# MULTIPLE SCLEROSIS

*A REAPPRAISAL*

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# PREFACE

While based primarily on the personal experience of the three authors, this book also reflects current thought in the ever widening field of the demyelinating diseases. It is published in the hope that it will be of interest to many, particularly the epidemiologist, clinician, ophthalmologist, clinical pathologist and research worker.

Part One deals with the epidemiology of multiple sclerosis. In a comprehensive study, Dr Acheson discusses the difficulties of the method including the problems of misclassification and comparability of data. The value of the various indices of frequency of the disease is compared. The author then goes on to discuss the influence of age, sex and social and occupation factors on the frequency of multiple sclerosis. The evidence on which our knowledge of the world pattern of the disease is based is described critically and an attempt is made to divide the world into high and low risk zones; the significance of local aggregations of cases is also discussed. The conflicting evidence on the effect of migration on risk is summarised and the second chapter closes with a critical account of the various hypotheses which have been advanced to account for the epidemiological evidence. Some suggestions are made about future work.

The chapters in Part Two are primarily based on those contained in our previous book but all have been extensively revised and contain new material based on recent literature. 'Familial Incidence and its Significance', the disputed role of trauma, the significant association of periphlebitis retinae and uveitis with multiple sclerosis, retrobulbar neuritis, the cerebral forms of the disease, short-lived and paroxysmal attacks and the clinical differences between multiple sclerosis and cervical spondylosis are among subjects receiving special attention in Chapters III-VI. In Chapter VII 'Methods of Assessing Disability' precede an evaluation of clinical features which have a bearing on prognosis, including the recognition of a 'Benign Form' of the disease. The subject of treatment is examined afresh in Chapter VIII. Emphasis is again placed on certain principles which if adopted in an early case would tend to improve the outlook. The possible value of A.C.T.H. in acute phases of the disease and the results of intrathecal injections of phenol for the relief of painful spasticity precede a section dealing with the care of the advanced paraplegic patient. A new chapter on 'The Medico-Social Problem' describes the difficulties confronting patient and relatives, hospital personnel, general practitioner and local authority and the steps taken to overcome them under the National Health Service in Great Britain. Finally measures are suggested that would

improve the physical and mental well-being of those multiple sclerosis patients who do not escape disability.

In Part III Professor Lumsden deals widely with the laboratory aspects of the disease during the life of the patient. In his view the recent spate of new facts on the chemistry and immunology of myelin and neuroglia ought now to permit a new and dynamic phase of laboratory research on the disease as studied in the *living*. 'There are many new threads of evidence in the clinical pathology of multiple sclerosis that are by no means yet widely known or understood and which are to be evaluated before a proper synopsis of its pathology can be attempted.' Chapter XI surveys what is known of the cerebrospinal fluid proteins and closely examines the evidence that the characteristically raised gamma globulin of multiple sclerosis is, in significant part, locally-derived immunoglobulin. This conclusion is of vital importance to an understanding of the pathogenesis of multiple sclerosis. On the other hand, the search for a specific laboratory test for multiple sclerosis and, above all, for a truly quantitative index of the severity of the disease is more likely to be found in the field of the lipid chemistry of the cerebrospinal fluid since, whatever the cause of the disease, its physical expression lies in the selective degradation primarily of myelin and secondarily of axoplasm. With this principle in mind, Professor Lumsden gives the results of a detailed study of cerebral lipids with special reference to demyelination in Chapter XIII. Linking these studies of proteins and lipids in the cerebrospinal fluid is an attempt, in Chapter XII, to survey current knowledge of amino acids, intermediate carbohydrate metabolites and enzymes, with special reference to the cerebrospinal fluid, in multiple sclerosis. It is hoped that Chapters X to XIII may fill a gap in the literature of the clinical pathology of neurological disease generally, although they are orientated more specifically to multiple sclerosis.

Finally Chapter XIV attempts to examine multiple sclerosis 'as an immunological disorder', (*a*) whether there are any characteristic immunological links, direct or indirect, with a variety of infections that could explain the epidemiological peculiarities of the disease surveyed earlier by Dr Acheson, and (*b*) the evidence for the existence and the nature of the 'auto-immune' anti-myelin antibodies formed in patients with multiple sclerosis. 'There is reason for sober hope that new trends in the clinical immunology of multiple sclerosis will finally provide an understanding of its pathogenesis.'

