Epidemiology of multiple sclerosis in the north-east (Grampian Region) of Scotland—an update

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SUMMARY The north-east of Scotland (Grampian Region) has undergone three incidence and prevalence surveys, including the present one, since 1970. Results from these indicate a true increase in the prevalence of the disease in the region. The incidence of the disease has remained continuously high and shows a slightly upward trend. Literature on the subject of repeated surveys in different regions of the world has been reviewed in detail. The need for a prevalence study from the south of the British Isles has been emphasised in order to enable one to judge if the increase in Scotland is in keeping with the pattern in the whole of the British Isles. The familial incidence of the disease was noted to be virtually unchanged between the three surveys. Certain other aspects of aetiological significance have been analysed, viz, clustering of patients at birth or at onset of the disease; ages of occurrence of childhood viral infections such as measles, mumps, chickenpox and rubella; and the role of canine distemper infection.

The area now known as the Grampian Region has been previously reported^{1 2} to have the highest prevalence of multiple sclerosis (MS) compared to any other surveyed area of comparable population (471 000). We have carried out a further study of incidence and prevalence of the disease as at 1 December 1980 to assess the present situation. In addition, historical details of possible aetiological relevance were enquired about, for example, age of occurrence of certain childhood viral infections, degree of exposure to dogs as domestic pets, and family history of neurological disease or of autoimmune diseases. The clinical features of the disease, with particular attention to its course and prognosis, were also studied and will form subjects of later publications.

Materials and methods

Due to administrative reorganisation since 1975, the north-east area has been reformed as Grampian Region. This corresponds closely with the area previously surveyed, but minor and appropriate adjustments had to be made in some boundary areas. A breakdown into the 28 areas containing a population of 10 000 or more as carried out in the previous two surveys^{1 2} to allow comparisons of prevalence in these small sub-units was not possible because of the reorganisation, but the new subdivision of the region into five districts still allowed for some comparisons between the three surveys. The

Fig 1 Districts of Grampian Region since 1975

1980 series was made up of the nucleus of those found in the earlier studies who were known not to have died or left the area, and to this were added all the new patients ascertained from a variety of sources since that time. These sources included hospital diagnostic record index, neurology departmental records, including the records of patients referred for visual evoked responses, patients found in long-stay wards, patients found in the local branch of the Multiple Sclerosis Society, and patients under care of the Community Nursing Services. After preliminary

screening of case notes of all the patients compiled from the above sources (1200), lists of suspected patients known to be cared for by individual general practices were prepared. National Health Service numbers, present address, and name of the general practitioner for each patient were personally obtained from records of the local Primary Care Department, and this made the tracing of patients much easier. The list of patients known to be in each general practice was then submitted to the practice with a request, as before, that they notify any other cases known to them but not to us, and remove any patients who were no longer on their lists. Information about current disability status (using McAlpine's Disability Scale³), about the number of relapses since the patient was last seen in the hospital, and also about other possible relevant factors, as mentioned above, was requested.

The returned questionnaires from the general practitioners added 13 further cases of multiple sclerosis to the number about whom information had already been available, but six cases had to be removed from our preliminary lists as notice of their death since the previous survey had not been received from other sources. In ten patients identified in the 1973 survey, further events had made the diagnosis of MS no longer tenable, and in two of these another diagnosis had been established at necropsy.

The 'balance sheet' showing the change between 1973 and 1980 is shown in table 1. All except five patients were examined at least once, and a large number had been examined several times by a member of the Neurological Services in Aberdeen.

After all the available information from the family doctor and from the hospital case notes had been entered on a patient's card, questionnaires were sent to each patient asking for details of the ages at which they had suffered from the various infective illnesses (mumps, measles, chickenpox, rubella, and herpes zoster). They were also asked for their address at the presumed onset of their disease, at their birth, and

during the major part of their childhood, and their occupation at the presumed onset.

