newcastle, UK [55]; ○-·-·-○ Osaka, Japan [53]; ○———○ Gisborne, New Zealand [16]; ○·····○ Mannheim, FRG [22]; ●———● pooled data [51]

Prevalence estimates from nearly 50 field studies, carried out in the years 1945–1985, when subjected to a meta-analysis [51], pointed to a relative excess of DAT among women and a consistent relationship between the ratios for successive age-groups above 60, the frequency almost doubling with each additional 5 years of age. A more recent re-analysis of 12 European studies [46] has confirmed these general findings.

Figure 1 brings together age-specific prevalence curves from the pooled data of 22 field studies [51] and also from seven individual surveys in different parts of the world, each of which was aimed to give full coverage of an unselected population sample of the elderly. The age-

Table 1. Incidence of dementia[a] in the elderly population, reported from population-based surveys; annual age-specific rates per 1,000 population

Author(s)	Survey area and period	Sample size[b] (persons aged over 60)	Age-group (years)			
			60–69	70–79	80 +	Total (60 +)
Bergmann et al. [7]	Newcastle, UK:					
	(a) 1960–1964	760 (2,000)	–	–	–	15.0
	(b) 1964–1967					
Hagnell et al. [41]	"Lundby", Sweden:					
	(a) 1947–1957	655 (4,224)	5.1	18.8	57.3	16.3
	(b) 1957–1972	696 (7,959)	2.9	14.8	33.7	10.7
Nielsen et al. [78]	Samsø Island, Denmark					
	1972–1977	1,564 (6,580)	2.8	22.7	34.6	12.0
Nilsson [79]	Gothenburg, Sweden					
	1971–1981	364 (2,655)	–	16.2	–	–
Kokmen et al. [60]	Rochester, Minn., USA:					
	(a) 1965–1969	–	1.4	6.0	16.5	–
	(b) 1970–1974	–	1.4	6.4	20.5	–
Cooper and Bickel [22]	Mannheim, FRG:					
	1978–1986[c]	314 (1,912)	4.7	12.2	39.6	15.4[d]

[a] Includes dementia and closely related diagnoses (senile psychosis; organic psychosis; severe organic mental disorder)
[b] Figures in brackets refer to numbers of "person-years" at risk
[c] Age-groups 65–69; 70–79; 80 +
[d] Corrected to age-distribution at survey outset

specific prevalence rises from under 3% for the 65–69 year age-group to around 25% for those aged over 85 years. There is no sign of a decline in prevalence in the highest age-groups, but because the numbers involved are small in each survey sample, this possibility cannot definitely be excluded.

Table 1 sets out figures for the incidence of dementia from the handful of studies which have monitored the occurrence of new cases in elderly populations. Leaving aside the Rochester study [60] which, because based on medical records, is not strictly comparable with the rest, these investigations have provided quite similar findings, with a variation in annual incidence between 10 and 16 per 1,000 in the elderly. DAT, which probably accounts for around 60% of all new cases [22, 84], may show a somewhat steeper age-related increase in incidence than the other forms of dementia [60]. The mean point prevalence of 6% and mean annual incidence of 1.5%, found in Mannheim [22, 23], imply that the course of clinically manifest dementia runs on average about 4 years. To this estimate must be added the early, pre-clinical stages of cognitive decline.

Data from successive waves of the "Lundby" study in Sweden [41] conform to a decline in incidence of both DAT and cerebrovascular dementia in recent decades, but here also the numbers involved are small, while the time intervals between survey waves may have been overlong for monitoring the appearance of new cases. According to a careful documentation in Rochester, Minn., over three quinquennia [60], the incidence of DAT remained steady during the 1960s and 1970s, whereas other forms of dementia showed some decline in frequency.

Risk Factors of DAT

The relative importance of genetic predisposition is still unclear. Familial Alzheimer's disease is a distinct subcategory, characterized by early onset and transmission as a mendelian dominant trait [21]. While the absence of a pedigree in other cases may be partly explicable in terms of mortality experience [32], it seems highly probable that environmental causes must be invoked to explain the occurrence of the common sporadic form. Systematic twin-pair studies of the kind required to establish the strength of heritability are still lacking, although a number of individual cases of monozygous twins discordant for dementia have been reported in the literature.