Dr Acheson wishes to thank Dr L. Kurland and Mr D. Hewitt for reading the proofs of the epidemiological chapters and making suggestions, and Mrs B. Hainge for preparing the manuscript and indices.

In the preparation of the section on Familial Incidence the senior author derived much help in the genetical analysis from Dr R. T. C. Pratt and Dr A. C. Stevenson. Others to whom he is grateful for helpful

criticism include Dr R. P. Mackay, Dr L. Guttmann, Dr F. S. Cooksey and specially Dr J. B. Gaylor who with meticulous care edited the clinical chapters. For permission to reproduce a number of tables in Chapter VII and Figure 7, he wishes to thank the Editors of *Brain* and for the latter Professor Henry Miller.

Professor Lumsden wishes to acknowledge his indebtedness to friends and colleagues, too numerous to mention individually, for their generosity with reprints of published work and for their valuable discussions in correspondence which have clarified points arising in their published work. A number of the illustrative Tables are based on published data by different authors, but the sources of these are fully indicated both in the Tables and in the text. Figures 12, 14, 17, 20, 21, 22, 23 and 25 have been reproduced, virtually *facsimile*, from the papers by their original authors to whom he is indebted, as to the Editors and Publishers of the Journals cited, for specific permission to use these illustrations. Full acknowledgements are made both in the captions and in the descriptive text, but it is a pleasure also to enumerate them here, viz., to Drs Rieder and Wüthrich of Basel for Figures 12 and 14 and to Drs Bücher, Matzelt and Pette for Figures 17, as well as to the Editors of *Klinische Wochenschrift* for these three; also to Drs Dencker and Swahn of the University of Lund and to their publishers, Messrs Gleerup, for permission to modify Figure 20; to Drs Allegranza and Marobbio and the publishers of *World Neurology* for similar liberties in respect of Figure 21; to Professors McIlwain and Cumings, who have kindly allowed Figures 22 and 25 to be prepared, respectively from the sources cited; and finally we are indebted to Professor Huszák and Dr Szechenyi and the Editors of *Brain*, for use of the graph for Figure 23.

Lastly, the authors wish to thank Mr Charles Macmillan and his co-directors for their patient co-operation and helpful advice.

DOUGLAS MCALPINE

London, 1965

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# PART I: EPIDEMIOLOGY

*by E. D. Acheson*

# CHAPTER I

# THE EPIDEMIOLOGY OF MULTIPLE SCLEROSIS

## I. THE EPIDEMIOLOGICAL METHOD AND ITS LIMITATIONS

The first aim of the epidemiologist is to identify populations with different risks of being attacked by the disease under study. These populations may be defined in various ways: for example, they may be groups of persons living in the same place at different times, or in different places at the same time; or they may be subgroups of the same community. Having established that real differences in risk exist, the high and low risk populations are compared in respect of the different hereditary and environmental influences to which they are exposed. These comparisons may yield a hypothesis which can be tested in further populations in the clinic or in the laboratory. The final aim of the epidemiologist is to prevent the disease by removing one or more influences in the chain of causation. History shows that diseases have been prevented by such means when knowledge of their pathogenesis has been no less rudimentary than is that of multiple sclerosis.

The early triumphs of epidemiology were won in fields where the disease under study (cholera, scurvy, pellagra, epidemic lead poisoning) was concentrated in space and time, and in circumstances where it was comparatively easy to differentiate affected from unaffected. More recently the epidemiological approach has been extended successfully to conditions like carcinoma of the bronchus and coronary heart disease which would not have been regarded as epidemic in the nineteenth century had they occurred with their present frequency.

In multiple sclerosis the situation is more unfavourable. Even in those parts of the world where multiple sclerosis is most frequent, it is unlikely that more than one person in 20,000 experiences a clinical onset of the disease each year. This paucity of material has important implications. In the first place it rules out the prospective method of study by which a population is first classified in terms of some characteristic and is then observed for the development of cases of multiple sclerosis. Secondly, the classical retrospective method of case-finding by door-to-door visiting is impracticable. Thus, if a city of 100,000 people were to be surveyed, some 30,000 families would need to be visited in order to collect (where the disease was common) perhaps 100 cases. To concentrate upon small communities does not solve the problem because, even with more complete ascertainment, the size of

the sample will introduce problems and limit the scope of the enquiry in other ways.

