The benign form of multiple sclerosis. A study based on 241 cases seen within three years of onset and followed up until the tenth year or more of the disease. By Douglas McAlpine. From the Institute of Clinical Research, The Middlesex Hospital Medical School, London W1. Brain 1961: 84; 186–203

That there are no agreed diagnostic criteria for multiple sclerosis has much limited legitimate comparisons between the series reported by individual investigators or from different geographical regions; and inevitably the domestic systems in use reflect the biases of each observer. For Douglas McAlpine (1890–1981) the diagnosis of multiple sclerosis requires information on the:
(i) History; (ii) Physical signs; (iii) Behaviour of early symptoms; (iv) Cerebrospinal fluid; [and] (v) Subsequent course of the illness. In most instances, consideration of these ‘facets’ allows the diagnosis to be made early in the disease; but, in a proportion, the unusual clinical picture or paucity of physical signs make for difficulties. While such cases can be classified as ‘possible’ or ‘probable’ until such time as further events clarify the situation, occasionally additional features sufficient for the clinical diagnosis of multiple sclerosis never materialize despite lengthy follow-up. Therefore, a specific ‘test’ for multiple sclerosis is needed. McAlpine and (Nigel) Compston (1918–86) have already reviewed the hospital records of all 651 cases seen at the Middlesex Hospital between January 1930 and December 1949 (‘Some aspects of the natural history of disseminated sclerosis. Part I. The incidence, course and prognosis. Part II. Factors affecting onset and course’ Quart J Med 1952; 21: 135–67).

Most patients participating in this clinic-based series have been seen annually for review. Responsibility for their care passed to Dr Paul Sandifer (1908–84) between 1941 and 1945 when McAlpine was serving with the British Army in the Middle East; and, from 1946, to Dr Michael Kremer (1907–88). After demobilization, Dr McAlpine re-established contact with his patients and, from 1955–59, he has seen all but the most disabled and those living far from London (in whom information has been requested by letter to the general practitioner) in the Institute of Clinical Research of the Middlesex Hospital Medical School. Now Dr McAlpine considers all cases seen since 1930 within 3 years of onset and followed prospectively for at least 10 years through to 1959.

He recognizes that the statistical analysis of his results might be confounded by the inclusion of cases dying from an accelerated course of the disease; by those seen on only a single occasion; and by inclusion of others in whom the diagnosis could be considered doubtful. However, despite these uncertainties, all but 17 of the cases known to him (of which 14 were first seen in the 1930s) are included.

The advantage of a prospective series is that incorporation of any new features (‘positive’ information) and the lack of an alternative explanation emerging over time in atypical cases (‘negative’ information) place confidence in the original, and still the ‘working’, diagnosis. Therefore, apart from one example of acute disseminated encephalomyelitis, the diagnosis is accepted as ‘multiple (disseminated) sclerosis’. This is further classified as ‘definite’ (a relapsing-remitting course with accumulation of physical signs; or a progressive course from onset with superimposed episodes and signs other than paraplegia); ‘probable’ (a single episode with incomplete recovery and the accumulation of additional signs, but no new symptoms, over time; or recurrent optic neuritis with signs outside the visual pathways); or ‘possible’ (a progressive history lacking features other than paraplegia; no evidence for involvement of the cerebrum, brainstem or optic nerves; inadequate investigation of spinal cord disease; or inadequate follow-up). In all cases issues such as age, family history and the results of examining the cerebrospinal fluid are taken into account. As for disability, Dr McAlpine retains the system adopted by his junior colleague in their 1952 paper, even though this is heavily weighted towards mobility and takes no account of vision, use of the arms or sphincter control—again taking the view that any ambiguities will be clarified by observation over the years. On this basis, the cases are categorized at each visit as ‘unrestricted’ for everyday life but not necessarily free from symptoms; ‘restricted’ and limited to walking half a mile but able to get on and off public transport; ‘markedly restricted’ being still capable of moving out of doors for up to a quarter of a mile with the use of sticks although incapable of accessing public transport; ‘mobile at home’ using support from furniture and unable to climb stairs; ‘immobile at home’ and confined to a wheelchair so not capable of moving independently; or ‘bedridden’. The patients are further grouped as ‘dead’ (n = 83; 34%), ‘disabled’ (n = 80; 33%) or ‘unrestricted’ (n = 78; 32%) at the end of each quinquennium (Fig. 1). But it is notable that a disproportionate number of patients in whom the course subsequently proved mild were those seen from the first year of their illness, whereas patients who died or were disabled had tended to present slightly later.