From all these and other clinical and social details from the assembled data, patients were classified into possible and probable MS categories as in the earlier series^{1,2} in which Broman *et al*'s (1965)⁴ modifications of Allison and Millar's (1954)⁵ classification was used, although on this occasion the categories previously labelled probable (group 1) and early probable and latent (group 2) were merged, while the category possible was retained as before. Probable MS therefore included patients with a history and physical signs of a central nervous system disease disseminated in time and place, in whom other neurological conditions had been excluded as far as possible. Also included in this category were patients at an earlier stage of the disease with a relapsing remitting course, who had few persisting physical signs of central nervous system lesion, but in whom diagnosis was supported by paraclinical evidence such as elevated immunoglobulin G in the CSF, prolonged visual evoked response latency or an abnormal CT scan. Possible MS included patients with a history and examination compatible with MS in whom other diagnoses had been excluded as far as possible. Evidence of multiplicity of lesions was sometimes lacking in these patients. This group included some patients with progressive spastic paraparesis where full investigations, including myelography, had excluded other likely causes of such a picture. Patients with optic neuritis alone were not included.

Finally, because of easy storage, ready access, and ability to carry out complete correlations and statistical analyses, all the above data were coded and entered on a main line computer. As in the 1973 study,² all patients were 'flagged' in the central Registrar's Office at Edinburgh by sending that office each patient's full name, age, National Health Service number, and address. This has proved to be invaluable in reliable ascertainment of deaths in the past.

Results

In all, 839 patients thought to have the disease were present in the region on the prevalence day, 1 December 1980. Six hundred and eighty-two were in the probable and 157 in the possible category.

DISEASE PREVALENCE

Despite stringent and only slightly altered selection criteria, the prevalence figures indicate a marked increase between 1970, 1973, and the present survey (table 2).

The new administrative districts created in the reorganisation of 1975 are shown in figure 1. The total population rose by 44 000 between the 1971 and 1981

Table 1 Analysis and details of 1980 survey

Source	Number of patients		
	Female	Male	Total
1973 Survey	402	232	634
Deaths between 1973 and 1980			
from the 1973 Survey	77	42	119
Left area between 1973 and 1980	24	9	33
Cases rejected from 1973 Survey	8	2	10
Remaining cases from 1973 Survey	293	179	472
Migration into Grampian after onset of disease elsewhere	20	5	25
New cases since 1973 Survey (alive on prevalence day 1 Dec. 1980)	236	106	342
Total cases in 1980 survey	549	290	839

Table 2 Prevalence of multiple sclerosis in the Grampian Region of Scotland (1970, 1973 and 1980)

Year	No of patients			Probable	Possible	M:F ratio	Prevalence rate/100 000	
	Male	Female	Total				Probable	All cases
1970	215	342	557	464	95	1:1.59	106	127
1973	232	402	634	517	117	1:1.73	117	144
1980	290	549	839	682	157	1:1.89	145	178

NB. The prevalence rates have been rounded up to the nearest whole number

census.⁶ Figures obtained in the 1973 survey from the small sub-units were rearranged to allow a comparison, and an excess noted in 1973 in the area now known as Gordon District has disappeared, while the neighbouring City of Aberdeen District has shown an apparent disproportionate increase. Apart from Gordon District, all the districts in the region have shown an absolute increase in numbers of cases which is statistically highly significant ($p < 0.001$) (table 3).

The change in Gordon District may have been due partly to boundary changes or in part to a true increase in prevalence in the City of Aberdeen.

PREVALENCE BY AREA OF BIRTH PLACE

Nearly three-quarters of the patients were born in the region (616 patients), about one-fifth outside the region (169), and the address at birth was unknown in the case of 54 patients. If MS was the result of exposure to an environmental agent in childhood, a degree of clustering of patients for their birth and childhood addresses might have been noticeable in a relatively static population such as ours. Patients were arranged in different groups by age, year of onset, and the place of residence during childhood. On statistical analysis using the χ^2 test, however, no difference was

noted between any of the districts. No trend was noticeable either on arranging the figures for the address at onset in a similar way.