Workers have therefore been forced back upon various indirect methods of ascertainment such as circularising local practitioners, or searching the records of local hospitals. Such methods unfortunately introduce further opportunities for error and bias because they depend for their efficacy as much upon the local standard and degree of organisation of medical care as upon the skill and patience of the survey team.

The relatively prolonged interval between onset of symptoms and diagnosis, and the difficulty in dating the onset in many cases introduce further complications. Furthermore, it is possible that the onset of symptoms, even when this is known with certainty, may be as remote from the primary aetiological events as is the onset of dementia in general paralysis from the original spirochaetal infection. Finally, multiple sclerosis shares with many other chronic conditions the absence of a specific laboratory test which can confirm the diagnosis. Unfortunately, even in the best hands clinical methods are uncertain.

Three important principles can be adduced from the consideration of all these difficulties. The first is the principle of economy; all reasonably reliable data should be used in trying to delineate high and low risk populations. Secondly, weight should only be given to large or consistent differences in frequency; all that we can reasonably expect to determine is whether the disease is common or rare in a population. Thirdly, the epidemiological attack should be concentrated on field situations which are as favourable as possible, i.e. on the study of steep gradients on risk.

## II. INDICES OF FREQUENCY AND THEIR RELATIVE MERITS

The direct measurement of the risk of being attacked by a disease requires the determination of the incidence or attack rate:

$$\frac{\text{Number of new cases in a period of time}}{\text{Average population at risk}}.$$

As we have seen, it is to this measurement and to the interpretation of differences between populations in respect of it that the epidemiological method is directed. Unfortunately, however, in a disease as rare as multiple sclerosis the collection of sufficient cases to determine directly this ratio requires either the survey of an inconveniently large population or the lapse of a decade or more. Other difficulties are: uncertainty of date of onset, delay between onset and diagnosis which must lead to an underestimate of incidence in recent years, and the fact that cases which ought to be assigned to the population under study may be

TABLE I

*Collected incidence and prevalence data (multiple sclerosis) for 25 surveys since 1945 where mortality rates for comparable areas were obtainable*

| | Survey data | | | | | | Mortality data | | |
|---|---|---|---|---|---|---|---|---|---|
| | Prevalence rate | | | Average annual incidence rate | Population of survey area, in thousands | Cases personally examined | Place | Years | Crude average annual death rate |
| | Place surveyed | Year | Author's best estimate of prevalence | | | | | | |
| Allison *et al.* | N. Ireland | 1951 | 51 | 2·7 | 1,371 | + | N. Ireland | 1942-50 | 2·8 |
| Siedler *et al.* | Missoula Co. | 1957 | 59 | 1·9 | 43 | + | Montana | 1950-4 | 1·3 |
| Kurland | Boston, Mass. | 1949 | 41 (white) | 2·6 | 846 | – | Massachusetts | 1939-48 | 1·2† (white) |
| Kurland *et al.* | Denver, Colo. | 1949 | 38 (white) | 2·2 | 416 | – | Colorado | 1951-5 | 1·1* (white) |
| Kurland | Winnipeg | 1949 | 42 (white) | 2·2 | 314 | – | Manitoba | 1939-48 | 1·4† (white) |
| Kurland *et al.* | San Francisco | 1949 | 30 | 2·1 | 775 | – | California | 1949-51 | 0·9* |
| Kurland | New Orleans | 1947 | 13 (white) | 0·8 | 602 | – | Louisiana | 1938-48 | 0·3† (white) |
| Poskanzer *et al.* | Northumberland Durham | 1958 | 50 | | 2,308 | + | Northumberland Durham | 1958-60 | 2·0* |
| Dean | Union of S. Africa | 1960 | 8 (white) | | 3,100 | + | Union of S. Africa | 1950-8 | 0·1* (white) |
| Maclean *et al.* | Rochester, Minn. | 1948 | 64 | 5·0 | 33 | + | Minnesota | 1947 | 2·1† |
| White *et al.* | Kingston, Ont. | 1949 | 57 | | 30 | + | Ontario | 1947 | 1·5† |
| Okinaka *et al.* | Kumamoto Sappora, Japan | 1957 | 2 | 0·3 | 758 | + | Japan | 1954-8 | 0·1* |
| Sutherland *et al.* | Queensland | 1960 | 12 | | 1,415 | ± | Queensland | 1950-8 | 0·7 |
| Alter *et al.* | Charleston, S.C. | 1955 | 19 (white) | | 188 | + | S. Carolina | 1953-7 | 0·5* (white) |
| Alter *et al.* | Halifax, N.S. | 1955 | 32 | | 198 | + | Nova Scotia | 1953-7 | 1·2* |
| Saint and Sadka | W. Australia | 1960 | 13 | | 705 | – | W. Australia | 1950-8 | 0·4* |
| Hyllested | Denmark | 1950 | 64 | 4·7 | 4,252 | + | Denmark | 1951-4 | 2·0 |
| Georgi *et al.* | Switzerland | 1957 | 51 | | 5,117 | – | Switzerland | 1954-8 | 2·5* |
| Alter *et al.* | Israel | 1960 | 16 | | 1,735 | + | Israel | 1954-8 | 0·5* |
| Sutherland | N. Scotland | 1954 | 67 | | 232 | + | Caithness, Inverness, Nairn, Ross, Cromarty, Sutherland, Orkneys, Shetlands | 1951-60 | 4·0* |
| | (*a*) Orkneys Shetlands | 1954 | 118 | | 40 | + | Orkneys Shetlands | 1951-60 | 5·9* |
| | (*b*) Remainder | 1954 | 56 | | 192 | + | Remainder | 1951-60 | 3·7* |
| Pratt | Stamford, Lincs. | 1949 | 44 | | 41 | + | Rutland, Soke of Peterborough and Kesteven | 1958-60 | 1·9* |
| Hargreaves | Cornwall | 1958 | 63 | | 339 | – | Cornwall | 1958-60 | 2·4* |
| Dassel | Groningen | 1959 | 56 | | 472 | + | Groningen | 1946-55 | 1·8 |
| Gudmundsson & Gudmundsson | Iceland | 1955 | 44 | 2·3 | 158 | + | Iceland | 1946-61 | 0·7* |