For us, this does not undermine the sampling of the cohort. Perhaps, in an era when no treatments were available, it indicates the ‘therapeutic’ benefit of professional interest and engagement
with Dr McAlpine and his team throughout the entire course of the illness. Age at onset does not appear to have influenced severity over time; but only 5 of 241 cases were aged >50 years at presentation suggesting, that by comparison with contemporary series, the diagnosis of multiple sclerosis was not considered in patients developing neurological symptoms beyond that age. Multiple sclerosis most frequently manifests in the third and fourth decades (74/241: 31%; and 99/241: 41%, respectively); and the sex ratio is 1.6 female: male but, conversely, with a higher proportion of males dead (42/92; 46%) than females (42/149; 28%). Of the 241 cases, 179 have survived >15 years; but 9 of 87 unrestricted at that stage later became disabled. Overall the proportion free from disability falls from 42% at 10–14 years, to 34% at 15–19 years and 31% at 20–24 years; whereas there is a steady increase in the proportion—44, 53 and 48%—disabled at each period, respectively. Using modern terms, we would classify the course of Dr McAlpine’s cases as relapsing remitting (96/241; 40%), secondary progressive (120/241; 50%), and primary progressive (25/241; 10%). Sometimes disability is not associated with progression: this is the assessment in 5/241 with disease duration of >20 years, and four others with onset 16 and 17 years before final assessment late in 1959.

Death within the period of observation is more likely in patients with a polysymptomatic presentation; but, conversely, those with symptoms attributable to a single site are not protected from disability. Disease duration in patients who died during the period of observation occurs after a mean of 11 years, most often in the context of secondary progressive disease—five apparently from unrelated causes. In nine the course of the neurological illness has been ‘malignant’, leading to death within 5 years of onset. Among those eventually classified as disabled, the further conversion from ‘unrestricted’ decreases over time, as expected, falling from 50% in the group still ‘unrestricted’ at 5 years to just 4 of 80 patients living but later becoming disabled who had nonetheless still been reasonably ambulant at 20 years (Fig. 2).

The focus of Dr McAlpine’s paper is the 78 patients who were ‘without restriction of activity for normal employment and domestic life but not necessarily symptom-free’ at last assessment. He is duty bound to point out that in only 25% of this group has the period of observation extended >15 years (15% and 5% at 20–24 and >25 years, respectively); and of these, 20 were ‘probable’ cases and 12 ‘possible’, 3 and 7 of whom in each category failed to attend for final follow-up making it necessary to rely on information from the general practitioner. Therefore, he has looked critically at all original diagnoses, especially those classified as anything other than definite, in order to judge the status of these cases; as a result, a few diagnoses are amended in each direction of certainty. Eventually, McAlpine decides to ignore all ‘possible’ cases from further consideration. Now emerges a further confound in consideration of the series. Some patients, ‘unrestricted’ at their last assessment, had initially been classified as disabled because they presented to a hospital clinic during a bad relapse from which subsequently they made a good recovery; and, self-evidently, others have moved up and down the disability scale as events unfolded during the relapsing-remitting course of their illness. These oscillations mainly occur during the first 5 years of observation. Seven of eight patients initially ‘restricted’, ‘markedly restricted’ or ‘mobile at home’ reverted to ‘unrestricted’ at the end of the first quinquennium although temporary disabilities were later documented in each. But one patient, eventually classified as unrestricted, had apparently remained disabled for >15 years before improving. Considering only those who had episodes beyond the first year (55 cases), the number of recorded relapses falls rapidly from ~0.7/year in the first 2 years to ~0.1 thereafter with apparent transition points at 2 and 10 years. One patient has influenced these statistics, remaining unrestricted despite experiencing for 7 of the 51 relapses recorded in all 55 patients between years 5 and 9, and 7 of the subsequent 22.

This is the series that first presents Dr McAlpine’s observation that onset only with visual symptoms in multiple sclerosis heralds a relatively benign prognosis: 21 of 37 patients presenting with isolated optic neuritis remain in the unrestricted category compared with 8 of 20 in whom optic neuritis was part of a more complex presentation. These data compare with the less favourable outcome in patients presenting with weakness or unsteadiness. They make up 60 of the 83 patients (72%) who died, 59 of 80 patients (72%) who were disabled and 38 of 78 patients (48%) who remain unrestricted. The same interpretation pertains to those with pyramidal tract involvement; 114/163 (70%) of those who died or were disabled had abnormal plantar responses at presentation compared with 26/78 (34%) who remained unrestricted; and the equivalent statistics for those with cerebellar signs are 67/163 (41%) dying or disabled and 11/78 (14%) unrestricted. As to whether the course is influenced by ‘treatment’, the modern reader will have doubts. Most were admitted to hospital in order to rest for at least 1 month; 45 of 242 receive ‘intravenous novarsenobillon (NAB), 4 courses per year, usually
preceded by artificial fever, induced by TAB vaccine, and followed by liquor arsenicals between courses'. Correlating outcome with treatment and comparing those who did and did not have fever therapy in addition to arsenicals, and noting that roughly three-quarters of patients in the unrestricted category had no treatments at all, ‘it is difficult to avoid the conclusion reached by [Philip] Cloake [1890–1969] in 1946 that prolonged administration of arsenic by injection and orally, preceded by artificial fever, may in some cases of multiple sclerosis favourably influence the course of the disease [Humphry Davy Rolleston Lecture: Roy. Coll. Phys., London. “The treatment of disseminated sclerosis by artificial pyrexia and prolonged administration of arsenic” (unpublished)]’.