Among possible environmental causes, viral encephalopathy, cerebral trauma and exposure to various neurotoxins have been implicated and their contributions examined in a number of retrospective case-control studies [2, 43]. No cases of natural or iatrogenic transmission between humans, or of experimental transmission to monkeys, have been confirmed. Case-control studies inquiring into a history of meningitis, encephalitis and herpes zoster infection, as well as of skin grafting, ingestion of animal brains, contact with animals and travel to focal endemic areas, have yielded no consistent findings. The observation that contact with domestic animals, particularly dogs, may be involved [2] awaits replication. An increase in myelo-proliferative disorders among first-degree relatives, reported by Heston et al. [44] suggested a possible viral aetiology but has not been confirmed by other workers.

Although enquiry into a history of earlier head injury has also been included in a number of case-control studies, the findings are inconclusive [20]. Dementia pugilistica, which is often cited as a paradigm for age-related dementing disorder superimposed on earlier brain damage, is unlike sporadic DAT in being usually preceded by dysarthria, tremor and other neurological abnormalities.

Associations have been mooted with exposure to a variety of potentially neurotoxic substances, including aluminium salts, organic solvents, pesticides and some pharmaceuticals [43]. Aluminium is a prime suspect, since it is found as aluminosilicates in senile plaques, can cause cytoskeletal changes in experimental animals and has been implicated as a cause of secondary dementia in patients on intermittent renal dialysis [26]. A direct link with the prevalence of DAT has recently been reported by a French research group (J.F. Dartigues, unpublished, 1990), while the aluminium content of drinking water has been shown to correlate with dementia-related mortality in different regions of Norway [31] and with the frequency of clinically diagnosed dementia among persons referred for CT scanning in different areas of England and Wales [72].

The absence of any hint of a male preponderance of DAT in population-based studies casts some doubt on the importance of industrial exposures as a causal factor. Nevertheless, an increased risk for late-life dementia has been noted among some occupational groups; notably miners who were regularly exposed to aluminium salts (M.R. Eastwood, personal communication, 1990) and persons working with organic solvents [73].

Epidemiology of PD and Parkinsonism

PD is characterized clinically by muscular rigidity, poverty of movement (bradykinesia) and a tremor that is typically regular and rhythmic, maximal at rest and most marked distally in the limbs. The main pathological features are degenerative changes in the basal ganglia, especially the substantia nigra and corpus striatum, together with less prominent alterations in the cerebral cortex. Four major sub-groups have been differentiated [5]: the sporadic form (PD or paralysis agitans); post-encephalitic parkinsonism, a familial form that is transmitted as an autosomal dominant trait; and secondary (or "symptomatic") parkinsonism, in which the disorder is caused by cerebral atherosclerosis, trauma, chronic intoxication or systemic disease. Idiopathic PD is thus, like DAT, to some extent a diagnosis of exclusion. It has been estimated that about one in five of patients with PD manifests some degree of dementia [11], which implies a distinct increase in relative risk for the age-groups concerned; the nature of the underlying neuropathology and its relationship to DAT is still a subject for investigation.

Incidence and Prevalence Studies of Parkinsonism

If mortality rates are employed as a measure of frequency, there will be a danger of gross under-estimation. PD was recorded as a cause of death in only 46% of diagnosed cases in Rochester [63] and in lower proportions elsewhere. Co-variation of death-certificate statistics with geographic or socio-demographic differences is thus difficult to interpret. Prevalence or, even better, incidence data would be much more useful in causal research, but there have been relatively few population surveys of PD to date. Table 2 summarizes data from seven of these studies, all but one based on predominantly white populations. To make the findings more closely comparable, they have been adjusted for age distributions, taking the U.S. population in 1960 as the standard [57].

