Schriftenreihe Neurologie
Neurology Series 20

Sigrid Poser

Multiple Sclerosis

An Analysis of 812 Cases by Means of Electronic Data Processing

With 28 Figures

Springer-Verlag
Berlin Heidelberg New York 1978

Privatdozentin Dr. Sigrid Poser
Neurologische Klinik und Poliklinik der Universität Göttingen
Robert-Koch-Straße 40, D-3400 Göttingen

ISBN-13: 978-3-642-87570-0 e-ISBN-13: 978-3-642-87568-7
DOI: 10.1007/978-3-642-87568-7

Library of Congress Cataloging in Publication Data. Poser, Sigrid, 1941– Multiple sclerosis. (Neurology series; 20) Bibliography: p. Includes index. 1. Multiple sclerosis—Cases, clinical reports, statistics—Data processing. I. Title. II. Series: Schriftenreihe Neurologie; 20. RC377.P67 616.8'34'09 78-2266

Softcover reprint of the hardcover 1st edition 1978

Offsetprinting and Binding: Brühlsche Universitätsdruckerei, Lahn-Gießen 2123/3130-543210

Foreword

The value of prospective long-term studies on the features and course of multiple sclerosis is determined by the reliability with which relevant information is documented. This involves two basic problems: 1) The documentation system used must be detailed enough to provide adequate data on the essential features and course of the disease in a given case; on the other hand, it must not be so complicated and cumbersome as to preclude its use in the routine care of MS patients. 2) Since no system can fully anticipate new problems and scientific approaches that may become important at some future time, the system must be open to provide the possibility of adding and correlating the data of special research studies with the basic data.

These considerations led to the development of the basic documentation system described here and employed for the analysis of clinical data in this monograph. The work was carried out with the help of the *Deutsche Forschungsgemeinschaft* as a part of its research program on multiple sclerosis and related demyelinating disease. A basic documentation pool including the data of more than 2000 patients has been accumulated in the last six years. The system has been put to practical use in a number of epidemiologic surveys completed or under way, in following up the cases in an epidemiologic observation area in South Lower Saxony, and in studies on spasticity, cerebrospinal fluid findings, clinical forms and neurophysiological aspects of MS.

The author deserves great credit for developing and improving the optical mark reader sheets and for her decisive work in the organization and maintenance of the system now in use.

Documentation programs are laborious, time-consuming and, over long stretches of the work, not endowed with the glamour that makes experimental approaches and laboratory studies based on intriguing hypotheses so fascinating. MS, as a disease of only the human species, cannot be fully comprehended in its etiology and pathogenesis, however, unless reliable data on the features and the course of the disease are accumulated in prospective studies, with sufficiently large data banks available to make possible

the selection of comparable cases for investigations focussed on special problems. This monograph by Dr. Sigrid Poser testifies to the diligence and continuity with which such basic work has been accomplished and is being continued.

February 1978

Prof. Dr. H. J. Bauer
Director, Neurological Department
University of Göttingen

Contents

1. Introduction

Abbreviations

MS	Multiple Sclerosis	
CSF	Cerebro-Spinal Fluid	
FRG	Federal Republic of Germany	
DFG	*Deutsche Forschungsgemeinschaft*	(German Research Society)
GD I	*Grunddokumentationsbogen I*	(Basic Documentation Sheet I)
GD II	*Grunddokumentationsbogen II*	(Basic Documentation Sheet II)

1.1 The Need for a New Documentation System

The etiology of multiple sclerosis (MS or disseminated encephalomyelitis) is still unknown. A causal therapy is therefore not possible, and the limited success of symptomatic treatment is felt by the individual patient all too often. These therapeutic limitations have wide social consequences, because MS runs a chronic course affecting mainly young people, and because it is one of the most common neurologic diseases.

The prevalence of MS in central Europe (see McAlpine et al., 1972) is approximately 50 patients per 100,000 inhabitants. An epidemiologic study in Lower Saxony yielded a rate of 36.8/100,000 inhabitants (Firnhaber, 1969). Thus, the number of MS patients in the Federal Republic of Germany (FRG) could be 22,000 or more. A proportion of cases are probably missed because of diagnostic difficulties, particularly in early and atypical cases (Käppeli et al., 1972, v. Büren et al., 1972). However, Schrader's (1974) figure of more than 100,000 MS patients for the FRG was not based on systematic investigations and could be an overestimate.