* Derived from the published mortality returns of the area stated in col. 8. † Taken from Kurland (1952), Table 10.

lost because they have since died or left the designated area. Finally, as this ratio is concerned with relatively early cases, diagnostic uncertainties are multiplied. For all these reasons the incidence rate has seldom been used (Tables 1 and 2) and workers have been forced to make deductions concerning incidence from prevalence and mortality rates. However, there are certain questions which can only be answered by incidence rates, for example, short-term time trends, and the risk of immigrant groups after migration, relative to that of the population of their adopted country (Acheson, 1963).

TABLE 2

*Recent additional prevalence data for which comparable mortality data were not available, or which were not yet published in final form*

| Source | Place surveyed | Crude prevalence rate | Population at risk in thousands | Cases personally examined |
|---|---|---|---|---|
| Presthus | Norway, W. | 32 | 214 | + |
| Oftedal | Norway, S.E. | 82 | 158 | + |
| Bammer | Aschaffenburg, Franconia | 99* (81) | 79 | + |
| Allison | Orkneys and Shetlands | 153 | 36 | + |
| *et al.* | Faeroes | 48 | 35 | + |
| Macchi | Parma, Italy | 12 | 389 | + |
| Sutherland | Cairns (Queensland) | 7 | 100 | + |
| *et al.* | Townsville (Queensland) | 7 | 90 | + |
| | Mackay (Queensland) | 6 | 47 | + |
| | Darling Downs (Queensland) | 12 | 142 | + |

* 37 communities selected at random.

The point prevalence rate

$$\frac{\text{Number of cases living on a date}}{\text{Population at risk on that date}}$$

is derived from a census of all persons diagnosed as suffering from the disease on a defined date, no matter how long they have suffered from it; it excludes all those who have died or left the area before that date. Persons at all stages of the disease are included. Here the figure is as much influenced by the duration of the disease as by the number of persons attacked, and in a disease as chronic as multiple sclerosis the crude prevalence rate may be 10-20 times the incidence rate (Table 1). For this reason in comparing the prevalence rates of different communities the possible effect of differential survival due to variations in severity of the disease and in treatment of complications must be borne in mind. Thus, in the extreme instance of a primitive community where disability is quickly followed by malnutrition and death, prevalence would in consequence be lowered so sharply that a spurious suggestion that the people were rarely or never attacked by the disease might result. The great advantage of the prevalence ratio is that it

makes use of all the cases and may permit stable ratios to be computed for quite small populations.