The adjusted prevalence ratios range from 7 to 18 per 10,000 and the incidence rates from 8 to 18 per 100,000, corresponding to a mean illness duration of about 10 years. The two studies with the strongest claims to full case-ascertainment, those in Rochester and Iceland, both yielded prevalence ratios of 16–18 per 10,000 and an annual incidence rate of 18 per 100,000, which suggests

Table 2. Population-based estimates of the frequency of Parkinson's disease[a]

Place and population size	Mean annual incidence per 100,000				Point-prevalence per 100,000			
	Time period	No. of cases	Observed rate	Adjusted rate[b]	Date	No. of cases	Observed ratios	Adjusted ratios[b]
Rochester, Minn., USA 47,800	1955–1966	97	19.3	17.9	1.01.65	75	156.9	165.5
Carlisle, UK 71,100	1955–1961	60	12.1	9.4	1.01.61	80	112.5	90.2
Iceland 187,000	1954–1963	272	16.0	18.2	31.12.63	304	162.6	179.8
Gippsland, Victoria 83,000	1959–1964	35	7.0	7.7	1.01.65	70	84.3	95.4
Göteborg, Sweden 40,000	1957–1961	118	5.9	–	1.01.60	270	67.5	69.5
Baltimore, Md., USA 2,070,000	1967–1968	471	11.4	–	1.01.70	1,630	78.8	80.9
Southwest Finland 403,000	1968–1970	179	14.8	11.6	31.12.71	484	120.1	93.5

[a] From Kessler [57]
[b] Adjusted to 1960 U.S. population as standard

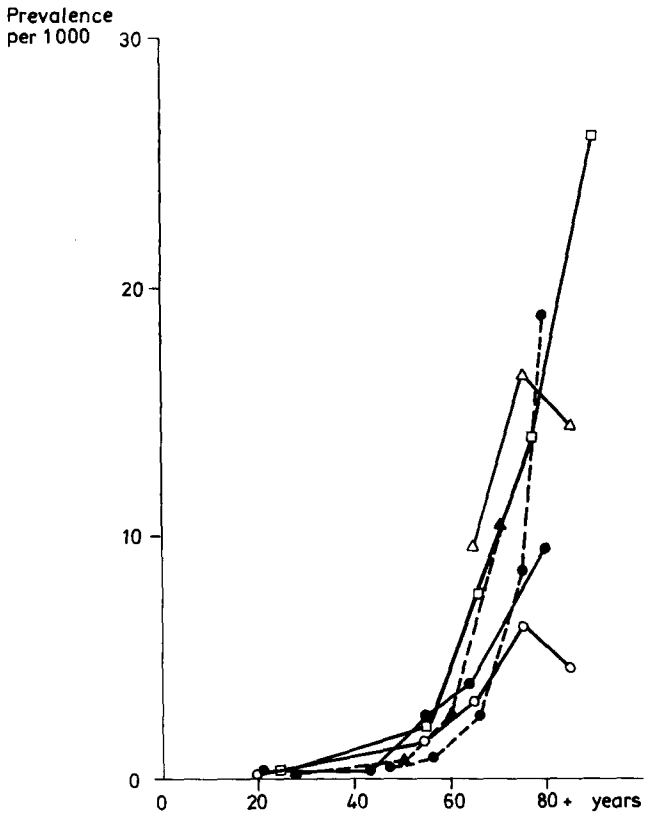

Fig. 2. Age-specific prevalence ratios for Parkinson's disease: after Evans and Caird [30]. □——□ Rochester, Minn., USA [63]; ○——○ Carlisle, UK [10]; ●——● Victoria, Australia [49]; △——△ Iceland [39]; ▲----▲ Baltimore, Md., USA [56]; ●----● Aberdeen UK [75]

closely similar levels of morbid risk in these two populations. With few exceptions, the epidemiological data have revealed a modest preponderance among males, the sex ratio being typically of the order of 1.4:1 [57], and also a somewhat earlier onset in men.

The Baltimore survey [56] reported a much higher frequency among whites than among negroes in that city, especially in younger adult age-groups. This disparity led to a good deal of speculation about ethnic differences in morbid risk for PD. More recently, however, a door-to-door survey of a biracial community in Mississippi showed virtually no difference in the age-adjusted prevalence ratios for whites and negroes, but a marked difference in the proportions of treated cases [83]; it thus seems probable that the Baltimore finding was an artefact of medical treatment and referral practices.

