Multiple sclerosis in the Republic of San Marino

G MORGANTI,¹ S NACCARATO,¹ M ELIAN,² P FERRARI,³ R KELLY,⁴ L KARHAUSEN,⁵ AND G DEAN⁶

From the Ospedale Nuovo,¹ San Marino, Oldchurch Hospital,² Romford, UK, Istituto di Scienze Sanitarie Applicate,³ Pavia, Italy, St Thomas's Hospital,⁴ London, UK, Commission of the European Communities,⁵ Luxembourg, and the Medico-Social Research Board,⁶ Dublin, Eire

SUMMARY Previous studies on the prevalence of multiple sclerosis in Italy have grossly underestimated the prevalence of the disease. The prevalence in the Republic of San Marino (near Rimini), in Sicily, and no doubt in the rest of Italy, is of the same order of magnitude as in Europe—that is, 40–60/100 000. The contrast of this with the very low prevalence in Malta (only 60 miles (96 km) away from Sicily) of 4/100 000 should provide a clue to the genetic and environmental factors responsible for multiple sclerosis.

In the past it has been reported that there is a gradient in the prevalence of multiple sclerosis from northern to southern Europe.¹ Several studies of the prevalence of multiple sclerosis in Italy and Sicily²⁻⁴ confirmed a low prevalence of between four and 19/100 000 in contrast to a prevalence reported from middle and northern Europe of 40–60/100 000. Among immigrants from Italy resident in Greater London, however, the risk of being admitted to hospital with a diagnosis of multiple sclerosis was not significantly different to the risk in the United Kingdom. The risk was also relatively high in the Greek and Turkish immigrants from Cyprus and the immigrants from Spain although not as high as in those born in the United Kingdom (table 1).⁵ In contrast to the Italian, Cypriot, and Spanish immigrants no Maltese patient with multiple sclerosis was in hospital in Greater London or in the West Midlands, although 10 (9.7) would have been expected at the United Kingdom born rates.^{5,6}

The high risk of being in hospital with multiple sclerosis among Italian born residents in Greater London and the absence of those born in Malta prompted studies to ascertain the prevalence of multiple sclerosis in Malta and in small cities in neighbouring Sicily, where in the large populations of Palermo and Messina the prevalence of multiple sclerosis had previously been reported to be low.^{3,4} Enna city in central Sicily was chosen for the first study and a high prevalence for probable multiple sclerosis of 53/100 000 was found.^{7,8} Studies in two other small cities of Sicily have confirmed a high prevalence.^{9,10} The mean prevalence of probable multiple sclerosis for the three cities studied in Sicily

was 41/100 000 (table 2). In contrast, the prevalence in Malta was indeed low 4/100 000.¹¹

If the prevalence has been seriously underestimated in Sicily it has probably been so in the rest of Italy. The Republic of San Marino presented an opportunity to ascertain the prevalence of multiple sclerosis in a small population with an excellent medical service.

Method

The Republic of San Marino is the smallest independent state in the world (60.6 km² (23.2

Table 1 Hospital first admissions for immigrants from Europe with multiple sclerosis resident in Greater London 1960–72

	Male	Female	Total	Expected number at UK born rates
<i>North and Central Europe</i>				
Germany	3	31	34	29.2
Poland	18	7	25	25.4
Austria	1	8	9	11.0
France	4	7	11	9.8
Belgium/Luxembourg	0	2	2	3.9
Netherlands	1	2	3	4.3
Hungary	3	4	7	6.1
Other	8	21	29	24.8
Total	38	82	120	114.5
<i>Southern Europe</i>				
Italy	12	12	24	27.2
Spain	0	8	8	16.4
Cyprus*	11	12	23	35.0
Malta	0	0	0	8.4
<i>Resident London and Birmingham</i>				
Malta	0	0	0	9.7

*Seventeen Greek Cypriots and six Turkish Cypriots.