AGE AT ONSET AND DURATION OF DISEASE

Mean age at onset was noted to be similar in the 1973 and the present survey (males = 34.1 years and females 34.7 years; all patients 34.5 years). Mean age on the prevalence day was 45.1 (range 11–94) years. The proportions of patients in different age groups at the onset of disease have been shown in figure 2. This shows that the largest percentage of patients had onset of disease in the third decade. Mean duration of the disease was also similar to that in the 1973 survey² (14.8 years). Ninety-two patients (11%) had survived for more than 30 years after the onset of the disease with a slight male preponderance in this group (M:F = 1.19:1).

AGE AND SEX SPECIFIC PREVALENCE RATES

Using the 1981 census⁶ figures for distribution by age and sex of the Scottish population, the specific prevalence rates were calculated. The overall prevalence rate was highest for the age group 45–54 years at 412/100 000; that for females in the same age group was 494.3/100 000, and for males 324.7/100 000. In actual numerical terms, therefore, 1 in 200 women and 1 in 300 men between the ages of 45 and 54 years were affected by the disease (fig 3).

Table 3 Comparison of disease prevalence between 1973 and 1980 surveys in different districts of Grampian Region

District	Year	No of cases observed	No of cases expected	χ^2	Prevalence rate /100 000
City of Aberdeen	1973	284	287	0.04	142
	1980	407	363	5.33	200
Kincardine & Deeside	1973	52	48	0.32	156
	1980	76	75	0.01	180
Gordon	1973	108	85	6.3	183
	1980	93	111	2.8	149
Banff & Buchan	1973	104	112	0.54	134
	1980	134	145	0.86	164
Moray	1973	81	97	2.60	120
	1980	129	115	1.74	159
Total	1973	629*			
	1980	839			

There were significant differences between the prevalence rates in different districts.

This is true in both surveys—1973— $\chi^2 = 9.29$ $p < 0.05$

1980— $\chi^2 = 10.81$ $p < 0.05$

*5 cases originally observed in the 1973 survey were omitted because of adjustment for boundary changes

Fig 2 Age at onset by sex (all patients observed between 1970 and 1980).

Fig 3 Age specific prevalence rates

INCIDENCE OF DISEASE

Incidence of the disease was calculated in three year periods between 1960 and 1980. This was done by dividing the number of patients whose disease began while they were living in the Grampian Region by the estimated population in each three year period.⁷ This included not only those patients who were living in the region at the time of the present survey but also those who had died or had left the area before the prevalence day but whose disease had begun while they were living in the region during the respective three year periods (fig 4).

Increased local interest and awareness following the 1970 survey might have contributed to the apparent increase in incidence recorded in 1973. The increasing use of investigations such as visual evoked responses, CT scanning, and CSF IgG estimation may also have increased diagnostic certainty between 1973 and 1980, but the overall trend of the disease in the decade does seem to be an upward one (fig 4). Incidence figures

Fig 4 Incidence rates for three year periods, 1959-80

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prior to 1959 are not so reliable, as accurate data about deaths and migration were not available. The slight fall off in incidence rates after the peak recorded in 1970-73 is unlikely to be very significant as some patients who have been seen only in recent years may have had only a single episode of neurological symptoms so that as yet they have not been classified even as possible cases of multiple sclerosis. The difference in the incidence figures for the period 1970-73 as shown in the report of the previous survey² compared with the present one is due to the late presentation of a number of patients whose disease had begun during that period but who were similarly not recorded at that time as established cases of multiple sclerosis.

CERTAIN AETIOLOGICAL CONSIDERATIONS

Environmental factors

Social class Nearly two-thirds of the patients belonged to social classes I to III. This was similar to the findings of the earlier survey in this region.⁸ This preponderance of the higher social class is highly significant ($p < 0.001$) when compared to the distribution in the general Scottish population.⁹

Occupation In the 1973 survey,² an excess of wood workers, nurses, and doctors was noted among the patients. This observation was, however, not confirmed in the present survey. In this survey, number of other occupations, such as clerk, shop assistant, typist, and teacher, was noted to be common.