Figure 2 displays age-specific prevalence curves based on six population surveys of PD in different countries. Agreement between the individual studies is not close enough to permit any precise comparison with the corresponding data on dementia shown in Fig. 1, but in broad terms it appears that the mean age of onset of PD precedes that of dementia by some years, and that the age-curve of prevalence climbs less steeply. Two of the studies indicate that there may be a decline in frequency above the age of 75 years, a trend which is more strongly pronounced in the few estimates of age-specific incidence for parkinsonism [65].

Risk Factors for PD and Parkinsonism

The importance of heredity is not firmly established. Evidence of family aggregation has led some researchers to postulate that idiopathic PD is transmitted as an autosomal dominant trait with partial penetrance, but twin studies have not confirmed this view [28]. In a U.S. study of 65 twin pairs [86], only 1 of 43 monozygous pairs was definitely concordant for PD. It seems improbable, therefore, that genetic factors can be of primary significance. Calne and Langston [14] have pointed out that this finding also casts doubt on the part played by risk exposures in childhood, since most twins are brought up together, and hence that we should be looking for environmental factors operating in early or middle adult life.

The world pandemic of encephalitis lethargica in the years 1917–1927 drew attention to infection as a possible cause, since following on von Economo's type A encephalitis many patients were left with, or subsequently developed, a parkinsonian syndrome. Those patients with early post-encephalitic syndromes were younger than and differed clinically from typical PD patients, whereas those with late sequelae showed much greater similarity to the sporadic form. Poskanzer and Schwab [81], observing that in Boston the mean age of hospital-treated cases had risen steadily since 1945, advanced the hypothesis that PD was usually a late consequence of the encephalitis pandemic of the 1920s and hence that, as the affected birth cohort disappeared by attrition, the frequency of PD in the general population would rapidly diminish. Since this has not in fact occurred, it now seems probable that the shift in age distribution of treated cases was another example of the Berksonian bias that can arise from selective referral and admission to hsopital [65]. In retrospect, the impact of epidemic encephalitis on the natural history of parkinsonism appears to have been fairly short-lived.

Apart from the post-encephalitic wave, mortality due to parkinsonism has not shown any definite secular trend, at least until recently. Duvoisin and Schweitzer [27] concluded that the prevalence had remained stationary for 40 years and, indeed, that the risk of dying from this disease had not changed appreciably during the present century. Throughout these years, no environmental influence has been shown to have exerted an influence one way or another. Schoenberg [82] emphasized the constant frequency of cases in Rochester over a 35-year period. These findings do not, however, argue for or against the role of any specific factor, especially as the effects of improved nutrition, sanitation or industrial protection may have served to balance those of, for example, encreasing environmental pollution. In any event, the premise may no longer be valid, since recent evidence from the United States suggests that PD-related mortality is on the increase (D.B. Calne, personal communication, 1990).

A number of possible toxic risk factors have been implicated, including salts of manganese [1] and chromium [25], organic pesticides [67] and neuro-excitatory amino acids found in certain types of plant [14], though analytic

studies have so far failed to confirm the importance of any of these substances as determinants of the prevalence of PD in populations.

Epidemiology of MND

The term „motor neuron disease" is used collectively for the syndromes of ALS, progessive muscular atrophy, progressive bulbar palsy and a number of rarer conditions. Though all these disorders have a similar neuropathological substrate and overlapping clinical features, they do not necessarily share a single common cause. Some forms are definitely hereditary, whereas others, including ALS, are usually sporadic. The group as a whole is characterized by wasting, weakness and fasciculation of skeletal muscles, nearly always with pyramidal tract involvement at some stage, and a fatally progressive course. The pathological hallmark is a selective degeneration and loss of anterior horn cells and motor cranial nerve nuclei. The clinical features are attributable to degeneration of motor nuclei at the spinal or brain-stem levels, or both, usually with some involvement of cortical Betz cells and demyelination of cortico-bulbar and cortico-spinal pyramidal tracts.

Dementia in association with MND is uncommon in most populations, but since the mean age of onset is generally around 60 years and the disease runs a fatal course, few of the affected persons survive into the peak period for DAT. Some cases are preceded by presenile dementing changes, not clearly related to an Alzheimer-type pathology [6], while the families of MND patients may carry a relative excess of dementia cases [48]. The significance of these observations remains uncertain.