Table 2 Prevalence of probable multiple sclerosis in three cities in Sicily

Cities	Prevalence day	Population	Probable multiple sclerosis			
			Male	Female	Total	Rate/100 000
Enna ^a	1 January 1975	28 189 (1976)	3	12	15	53.2
Monreale ^b	30 June 1980	25 403 (1980)	6	5	11	43.3
Agrigento ¹⁰	1 January 1975	49 979 (1976)	7	9	16	32.0
Total		103 571	16	26	42	40.6

sq m)) and is dominated by Mount Titano (750 m (2460 ft) above sea level). Most of the population live in San Marino town on Mount Titano or in eight small villages. The Republic is 22 km (14 m) from Rimini between the Italian regions Marche and Romagna. The population at 31 December 1979 was 21 322 (M 10 683, F 10 639) of whom 18 323 were Sammarinese citizens and the remaining 2999 mostly Italians. It is extremely difficult to obtain San Marino citizenship as Sammarinese have many advantages such as low taxation and excellent health and social services. There is a new and modern hospital and medical and social services records are well kept. San Marino presents therefore an ideal population for epidemiological studies. We studied the records of all patients who had been admitted to the medical department of San Marino hospital for the previous 20 years to find those who might have been suffering from multiple sclerosis. The patients with a history suggestive of possible multiple sclerosis who were still alive were then examined.

All residents of San Marino are entitled to free medical services whether they receive these services in San Marino or if they consult doctors elsewhere in Europe. Because patients avail themselves of these free services, which are well documented when their bills are paid by the San Marino State services, records are available not only for those who have been seen in San Marino but of those who consulted doctors elsewhere. We also asked each patient with multiple sclerosis whom we saw whether they knew of anyone else in San Marino with the disease.

We were concerned that there might be some sufferers who had not been seen by a doctor either in general practice or at the San Marino hospital for many years and who were not recorded in any of the San Marino health service records. We therefore searched the records of the neurological clinics in the neighbouring cities for the previous 30 years looking for any patients with possible multiple sclerosis who were resident in San Marino. The cities included Bologna, Modena, Ravenna, Ferrara, Forlì, Ancona, and the Centro Studi Sclerosi Multipla at Gallarate. All the patients were examined by Sammarinese and Italian and also by non-Italian neurologists.

San Marino has an excellent pension scheme for the disabled. The records of all residents who were

receiving disability pensions were studied to find if any of the disabilities suggested a diagnosis of multiple sclerosis.

Results

Tables 3 and 4 show in an abbreviated form the history and clinical findings of probable and possible sufferers resident in San Marino. There were, on prevalence day 30 June 1982, 11 probable patients, three men and eight women, and three possible patients, all women.

Three patients with probable multiple sclerosis were not recorded in any of the records systems of the hospitals or pension schemes in San Marino. One patient was discovered accidentally by another patient who visited her house while crusading as a Jehovah's Witness (woman 6, table 3). Two further patients were found in the records of the neurology department at Bologna University who had been diagnosed in 1956 and 1954 respectively and they are of special interest (women 7 and 8, table 3).

One woman (No 7, table 3) was admitted to the neurological clinic at Bologna University in 1956 with weakness in both legs, paraesthesia, and a feeling of constriction of the abdomen. She had weakness of the right side of the face, spastic weak legs, and extensor plantar responses. The Wasserman reaction test result was negative and the cerebrospinal fluid was normal. Mielopatia discredita was diagnosed. We visited her at her home in San Marino. She had been unable to walk since 1976 and was well looked after by her family. From her history and the clinical findings there is no doubt that she is suffering from probable multiple sclerosis. She had not been seen at San Marino hospital. The second patient found from the records system at Bologna (case 8) was admitted to the neurology clinic in 1954 complaining of blurring of vision and unsteadiness in her legs. The blurring of vision had improved and was then followed by weakness in her legs. She was diagnosed in Bologna in 1954 as suffering from multiple sclerosis. Confined to a bed to chair existence since 1960 she had not left her home since then. She was well looked after by her sons. Again, she had never attended a local hospital.