Another index of frequency much used in the past was the proportion of all cases (e.g. clinic attendances, hospital admissions, autopsies, etc.) diagnosed as multiple sclerosis. Here further imponderables such as the frequency of other causes of attendance, admission, etc. and the admission policy itself may lead to apparent differences in the frequency of the disease, and there is rarely sufficient information to permit age differences to be taken into account. Except in special circumstances (Acheson and Bachrach, 1960), little more than impressions can be gleaned from such figures although experience has shown that more weight can be attached to the impression that the disease is common in a place than to reports that it is rare. Unfortunately this continues to be the only type of data available for the whole of European and Asiatic Russia, and the continent of South America.

Even in a disease like multiple sclerosis where there is commonly an interval of many years between onset and death, it may also be possible to obtain an index of the frequency of the disease from mortality rates. This is fortunate because mortality data provide the only information available for large parts of the world. The use of this type of data has come in for heavy criticism (Allison and Millar, 1954; Hyllested, 1956), partly because of the general scepticism concerning the acceptance of uncorroborated data collected routinely, and partly because of special objections concerned with the certification procedures.

### *The Problem of Misclassification*

In the absence of any specific laboratory test, or diagnostic biopsy technique, autopsy provides the only means of confirming a clinical diagnosis of multiple sclerosis. It is unfortunate therefore that post-mortem information can so rarely be available to check the estimates of population surveys. Thus, at the time of their original publications on prevalence, both Allison and Millar (1954) and Kurland (1951) could report autopsy findings in only three cases. Not only does the protracted course of the disease delay autopsy confirmation but the circumstances of death (usually at home or in a hospital without facilities for detailed examination of the nervous system) reduce the proportion performed. Autopsy is more likely to be carried out in rapid, difficult or 'interesting' cases which constitute an unrepresentative fragment of the material. Thus Alter (1962) found that an autopsy was available in only one of 64 'probable' cases of multiple sclerosis in Negroes examined at the Neurological Institute at New York and this woman had died in the casualty department in an epileptic seizure. Under these circumstances a comparison of a series of autopsies with the diagnoses made in life (Pohlen, 1942) does not necessarily give a picture of the overall reliability of diagnosis in multiple sclerosis.

The absence of an effective final court of appeal implies not only that misclassification is likely to occur but that its extent cannot be measured. Under these circumstances it can never be proved that an apparent difference in the frequency of the disease between two populations is not an artifact due to differences in diagnostic criteria, or standards of medical care. This realisation has led first to a proper caution in the interpretation of small differences, and second to a wider acceptance of more or less standardised diagnostic criteria (Allison and Millar, 1954). It is unfortunate, however, that with attention closely focussed on the very real diagnostic difficulties, other equally important causes of misclassification which can be reduced by careful planning have sometimes been overlooked (e.g. the degree to which prevalence day is backdated; the size of the community surveyed).

**Factors Leading to Underestimation of the Frequency of Multiple Sclerosis.**—These may be classified as follows:

(1) Errors in ascertainment which fail to bring forward the patient or his records for appraisal.

(2) Erroneous classification of the suspected case as unaffected or as a member of another population.

Whichever index of frequency of multiple sclerosis is used, the nature of the disease dictates that substantially fewer than the actual total number of patients first suffering from (incidence), having (prevalence) or dying with (mortality) multiple sclerosis will be ascertained. Thus in the case of incidence and prevalence ratios those patients who have experienced symptoms but who have either not taken advice or have not had a diagnosis of multiple sclerosis suspected or recorded at the time of the study will be classified as unaffected. In addition a proportion of those in whom the diagnosis has been made may not be found either because of a failure of human memory or of medical records. The magnitude of these phenomena, which are partly due to the gradual onset of the disease, its early intermissions, and reluctance to diagnose an incurable and protracted disease in its early stages, and partly to inadequate medical records, is shown by Stazio, Kurland *et al.* in a follow-up study of Kurland and Westlund's 1951 survey of Winnipeg (Kurland, 1952; Westlund and Kurland, 1953). These workers uncovered a further 42 probable cases known to have been resident in Winnipeg who had symptoms prior to 1951 and who had not been included in the original estimate of 140 cases. Although this error has not been measured elsewhere it must exist in other prevalence studies; it will presumably be of even greater significance in estimates of incidence which are necessarily based on cases with onset of symptoms in recent years.

In indirect population surveys the degree of ascertainment of cases must depend upon many additional factors; the standard and availability of primary medical services (i.e. those medical services which