Although the differences from the general population were statistically significant, no firm conclusions could be drawn because the numbers in each occupation group were small.

Exposure to dogs In view of the renewed interest in the possible role of canine distemper virus in the aetiology of MS, patients were questioned about contact with dogs as domestic pets. Out of 697 patients who answered this question, just over half had never kept a dog as a pet. Of the ones who had, only about one-sixth reported that their dogs had suffered from canine distemper. Without control values from the general population no firm conclusions can be drawn.

Age of occurrence of childhood viral infections Epidemiological data on the age of occurrence of childhood viral infections, in particular, measles, suggests that it is earlier in low MS frequency compared to high frequency regions.^{10 11} Our figures are in keeping with this (table 4). The age of occurrence of measles was more than five years in two-thirds of the patients (64.35%). In comparison to the control population the age of occurrence was later in the MS

Table 4 Frequency and age of occurrence of certain virus infections

	Chicken pox	Mumps	Rubella	Measles		Herpes zoster	
				MS patients	*Controls	MS patients	†Controls
Number of patients with no history of infection	220 (34.9)	253 (39.6)	358 (58.3)	92 (14.0)	—	551 (85.7)	48 (96)
with history of infection	411 (65.1)	385 (60.4)	256 (41.7)	567 (86.0)	—	92 (14.3)	2 (4)
Age of occurrence							
0-4 years	89 (21.7)	64 (16.6)	39 (15.2)	186 (35.7)	12,578 (39.3)	1 (1.1)	
5 years & over	285 (69.3)	290 (74.4)	192 (75.0)	335 (64.3)	19,407 (60.7)	85 (94.4)	
Age unknown	37 (9.0)	31 (8.0)	25 (9.8)	46	—	6 (6.5)	
Total number with history available	631 (100.0)	638 (100.0)	614 (100.0)	659 (100)	31,985	643 (76.6)	
				p>0.05	$\chi^2=3.02$	p<0.07	

* Figures showing ages of reported measles cases in the City of Aberdeen between 1911 and 1973. Data for war years (1914-1918 and 1940-1944) not available.

† Control figures from Ref 42. Please see text.

Figures in brackets are percentages.

patients, but the difference was only marginally significant at the 5% level (table 4). Herpes zoster occurred in 14.3% compared to 4% in the controls ($p<0.02$). Control figures for other childhood infections were not available.

Genetic factors

Familial incidence of multiple sclerosis Ninety-three patients had one or more than one first degree relative affected with the disease. Sixteen of these were, in fact, present in the present survey, thus constituting 77 families (77/284=9.3%). This figure is similar to that in the two earlier studies in this region when a familial incidence of 9.2% and 9.6% was noted.⁸

Familial incidence of other neurological and autoimmune disease There is increasing evidence now that MS has an autoimmune basis. An increased familial incidence of diseases with an autoimmune basis has been reported in a number of conditions, for example, thyroid disease, pernicious anaemia, etc, where an autoimmune pathogenesis is suspected. We decided to see if a similar pattern of increased incidence of other autoimmune diseases existed in the families of MS patients in this region. In addition to the incidence of the autoimmune diseases we also inquired about the occurrence of certain other neurological disease in the families. Apart from multiple sclerosis itself, 21 cases of Parkinson's disease and ten cases of poliomyelitis were found in the relatives of 778 cases of multiple sclerosis. Seven cases of rheumatoid arthritis out of 375 cases were also found. In 11 other diseases enquired about (neurological and autoimmune) no obvious increase in

numbers was noted. In the absence of control values for the population under study no firm conclusions can be drawn but the incidence of rheumatoid arthritis and Parkinson's disease does seem greater than expected.