Prevalence and Incidence Studies of MND

Death-certificate rates provide a much more useful indicator of the frequency of this disease than they do for either DAT or PD. A study in North Carolina [45] revealed that over 70% of diagnosed cases of MND had the condition recorded on the death certificates, while in Norway and the Netherlands the proportions were considerably higher [65]. In all countries for which mortality statistics are available, MND occurs and has accounted for over 1 per 1,000 adult deaths. Age-adjusted mortality rates in most developed countries have lain between 0.5 and 1.2 per 100,000 population, with a male preponderance averaging about 1.6:1. This generally higher risk for men remains unexplained, but may offer a clue to the nature of the aetiology.

Because of the relative rarity of this disease, age-specific prevalence and incidence estimates, based on first-hand data gathering, are still scarce. Figure 3 shows age- and sex-specific mortality curves, based on national statistics for Finland [50] and England and Wales [12]. These curves, if transposed to the left to allow for a mean illness duration of 3–5 years, should give a rough approximation to the corresponding incidence curves for the disease, as, for example, a comparison of age-specific mortality and incidence curves for the Israeli national population suggests [52]. All these national data, as well as those for a province of Italy [38], point to a steady increase in morbid risk from 40 up to 65–70 years, followed by a distinct decline. The Finnish data are unusual in showing no sign of a male preponderance.

Table 3 summarizes data from eight population-based studies that reflect directly on the frequency of MND in different populations. Four of these studies, all relatively reliable in terms of diagnosis, sample-size and completeness of coverage, reveal a fairly constant prevalence of 6–7 per 100,000 population in widely separated areas. The fact that lower rates were reported from the studies in middle and eastern European countries can be more readily ascribed to incomplete case-finding, due to reliance on hospital records, than to true geographic differences. Even so, the relative uniformity of prevalence may be misleading, since in the more reliable studies the incidence rates varied between 0.76 and 1.4 per 100,000.

Risk Factors of MND

The latter point is of some importance, because an apparently uniform frequency of MND in populations has been used to argue that environmental conditions have

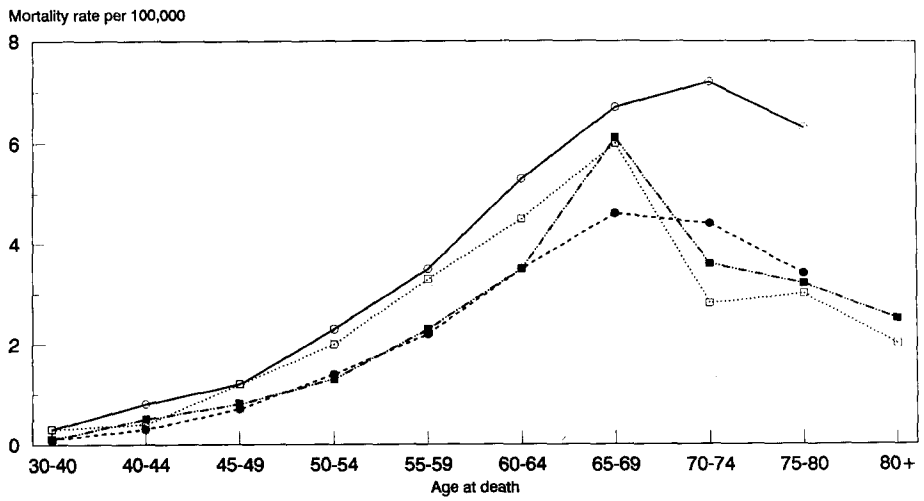

Fig. 3. Age-specific mortality due to motor neuron disease. England and Wales, 1959–1979 (○, males; ●, females), and Finland, 1963–1972 (□, males; ■, females). Sources: Buckley et al. [12] and Jokelainen [50]

Table 3. Population surveys of motor neuron disease[a]