Despite searching for patients with multiple

Multiple sclerosis in the Republic of San Marino

25

Table 3 Probable number of patients with Multiple Sclerosis resident in San Marino 31 December 1982

No	Age	Date and 1st symptom	Remission	Men Relapse	Remission	Examination
1	31 6 June 51 Sammarinese	Jul 76 Paraesthesia R face. Diplopia	Yes	31 May 77. Weakness; paraesthesia left arm 6 June 78. Paraesthesia of abdomen 7 May 79. Relapse Switzerland; Bologna hospital; difficulty in starting micturition 5 May 80. Unsteady and weak gait; improved again 30 May 81. Relapse, severe weakness and ataxia of legs	Yes Yes Yes Yes	Tendon reflexes brisk L>R Ataxia left arm Dysidiadochokinesia; weak R leg; R Babinski equivocal; spastic R leg Nystagmus; spastic R leg; ataxia; plantar response ↑ equivocal left
2	26 19 Jul 56 Sammarinese	24 June 76 Blurring vision both eyes	Yes	1976 Paraesthesia R leg 1977 Diplopia; difficulty in starting micturition	Yes	Nystagmus; pallor L disk; plantar response equivocal
3	31 21 June 51 Sammarinese	March 82. Hyperaesthesia followed by weakness L leg; increased over 15 days until unable to move leg. Followed by paralysis R leg. Urinary retention	Yes	Recovered and after 4 months could walk with a stick and after 6 months walked unaided; Sept 1982 paraesthesia and weakness right hand with return of leg weakness; recovered after a few days; balance remains impaired	Yes	Leg tone increased; some weakness; reflexes +++ L>R clonus ankles; plantar response ↑↑; abdominal reflexes absent; CSF oligoclonal bands
<i>Women</i>						
1	45 25 Jul 37 English married Sammarinese (Lived in San Marino since 1960)	Jan 1970 Diplopia	Yes	1970 Weakness R leg and two weeks later L leg; paraesthesia fingers & hands; relapse, weakness of legs a few months later 1971 L leg very weak 1972 Clonus L leg, worse in cold weather 1977 Weakness L face 1981 Walks with aid only	Yes Yes	 Nystagmus; ataxia of arms; spastic weak legs; plantar response ↑↑
2	32 Born 1950 Sammarinese	1967 Aged +/- 17 years. Yes Paraesthesia face	Yes	1969 Diplopia 2 weeks; weakness both legs; urinary difficulty; ataxia of arms 1979 Relapse; unsteady arms and legs 1981 Relapsed again	Yes	 Ataxia, titubation of head; nystagmus; spastic legs; clonus ankles and knees; plantar response ↑↑; vibration sense absent in legs
3	49 24 Aug 33 Sammarinese	1953 Paraesthesia left leg; vertigo	Yes	1955 Relapse same symptoms 1956 Relapse; weakness in both legs 1962 Deteriorated gait 1970 No longer able to walk; ataxia of arms severe; married an epileptic; sphincter problems	Yes	 Paraparesis; tendon reflexes +++; plantar response ↑↑; pallor of both fundi Spastic paraparesis; nystagmus; ataxia of arms; pallor both disks Decubitus ulcers; scanning speech; nystagmus; ataxia; spastic paralysed legs; vibration sense absent in legs

Table 3 Probable number of patients with multiple sclerosis resident in San Marino 31 December 1982
—continued