Although social and medical care for MS patients has been inadequate in the past and still needs much improvement (Heier, 1973), there has been an interest in the etiology and pathogenesis of the disease for years. A broad spectrum of scientific methods have been applied, and a variety of hypotheses presented. Nowadays, the idea of a slow virus infection prevails; some authors discuss the additional role of immunologic factors (see Bauer, 1970).

With increasing specialization in research methods, it has become increasingly difficult to relate the clinical symptomatology of MS to scientific data. It is possible that the term "MS" represents a syndrome rather than a disease. The form, duration, intensity, localization, and time course of MS vary considerably. These complications have to be kept in mind in the interpretation of laboratory results and in clinical trials.

The correlation of laboratory findings with clinical data presents problems. The majority of patients are treated in hospitals where both the inter-

est in and facilities for scientific work are limited. Conversely, institutions and university hospitals have special facilities and staff but usually only a limited number of patients.

The documentation of clinical findings varies from hospital to hospital. As a result, the correlation of research findings to symptomatology has always been limited to small groups (Bradshaw, 1964; Vymazal et al., 1966; H. Strötker, 1968; S. Strötker, 1969; Schwartz et al., 1970; Castaigne et al., 1971; Stenuit, 1972; Bader et al., 1973; Jersild et al., 1973b; Olsson et al., 1973; Salmi et al., 1973; Schuller et al., 1973; Tichy et al., 1973; Frick et al., 1974).

In clinical studies the number of patients is usually too small for useful statistical analysis. For instance, it is still not known whether or not the age at disease onset has an influence on the prognosis of MS.

In 1970 a program "Etiology and Pathogenesis of Multiple Sclerosis and Related Diseases" was started as a *Schwerpunktprogramm* (Priority program) of the *Deutsche Forschungsgemeinschaft* (DFG). The main purpose was to relate laboratory results to clinical data on a large scale. A standardized documentation system was planned for the collecting of clinical data, and an electronic data processing program for subsequent storage and analysis. The data should finally be available to all members of the project (17 hospitals, as well as research groups in virology, immunology, morphology, epidemiology, biochemistry, documentation, and histocompatibility).

The first step was therefore to find a suitable documentation system. Numerical data are not difficult to record in a standardized form: however, case histories and clinical data present problems (Ehlers et al., 1975).

Traditional medical records are usually incomplete and often imprecise. Systematic analysis of such records is difficult, if not impossible (Immich, 1964; Jenkins, 1966; Doll, 1968; Kröner, 1969; Wagner 1969; Feinstein, 1970; Gordon, 1970; Wersig et al., 1971). It is evident that documentation of clinical data, the main topic of this paper, must be revised if further research is to be productive.

Roser et al. called for standardized clinical data as early as 1841. This idea was not followed up until Bleuler complained in 1919 of the insufficiency of medical records in his book *Das autistisch-undisziplinierte Denken in der Medizin und seine Überwindung* (*Overcoming Autistic, Undisciplined Thinking in Medicine*).

At about the same time, Kraepelin (1919) developed a new system of recording clinical data on a *Zählkarte* (a precursor of punching documents). He registered not only the personal data of each patient but also the etiology, pathogenesis, and course of the disease. It has taken a long time for this system to be generally accepted, and it is still being developed.

1.2 Current Methods of Documentation in General Neurology

Standardized recording techniques have already been applied in the following fields of neurology: Electroencephalography (Metcalf et al., 1960; Doose et al., 1962; Bochnik et al., 1964; Oberhoffer, 1967; Helmchen et al., 1968; Baust, 1971; Penin et al., 1972), echoencephalography (Galicich et al., 1971), neuroradiology (Korein et al., 1965, 1966; Kricheff et al., 1970), brain scanning (Heiss et al., 1970), electromyography (Baust, 1971, Micheloyannakis et al., 1974), and neurootology (Claussen, 1973).

These techniques have made possible analysis by electronic data processing in these fields.

Metcalf et al. (1960) and Doose et al. (1962) used the punch card system to correlate EEG findings with clinical data. Oberhoffer (1967) introduced the optical mark reader documentation system into neurology for the same purpose. Penin et al. (1972) continued along this line, and Patzold et al. (1973) and Haller et al. (1973) were the first to publish results obtained this way.

Moiseeva (1967) worked on a systematic classification of reflexes with a view to computerized diagnosis and decision-making in the future. In 1969 Schmitt published his experiences with electronic data processing in the Bad Homburg Neurologic Hospital, but did not mention the documentation of his neurologic findings. Baust developed a new system of medical recording in neurology with an on-line computer terminal (Baust, 1971, 1973). The work of v. Albert (1973) and Patzold et al. (1975) on an optical mark reader documentation system is still in progress. Vastola et al. (1973) recommended the use of a computer for screening ambulatory neurologic patients.