Source of data	Period of survey	Survey area	Base population	No. of cases	Patients alive on prevalence day	Annual incidence rate per 100,000	Prevalence per 100,000	
							observed	range[b]
Kurland et al. [65]	1925–1964	Rochester, Minn., USA	30,000	17	2	1.3	6.7	0.8–24.1
Brewis et al. [10]	1955–1961	Carlisle, UK	71,000	5	5	1.0	7	2.3–16.4
Gudmundson [39]	1954–1963	Iceland	187,200	24	12	0.76	6.4	3.3–11.2
Haberlandt [40]	1941–1955	Westphalia, Germany	?	102	–	?	2.5[c]	–
Lorez [69]	1951–1967	N. W. Switzerland	300,000	89	20	1.4	6.6	4.1–10.3
Kreindler et al. [62]	1950–1962	Rumania	18 ml.	650	–	?	3.7[c]	–
Cendrowski et al. [19]	1955–1965	Poznan, Poland	2.5 ml.	73	56	0.13	2.2	1.7– 2.8
Khondkarian & Maksudov [58]	1965–1970	USSR	?	1,465	–	?	1.2[c]	–

[a] After Bobowick and Brody [9]
[b] 95% confidence intervals on the rate, based on Poisson distribution
[c] Average estimates

no influence on the morbid risk [52]. Since most cases occur sporadically and a family history can be elicited in only a small fraction [47], it seems highly likely that environmental pathogens are in fact involved. Indeed, there is now evidence that the morbid risk for MND varies within countries. In the United States, mortality rates are relatively high west of the Mississippi and lower to the east [8]. In England and Wales, a higher mortality has been found in the prosperous southern and southeastern counties, a pattern similar to the distribution of poliomyelitis cases 40 years earlier [71], although the late neuromuscular sequelae of poliomyelitis appear to be distinct from MND [24].

Neither geographic nor occupational variation in mortality rates has as yet been explained in terms of any specific risk factor. An increased mortality in persons working in contact with animal hides [42] may suggest a viral aetiology, but could be due to an exposure to toxic substances. Outbreaks of neurological disorder following consumption of grain treated with an ethyl mercury compound [54] have manifested typical signs of ALS and progressive muscular atrophy. Campbell et al. [17] found a history of exposure to lead in 15% of patients with MND, compared with only 5% among matched controls. A history of recent fracture or axial skeletal disease was also more frequent among the MND patients, suggesting that some cases may have been caused by the release of lead deposited in bones. In addition, a number of organic chemicals such as benzol and tricresylphosphate are believed to have given rise to MND in individual cases, though a history of exposure to such substances has seldom been noted in case studies.

The frequency of MND may now be on the increase in industrial countries. Age-specific mortality has risen in the United States since 1960, most markedly in the higher age-groups [68]. Among women aged 80–84 years, this increase amounts to nearly 400%. In England and Wales, age- and sex-adjusted mortality rates rose from 1.2 to 1.6 per 100,000 in under 20 years [12]. The overall trend is consistent with an increased population exposure to one or more environmental pathogens.

Western Pacific Foci of Parkinsonism-Dementia and MND

Since the early 1950s, the high concentration of MND and related neurological syndromes among the Chamorro people of Guam has been studied intensively. In the early 1960s, this people had a prevalence of around 1 per 1,000 and an incidence rate of 32 per 100,000 [9]. When the age-specific rates were applied to the U.S. population, the adjusted annual mortality was 108 per 100,000 males and 42 per 100,000 females, or from 50 to 100 times as high as in most parts of the world. Affected persons tended to be younger than those with sporadic MND elsewhere, and to have a somewhat longer survival time. In addition to the classical neuropathological features, widespread neurofibrillary degeneration and involvement of subcortical centres was reported. While the syndrome resembling ALS (lytico) is distinguished locally from that of parkinsonism and dementia (bodig), the two are found in parallel high incidence in the same villages and families, and sometimes occur in the same individual [35].

A number of other endemic foci have been located in the Western Pacific. On the Kii Pensinsula of Japan, a survey in one village yielded nine cases of MND, corresponding to an uniquely high prevalence of over 7 per 1,000 population [59]. Across the peninsula, prevalence ranged from this peak ratio down to zero. The cases resembled those on Guam in respect of their clinical symptomatology, sex ratio, age of onset and illness duration.