What can be made of these painstaking but epidemiologically imperfect observations that proved so influential in counselling individual patients until population-based studies started to appear some decades later? McAlpine’s discussion is historically orientated. (Jean-Martin) Charcot (1825–93) and his student Pierre Marie (1853–1940) had each recognized and recorded in their lectures that multiple sclerosis might run a benign course. The series of 200 patients reported by Byrom Bramwell [(1847–1931): 1917] included two who remained well at 34 and 37 years after onset, respectively: ‘it is probable that in a few rare and exceptional cases the disease is permanently arrested’. As (Russell) Brain (1895–1966) wrote in 1936: ‘if a remission may last thirty years why not a lifetime? The overwhelming number of patients in whom the disease is progressive should not blind us to the probability that the continuous series from the most acute to the most benign forms extends further to include those in whom a first attack is never followed by another’. While the so-called clinically isolated syndrome is represented in Dr McAlpine’s series by 23 patients, this is somewhat different from the benign course observed when multiple sclerosis is initially relapsing and remitting. More generally when considering individuals who remain unrestricted, McAlpine points out that ‘either these cases represent a benign form of multiple sclerosis or alternatively the original symptoms were those of an acute disseminated encephalomyelitis’. In turn, this raises the old conundrum of the relationship between multiple sclerosis and acute disseminated encephalomyelitis—the histological evidence and natural history of each condition allowing different commentators either to favour or discard the ‘unitary hypothesis’. For Dr McAlpine it is the presence, or not, of a precipitating event that makes the distinction. Many examples of ‘primary’ or ‘spontaneous’ acute disseminated encephalomyelitis mature into otherwise typical forms of multiple sclerosis over time; but only one certainly, and another possibly, of his 241 cases could be confused with acute disseminated encephalomyelitis. Therefore, Dr McAlpine is confident about the diagnoses and concludes with a novel descriptive classification for the course of the disease: ‘malignant’ multiple sclerosis in which ‘resistance to the disease is low, relapses are severe and frequently leading to death within a few months or years’; ‘chronic’ multiple sclerosis, the majority, in which ‘relapse rate and degree of disability are extremely variable but there is a tendency to progression after the first few years, or exceptionally from the onset, with increasing disability and usually premature death’; and ‘benign’ multiple sclerosis in which the initial attack may be slight or severe but recovery is good, relapses mild and infrequent, or even absent, with the possibility of permanent cure’.

Of the conclusions reached, several have stood the test of time: the patient with signs of an established paraplegia or cerebellar signs within 3 years of onset is likely to become disabled and die early; and the main characteristics of a benign course are monosymptomatic presentation especially with isolated optic neuritis, a low relapse rate, episodes that spare the motor system and lack of disability at around 10 years after onset. Although events had necessarily to be awaited in these particular cases, those in his series unrestricted in 1959 could take comfort that
‘the gloomy prognosis that is foreshadowed by the diagnosis must be modified…a more positive attitude must be taken towards…treatment…a more prolonged period of rest and after-care in the early stage of the disease might beneficially influence the subsequent course of the disease’; and ‘for those who conduct therapeutic trials in multiple sclerosis, existing difficulties are increased’.

These were wise words. Shamanists proselytizing maverick claims for treatment in a disease where the outcome cannot easily be predicted and in which the natural history may vary from rapid disability and death to no noticeable interferences with aspects of daily living after several decades have shamelessly manipulated down the years uncertainty relating to the clinical course; and even the well intentioned, adopting more logical therapies, have repeatedly been beguiled by the natural history of multiple sclerosis. That the clinical course can be benign is again emphasized in the paper by Bengt Skoog and colleagues whose cohort from Göteborg (Sweden), which we now report in 2012, started prospective observations on the natural history of multiple sclerosis in 1950 with 13 of 307 affected individuals followed for up to 59 years remaining free from significant disability or progression despite intermittent disease activity over a period of observation that takes each beyond the average age of normal life expectancy (page 900).

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