No	Age	Date and 1st symptom	Remission	Women Relapse	Remission	Examination
4	34 22 Oct 48. Sammarinese (Married Italian, legally Italian)	1972 Difficulty in walking	Yes Seen at Neurological Clinic, Bologna. MS diagnosed	Relapses; weakness in legs and arms R>L; unsteadiness of gait		Spastic legs; plantar response↑↑; ataxia; nystagmus; abdominal reflexes absent 1979 Investigated neurological clinic, Hertogenbosel, Holland. MS diagnosed. CSF, gammaglobulin +
5	61 21 Oct 21 Sammarinese	1960 Loss of vision left eye	Yes, slowly	1960 Paraesthesia legs and head; left hemiparesis 1961 Paresis right arm 1962 Vertigo; vision normal; paraesthesia returned 1963 Vertigo severe 1981 Since 1963 minor attacks of paraesthesia, otherwise well	Yes	Reflexes brisk L>R Left disk pale; reflexes brisk L>R paraesthesia; plantar response↓↓
6	34 1948 Italian	1960 Weakness both arms and legs, unable to walk after three days; slowly improved over 15 days	Yes	1960 Three months after first attack R facial paralysis; MS diagnosed Minor attacks of weakness in legs since 1980 Weak both legs, walks with difficulty	Yes	Nystagmus; spastic legs Nystagmus; weak spastic legs; reflexes +++ L<R plantar response↑↑; ataxia L<R
7	68 25 Jul 14 Sammarinese	1949 Noticed she dropped things from her right hand	Yes	1952 Weakness and stiffness in L leg 1956 Admitted neurological clinic Bologna University; weakness in legs; paraesthesia and sense of constriction of abdomen 1958 Incontinence of urine; legs became more weak; walked holding on to furniture 1976 Fractured R femur and not walked since 1981 In wheelchair; incontinent; well looked after by family; no records of her neurological illness at San Marino hospital	Yes Yes	Weakness R face; weakness both legs; plantar response↑↑; hypoesthesia R side; WR and CSF normal; "mielopatia disrastica" diagnosed
8	68 27 Jul 14 Sammarinese	1945 Noticed legs were unsteady and sometimes gave way beneath her, particularly R leg	Yes	1954 Blurring of vision first R eye then L eye lasting about 15 days Admitted neurological clinic, Bologna Hospital (MS diagnosed) 1955 Improved but then speech became slurred; gait became shuffling; speech improved Since 1960 lived a bed to chair life; not out of doors for 20 years, sometimes incontinent 1981/2 Looked after by 3 sons. No records at San Marino Hospital	Yes Yes	Nystagmus weak L side of face slowing finger nose test; pronounced weakness of legs; spastic gait; abdominal reflexes absent; plantar response↑↑ Slight dysarthria; legs totally paralysed; ataxia both arms R>L: abdominal reflexes absent; knee and ankle jerks brisk; pallor of both disks; clonus both legs; plantar response↑↑

Multiple sclerosis in the Republic of San Marino

Table 4 Possible number of patients with multiple sclerosis resident in San Marino 31 December 1982

No	Age	Date and 1st symptom	Remission	Relapse	Remission	Examination
1	43 6 Apr 39 Sammarinese	1969 Vertigo; paraesthesia R side of body; pain R arm and lumbar region; improved after x ray treatment to neck; syringomyelia suspected	Yes	1979 1981 says sometimes diplopia looking L; whole story vague		Mild vertical nystagmus hypoesthesia R side of body; brain scan normal; pandy +/- VER normal
2	33 22 May 49 Sammarinese	1972 Noticed dilated R pupil	Yes	1975 Pain diminished strength R arm; weakness R leg; had to stop driving car 1977 Loss of sensation in hands; pain in neck; complained of loss of strength in arms 1981 No objective symptoms or signs	Yes	Anisocoria R>L Refuses VER test
3	30 2 Nov 52 Sammarinese	1979 "Heaviness" of both legs; great difficulty in walking because of weakness in legs; lasted one month	Yes	June 1982. A strange sensation "hot and cold" in both legs below knees for one month; Oct 1982. Vertigo and unsteady gait followed by diplopia for 10 days and lack of taste in tongue; followed by urinary frequency	Yes	Unsustained nystagmus; fundi, normal; some weakness L leg; deep tendon reflexes brisk; plantar response L equivocal, R flexor lower abdominal reflexes absent; no ataxia; CSF no abnormality found; VER normal

VER= Visual evoked response.

sclerosis for three years, there may be more patients in San Marino who have not yet been traced or perhaps diagnosed. Repeated studies in other areas have found a higher prevalence of multiple sclerosis than earlier studies. Calculating the prevalence on 11 patients in a population of 21 322, the prevalence of probable multiple sclerosis among the residents of San Marino is 52 per 100 000 (51.6), (28.1 per 100 000 male, 75.2 per 100 000 female). If possible and probable patients are included, the prevalence is 65.7 per 100 000. The prevalence in San Marino is similar to that found in Sicily and in other studies in northern Europe. Prevalence studies in small populations are bound to vary considerably by chance, and in San Marino there is a much higher prevalence for woman than for men. In Enna also there was a higher proportion of women than men than is found in most studies, where the usual ratio is 3:2 but when the three small cities studied in Sicily are taken together the ratio was also approximately 3:2 (3.2:2) (table 2).

In searching for patients with possible multiple sclerosis several other interesting disorders were seen—for instance, a young man who in January 1974 had been bitten by a dog that was thought to have rabies. He was given a course of antirabies injections and after seven injections he developed paraesthesia and weakness in the legs. There was hyper-reflexia, greater on the right side than on the left, clonus of the right foot, the right plantar response was extensor, and the abdominal reflexes were absent. He slowly improved but he still has weakness in his legs.