These studies have given rise to speculation about a common underlying aetiology for the different types of neurological syndrome found in such remarkably high concentrations, in combined or intermediate clinical forms and with a mixture of pathological changes. All the variants appear to have declined in frequency simultaneously since the early 1960s, pointing to a reduction in morbid risk over a single generation which is much more consistent with dietary causation than with a genetic transmission. Since persons emigrating from the high-risk areas to other parts of the world have been known to develop the typical clinical picture up to 30 or more

years later [34], it seems that a very prolonged latency period may follow that of exposure to risk. On the other hand, the earlier age of onset in the endemic areas denotes an intensity of exposure sufficient to cause clinical manifestations in many cases before the results of age-related neuronal attrition could have made themselves felt.

No specific cause has yet been established for the constellation of MND, parkinsonism and dementia found in these Western Pacific peoples. Because the underlying neuropathology does not conform to the classical picture of each distinct disease as found in Europe and North America, it has been argued that the Western Pacific syndromes are nosologically different, and that no inferences can be drawn from them concerning the aetiology of "true" PD or MND. However, the keen interest of neuroepidemiologists in the Western Pacific disorders makes it clear that the isolation of any specific causal factors would be of great importance as a possible paradigm for the aetiology of the sporadic conditions, and would greatly stimulate research in this field.

Gibbs and Gajdusek [36] concluded after nearly 20 years of research that there was no convincing evidence of an infective origin. In recent years, the focus of attention has shifted to possible toxic or dietary causes. Manganese, a known cause of parkinsonism, may be implicated because of raised levels in drinking water [61] or of dust from open-cut mining [88]. It has been pointed out that all the affected areas are located on about the same longitude, 137°, and share distinctive mineralogical features [18]. On Guam, a deficiency of both calcium and magnesium in soil and water has been reported [35]. An alternative explanation is based on the presence of a neuro-excitatory aminoacid, beta methylamino-alanine, in the cycad nut, which for more than a century was a major source of flour for the Chamorros on Guam, but has now been replaced by imported foodstuffs [85].

Relative Distributions of DAT, PD and MND in Other Populations

However closely the various syndromes were associated in the Western Pacific focal areas, the evidence of linkage among populations in other parts of the world is generally weak or non-existent. This may be, of course, because the necessary epidemiological studies have yet to be undertaken. Any attempt to test for such associations is up against the central difficulty of getting reliable incidence or prevalence data for the different syndromes at area and regional levels. The scanty data so far available suggest that, while some degree of association between PD and MND may well exist, it does not extend to dementia. Thus Flaten [31], comparing mortality rates for dementia, parkinsonism and ALS in three groups of municipalities in Norway, found that those with the highest aluminium content in drinking water had a significantly raised mortality from dementia, but no increase due to the other conditions. The regional maps he supplies show quite distinct patterns of distribution for the three disease categories. Similarly, regional mortality data for dementia and MND in England and Wales [33] display quite different distributions. Dementia-related mortality appears to be highest in the northernmost counties, in Lincolnshire (east coast) and in a group of counties to the west and south of London. The distribution of MND-related mortality is different for men and women, but the counties with high rates for both sexes are clustered in the south-east of the country. Martyn (personal communication, 1990), examining regional mortality from dementia, PD and MND, found no significant associations between them.

The demographic distributions summarized above also fail to show any definite association, apart from a general increase in age-specific incidence and prevalence up to 70 or 75 years, beyond which point dementia prevalence continues to rise steadily, whereas the other diseases tend to decline. Epidemiological surveys of dementia show no evidence, either of the male preponderance manifested by both PD and MND, or of the links with certain occupations which have been reported for MND. Such information as we have on social-class distributions tends to suggest that the morbid risk for late-life dementia is raised in the lowest socio-economic groups of the population [74], whereas MND tends to occur more frequently in middle-class groups and skilled occupations [47, 71]. Although at this stage any conclusions must be tentative, it does not seem that there are identifiable sub-groups of the elderly population which are characterized by an increased relative risk for all three disease categories.