MORTALITY RATES

One hundred and fifty-two patients known to us as suffering from possible or probable multiple sclerosis died between 1974 and 1980. The annual mortality rate using the 1961 census figures¹³ was 5.0/100 000. This figure was strikingly different from the official figure of 1.8 per 100 000 for Grampian Region reported by the Registrar General's Office for the period 1974 to 1981.⁶ This figure, of course, is based on death certificates giving multiple sclerosis only as the primary cause of death. A similar discrepancy in the mortality figures for the region from 1971 to 1975 was noted by Shepherd.⁸

Table 5 shows the inadequacy of the official figures as a true indicator of the number of deaths in patients with multiple sclerosis. As the official mortality figure for the Grampian Region was similar to that for the rest of Scotland (2.1/100 000),⁶ it is likely that a similar discrepancy may have occurred in other regions as well.

Mean duration to death was 24.5 years. This figure by direct measurement is less than would have been obtained by the indirect method suggested by Poskanzer *et al.*¹⁴ This estimation was obtained by doubling the duration of the disease on prevalence day, and with our subjects a figure of 29.6 years would have been obtained. Females survived slightly longer than males (F:M=25.7 : 23.5 years), a fact also

Table 5 MS deaths 1971–80 in the Grampian Region

	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	Total
No of deaths	21	21	19	23	19	27	12	24	17	30	213
Source of information											
1*	10	5	9	5	15	19	10	19	13	19	124 (58%)
2*	7	11	10	15	3	5	2	2	0	3	58 (27%)
3*	4	5	0	3	1	3	0	3	4	8	31 (15%)
Total	21	21	19	23	19	27	12	24	17	30	213 (100%)

1* Mortality figures from Registrar General's annual computer printout. These contained patients in whom death had been notified as a contributory as well as a primary factor.

2* Death certificate copies obtained on cases from General Register Office, Edinburgh, who had been 'flagged' by us from earlier surveys as suffering from multiple sclerosis. These would be notified to us even if multiple sclerosis was not mentioned on the death certificate.

3* Mortality information from local sources including necropsy reports¹² and GP questionnaires.

reflected by a lesser ratio of females in the mortality group (M:F=1:1.5) compared to the prevalence group (M:F=1:1.89).

Discussion

This third survey of MS in the Grampian Region (north-east) of Scotland has reaffirmed that the disease continues to occur there more frequently than in any other surveyed area of comparable population in the world.

There has been a sharp increase in prevalence since the 1973 survey (table 2). Increased local interest might have played some part in early case referral but is likely to be of minimal significance and cannot be quantified. No significant changes in the basic diagnostic criteria have occurred, and the diagnosis is still based mainly on clinical grounds. Altered criteria for ascertainment would be unlikely to have played any major part since one of us (AWD) has been present here since 1965 and has participated in all three surveys.

The mean duration of disease has not significantly changed between the three surveys. The death rate for 1971–74 was 4.1/100 000¹⁵ and is close to (in fact less than) the mean annual death rate between 1974 and 1980 (5.0/100 000). Increased survival cannot therefore be the cause of the increased prevalence in recent years. The migration figures suggest no net influx of patients (table 1). An additional 18 patients with MS were in fact present in the region at the time of the 1973 survey but were missed. The population of the region has increased from 438 631 to 470 596 between the 1971 and 1981 censuses,⁶ and if one adds the number of patients in proportion to the population increase (56 patients) and the 18 patients who were missed in 1973 to the total of 634 patients reported in the 1973 survey, the present survey figure of 839 is still significantly greater than expected (table 2). Other indicators of a true increase in the number of patients include an overall upward trend of incidence (fig 3) in the decade 1970–80 and a sharp increase in the number

of female compared to male patients in spite of no great difference in their survival. If increased local awareness and interest were to have played a major role, the proportion of female to male patients might have remained constant, but contrary to that the F:M ratio in the patients diagnosed since 1973 has increased to 2.22:1 compared to 1.73:1 in 1973.²