Conclusion

Previous studies on the prevalence of multiple sclerosis in Italy grossly underestimated the prevalence of the disease. In three cities in Sicily and in the Republic of San Marino recent studies show that the prevalence of multiple sclerosis in San Marino and Sicily is of the same order of magnitude as has been reported in other studies in Europe, that is 40–60/100 000. These findings are supported by the risk of developing multiple sclerosis in Italian immigrants in London. Other recent studies in Copparo,¹² Trento (G Kossi *et al*, personal communication), and Beddagho, Sardinia,¹³ have also shown a similar high prevalence. The high prevalence in San Marino and in Sicily and, no doubt, in the rest of Italy, contrasts with the very low prevalence, 4/100 000 found in the islands of Malta only 60 miles (96 km) from Sicily. This sudden rather than gradual fall in the prevalence of multiple sclerosis between Sicily and Malta should provide a clue to the genetic and environmental factors responsible for the syndrome.

We thank Signora Franca Montanari, San Marino, and Professor A Marinoni and Professor E Torre, Pavia. We also thank the neurologists and the staff of the neurology records departments at the hospitals of Bologna, Modena, Ferrara, Ravenna, Forli, and Ancona and also the Centro Studi Sclerosi Multipla, Gallarate. Finally, we thank the patients who

collaborated with us in this study.

This research was supported in part by the Commission of the European Communities and the Committees of Medical Research and Public Health.

References

- ¹McAlpine D, Lumsden CE, Acheson EC. *Multiple sclerosis: a reappraisal*. 2nd ed. London: Churchill Livingstone, 1972.
- ²Borri P, Tavalato V, Ballatari E, Cazzullo C. Epidemiological survey on multiple sclerosis in Italy. *Riv Patol Nerv Ment* 1976; **97**: 205–10.
- ³Savettieri G, Piccoli F, Chiaravalle E, *et al*. Epidemiological survey on multiple sclerosis in the city of Palermo (Italy). *Acta Neurol* 1978; **33**: 526–31.
- ⁴Bramanti P, Messina C, Scuderi D, Vita G. An epidemiological study of multiple sclerosis in the province of Messina. *Acta Neurol* 1978; **33**: 532–9.
- ⁵Dean G, McLoughlin H, Brady R, Adelstein AM, Tallett-Williams J. Multiple sclerosis among immigrants in Greater London. *Br Med J* 1976; **i**: 861–4.
- ⁶Dean G, Brady R, McLoughlin H, Elia M, Adelstein AM. Motor neurone disease and multiple sclerosis among immigrants to Britain. *British Journal of Preventive and Social Medicine* 1977; **31**: 141–7.
- ⁷Dean G, Grimaldi G, Kelly R, Karhausen L. Multiple sclerosis in southern Europe I: Prevalence in Sicily 1975. *J Epidemiol Community Health* 1979; **33**: 107–10.
- ⁸Grimaldi G. Esperienze sulla sclerosi multipla in Sicilia. Atti 111 Convegno Nazionale di Neuroepidemiologia. Milan: Societa Italiana di Neurologia 1982.
- ⁹Savettieri G, Daricello B, Giordano D, Karhausen L, Dean G. The prevalence of multiple sclerosis in Sicily I: Monreale city. *J Epidemiol Community Health* 1981; **35**: 114–7.
- ¹⁰Dean G, Savettieri G, Giordano D. *et al*. The prevalence of multiple sclerosis in Sicily II: Agrigento city. *J Epidemiol Community Health* 1981; **35**: 118–22.
- ¹¹Vassallo L, Elia M, Dean G. Multiple sclerosis in southern Europe. II: Prevalence in Malta in 1978. *J Epidemiol Community Health* 1979; **33**: 111–13.
- ¹²Rosati G, Granieri E, Carreras M, Tola R. Multiple sclerosis in southern Europe: a prevalence study in the sociosanitary district of Copparo, northern Italy. *Acta Neurol Scand* 1980; **62**: 244–9.
- ¹³Rosati G, Pinna L, Granieri E, *et al*. The distribution of multiple sclerosis in Sardinia. *Riv Patol Nerv Ment* 1977; **98**: 46–64.