Discussion

DAT, idiopathic PD and MND are all conditions in which there is inferential evidence that the clinical onset, usually occurring late in life, is due to the combined effects of (a) age-related neuronal attrition, and (b) a predisposition determined at some earlier part of the life-span by subclinical neurological damage, caused by exposure to one or more environmental noxae. In each case, the clinical syndrome first becomes manifest when the affected neurotransmitter systems are so depleted that a threshold of functional decompensation is crossed. The predisposing risk factors for each disease may be toxic, infective or traumatic in nature, the underlying pathogenetic changes being unlikely to prove specific to any one form of aetiological agent.

The scanty epidemiological research findings tend to suggest a causal heterogeneity. Geographically there appear to be no striking associations between the different distributions, with the remarkable exception of those on the Mariana Islands and in other Western Pacific focal areas. The socio-demographic correlates of dementia also seem to differ from those of the other conditions. All three groups display a marked increase in prevalence with rising age, but whereas in the case of dementia this trend is exponential and continues upwards to the age of 90 years or beyond [46], epidemiological data suggest that the morbid risk for parkinsonism and that for MND may have peaked by 70–75 years and thereafter decline.

This apparent difference, together with the fact that the age-specific prevalences for both parkinsonism and MND usually show a male excess, while that for DAT tends to be higher among women [51], gives rise to a suspicion that the two former conditions are to some extent associated with occupational risk, whereas the frequency of DAT, at any rate in its senile form, is essentially independent of occupation. These conclusions are, however, tentative, since the possibility that the decline in prevalence of PD and MND in old age may be an artefact, due to incomplete case reporting, cannot yet be excluded. The most recent U.S. data suggest a rise in frequency in the highest age-groups when compared with earlier studies ([68]; D.B. Calne, personal communication, 1990).

The question as to which type of environmental pathogen is of key importance in deciding the levels of incidence and prevalence of each diagnostic group in modern society must remain open until the necessary research has been undertaken. The general hypothesis that seems best to fit the findings so far reported is that the underlying nerve-cell damage and decay are most often caused by the action of neurotoxic metallic compounds, arising from their presence, partly in varying natural concentrations in soil and water, but in some instances also in industrial processes, in water supply systems, as food additives or due to other forms of human activity. If this hypothesis is correct, exposure to natural concentrations might be expected to result, in most regions of the world, in late-onset, slowly progressive clinical manifestations, whereas more intensive exposures in endemic focal areas, or of a man-made nature, might well lead to earlier-onset, rapidly progressive disease, even before age-related changes have had time to develop. The evidence hints at a selective action of aluminium and possibly other light metals on the hippocampus, nucleus basalis of Meynert and septal nucleus in DAT; of metals of moderate density, such as manganese and chromium, on neurons of the substantia nigra in PD, and of heavy-density metals such as lead and mercury on cranial motor nuclei and anterior horn cells in MND [3]. Such a pattern of selective targeting, whose basis is so far wholly unclear, could account both for the similarity of pathogenesis and morphological change underlying the various clinical syndromes and for their differing distributions in populations. An increased, genetically determined susceptibility of the central nervous system to these exogenous toxins might explain the occurrence of familial forms of each disease, and conceivably also the apparent ubiquity of Alzheimer-type changes in later life in Down syndrome [80]. Much, however, has yet to be elucidated with regard to the bio-availability of the different compounds, variation in susceptibility of the human central nervous system to them and the key periods of the life span at which risk exposure occurs or its pathogenic consequences are most harmful.

Clearly, it would be quite premature at the present stage of knowledge to concentrate on any single line of causal enquiry, at the expense of others which also hold promise. A strong case has been made for more intensive study of the role in aetiology of neuro-excitatory amino acids [15]. While the quest for infective agents has so far proved consistently negative, there is still a possibility that one or more types of slow virus, transmitted for example by domestic animal carriers, may be implicated. The long-term neurological consequences of trauma of the central nervous system in early life remain largely unexplored. The crucial point, however, is that pursuit of each of these lines of investigation calls for population-based case-control and cohort studies and, more generally, for the application of epidemiological techniques. The brightest prospects for rapid advance in this field now lie in the development of joint research programmes, in which epidemiologists, clinicians and laboratory scientists can work closely together.

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