In most places where the prevalence of MS has been studied on more than one occasion, an increase has been reported^{16–29} with the exception of Winnipeg,³⁰ Boston,³¹ and the Faroes.³² The Mayo Clinic series³³ provided a 60 year follow-up of incidence and prevalence. Incidence showed a very minimal increase, and the prevalence rate was stable for those who had been resident from the onset of this study. A disproportionate influx of patients already affected with the disease was thought to account for the increase in prevalence from 46 to 86 per 100 000 between 1905 and 1964. The studies from Orkney and Shetland,³⁴ covering a period of 20 years, showed a relatively constant incidence rate but a marked rise in prevalence rate from 110 to 309/100 000 between 1954 and 1974 in the Orkney Isles. These rates appear slightly less dramatic when one considers that the population at risk was about 20 000. The actual increase in numbers was from 23 in 1954 to 54 in 1974. The increased prevalence despite a relatively stable incidence was thought to be due in part at least to increased survival. A more complete ascertainment and differential emigration of unaffected people were considered as possible contributing factors. The authors noted a slight drop-off of incidence rate in the later years and considered that this was because of incomplete ascertainment of undiagnosed cases accentuated by the fact that they did not include possible cases in their calculations. In studies from Iceland,²² where the population at the time of the most recent survey (1974) was over 200 000, incidence and prevalence rates were estimated for the period 1904–74. It is doubtful whether much reliance can be placed on the very early figures, but the later studies suggested

an abrupt rise in incidence in the post war period 1945–54, the rates doubling from 1.6 for 1923–24 to 3.2 in the next decade but falling again thereafter. Prevalence rates increased steadily from 10 per 100 000 in 1924 to 53 in 1954 and 'essentially stabilised thereafter'. It was considered that the data suggested an epidemic of MS in the post war years similar to that described in the Faroes.³²

Our data, although they cover a relatively short period of 20 years, do show an upward trend in incidence but more importantly a continuing high incidence, about twice the highest rate recorded in Iceland at the height of the 'epidemic'. Incidence rates in the Orkney and Shetland study varied from year to year from 3 to 12 per 100 000. While this related only to probable cases and might seem more reliable, it must be remembered that one single extra patient developing the disease in any one year increases the incidence rate per 100 000 in such a small population by about 5. In terms of actual cases in the Orkneys or Shetland Isles, the variation in one island from one year to another was from nil to four new cases recorded. In Grampian Region our incidence figure of around 7 per 100 000 represents the identification of approximately 33 cases of probable or possible new cases per year.

INFECTIONS

Previous epidemiological data on the age of acquisition of measles suggest that it occurs at a much earlier age (usually under 5 years) in communities near the equator with low MS frequency, compared to ones in northerly regions with higher MS frequency.¹¹ At least in three different studies^{35–37} an older age of acquisition of measles has been reported in MS patients compared to controls, although in none of them did the difference reach a highly significant statistical level. In the present investigation also an older age of acquisition of measles was noted among the MS patients compared to the general population of the region between 1911 and 1973 (table 4). Another observation of interest is that in fatal cases due to measles the incidence of central nervous system complications was directly linked to age of occurrence,^{38–39} suggesting an age dependent neurotropism.

Our figures show that not only measles but other viral infections, such as chicken pox, mumps, and rubella, also occur in a high proportion of MS patients at an older age, although due to lack of control figures, firm conclusions about these latter infections cannot be drawn. Age dependent neurotropism has been shown in a number of viral infections.^{40–41} It is therefore tempting to speculate that MS may be the result of host determined response to measles or

perhaps more than one viral infection acquired at a later age than average.

Herpes zoster was reported by 14.3% of patients (table 4), the majority having had it after the age of 10 years. We do not have figures from a control population in our region, but, using control figures from the study of Lenman and Peters,⁴² whose patients came from a geographically adjacent area only 70 miles or so away from our region, a significantly higher incidence of herpes zoster was also noted in our patients ($p < 0.02$). Their control sample consisted of unselected patients attending a neurology clinic for diseases other than MS. It may be that the disturbed cell mediated immunity in MS patients allowed the varicella zoster virus to reactivate. The relation between animal viruses, particularly canine distemper and MS, has been recently reviewed.⁴³ Most of the data do not favour an association between exposure to dogs and occurrence of MS. Although our data in the absence of a control population are not conclusive, the figure of more than 50% of non-dog owners is against a causal relation.

FAMILY HISTORY

The numbers of patients with a family history of MS has remained fairly constant in the three surveys in this region (9.2% in 1970; 9.8% in 1973; 9.3% in the present study). The figures from the Grampian region are only exceeded by the figures of 16.7% from Denmark⁴⁴ and 11.6% from Orkney and Shetland.⁴⁵

OCCUPATIONAL HISTORY

The excess of woodworkers, including joiners, and nurses in the 1970 study⁸ has not been confirmed in the present investigation. Although a number of occupations has been noted to be commoner in the MS population in the present study, the results had to be interpreted with caution, as a bias had been introduced in the controls due to selection of certain occupations for the purposes of statistical analysis, necessitated by very small numbers in many occupations. The excess of clerical staff, however, was highly significant, a finding also noted in 1970,¹⁵ although the overall excess of females in the entire MS group might have been responsible for this. A review of the literature in relation to this subject reveals diverse results, making it unlikely for MS to be an occupationally linked disease.

URBAN/RURAL DISTRIBUTION

Conflicting data exist as well about urban versus rural distribution of MS patients. Studies from Sweden,⁴⁶ Norway,⁴⁷ Denmark,⁴⁸ and Lower Franconia⁴⁹ show an excess in the rural population, while a strong support in favour of urban excess comes from the US Veterans Study⁵⁰ and from Israel.⁵¹ Studies in this

region on this occasion (table 3) showed an urban excess, but earlier studies¹⁵ in which comparison could be made of individual areas within the city showed variable results, possibly related to varying proportions of different social classes in different parts of the city. The area of highest prevalence in 1970 and 1973 was in a rural area. Reports from Northumberland and Durham,¹⁴ Switzerland,¹⁹ Iceland,²¹ and South Africa⁵² and a reappraisal of figures from West Australia⁵³ show no significant difference between urban and rural distribution. It therefore seems that no clear pattern exists in the urban versus rural distribution of MS throughout the world.

SOCIAL CLASS

Miller, Ridley, and Schapira⁵⁴ first drew attention to the increased frequency of MS in the Registrar General's social classes I and II compared to classes IV and V. Since then at least three studies,^{8 14 50} including one in this region, have also shown an excess in professional workers (social classes I and II). The data from the present study confirm this. No obvious reason for an excess in social classes I and II, however, is apparent.

MORTALITY

Mean annual MS mortality in the region has remained fairly stable in the last decade (table 5). Since the formation of Grampian Region, the Registrar General's office has been kind enough to send us the annual mortality computer printouts, which are based on death certification for MS where this appears as the primary or as an associated cause of death. Table 5 shows, however, that 40% of the deaths in this series were not obtained from this source and highlights the value of flagging cases with the General Register Office in Edinburgh so that notice of death can be obtained even when multiple sclerosis is not mentioned in the death certificate. The mean duration of the disease in the 213 patients who died due to the disease was 24.5 years (males 23.5 years; females 25.7 years) and the M:F ratio was 1:1.57.

Conclusion

The prevalence of MS in the Grampian Region (north-east) of Scotland has increased, due in part to some increase in the actual incidence of the disease. The familial incidence over a longitudinal period has not increased. Further studies about age of childhood viral infections, perhaps with a follow-up of a cohort from childhood, are required. It seems that exposure to dogs is unlikely to be of any aetiological significance.

Finally, further careful epidemiological studies from comparable areas of England and Wales are

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urgently needed to show if the apparent high prevalence in the north-east of Scotland represents more than the fact that the region, for various reasons, has allowed a more complete ascertainment than has been possible elsewhere in the UK, with the exception of the Orkney and Shetland Isles.

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