1.3 Documentation of Special Neurologic Diseases

Standardized documentation systems exist mainly for those neurologic diseases in which diagnosis and case control are based on clinical data rather than on laboratory findings. This applies to MS as well as to Parkinson's disease. Standardized registration of patients with parkinsonism is well established (Fairman et al., 1956; Canter et al., 1961; Webster, 1968).

The first documentation systems for MS were developed in the context of therapeutic studies (Arkin et al., 1950; Alexander, 1951). Details of signs and symptoms were omitted in favor of information about disability. This method was extended by Kurztke (1961, 1965) and applied to a large-scale study on the influence of ACTH on acute bouts of MS by Tourtellotte et al. (1965) and Kuzma et al. (1965).

This tendency to concentrate on disability was shown by other authors with a view to giving a prognosis (McAlpine et al., 1952; Thygesen, 1953; Hyllested, 1956; Bauer et al., 1963; Broman et al., 1965; Fog, 1965a; Pedersen, 1965; Gilland, 1965; Cendrowski, 1971). Usually, a mixed group of patients were examined. Retrospective analysis of the duration and course of their disease together with their present disability gave a general prognostic index. Fog et al. (1970) determined the individual prognosis for 73 patients by analyzing their case histories. Kurtzke et al. (1968, 1969) followed up the performance of American veterans over longer periods of time. However, in addition to the disadvantage of bias of selection, in this study grading of the disability was done in retrospect, based on medical records and not on a specially designed examination.

A standardized system for the documentation of signs and symptoms of MS has not yet been developed[1]. One of the early descriptions of the disease was by Charcot in 1868, and MS symptoms have appeared in medical records since then. These records were the source of numerous statistical analyses (E. Müller, 1904; Berger, 1905; Bramwell, 1905, 1917; Böhmig, 1925; Obständer, 1926; Marburg, 1932; Sällström, 1942; Lazarte, 1950; MacLean et al., 1951; Abb et al., 1956; Papac, 1957; Morsier, 1971). The value of retrospective studies of this kind is limited; records are often incomplete and sometimes illegible, various diagnostic criteria are applied, and definitions used for the description of signs and symptoms are not always given. A few authors (R. Müller, 1949; Leibowitz et al., 1964a, b; Panelius, 1969) have based their statistical analyses of clinical findings on specially designed examinations of patients.

The course of events is particularly important in chronic disease, which is characterized by bouts and remissions. Since data taken from traditional medical records and the patients' own recollections are often inaccurate, the only way to get reliable information is to keep standardized records from the very onset of the disease. This is difficult to achieve and requires good communication and cooperation with physicians, who might be more positively motivated if shown the advantages of such a system (Proppe, 1960).

The concept of the DFG's program on MS was to approach questions of etiology and pathogenesis with a wide range of well-documented data. It was hoped that this large-scale computerized analysis might reveal new information about the disease. This paper describes the development and use of a standardized documentation system for clinical MS data, which was simple enough for multicenter use, and yet sufficiently detailed for scientific analyses and correlations.

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[1] Simultaneously with the system presented here, Fog et al. (1976) developed a detailed punched card documentation system.

2. Methods

2.1 Different Forms of Documentation

2.1.1 Punched Cards

Punching documents were developed from the *Zählkarte*. The available data are written on these punching documents in coded form and then transferred to punched cards by punch operators. The punched card is one of the most frequently used devices for reading data in fields where information is basically numerical (for instance, laboratory results). All nonnumerical data must be coded before the punching process, a disadvantage that can be eliminated in other systems (see below). The registration of personal patient data (name, sex, date of birth, marital status, residence) on punching documents presents no real difficulties because the items of data are well defined. Problems arise with the documentation of diagnoses. A standard classification system does not exist. For instance, WHO's international key for diagnoses is not generally accepted in the field of neurology. Individual codes are used (Seitz, 1973), which makes standardized documentation difficult. In the field of psychiatry the international code is in general use in Germany (Helmchen, 1974), and a common system of recording patients' personal data and diagnoses is possible (Eckmann et al., 1973).

A standardized system of recording clinical findings on punching documents has been used only in a few hospitals (Hosemann, 1946; Proppe et al., 1953; Ehlers, 1967b). A few multicenter studies have been made in the context of smaller, easily defined problems (Dold, 1970).

2.1.2 Modern Methods

The newly developed methods of recording and processing data facilitate large-scale documentation. The advantage of the optical mark reader system (Ehlers, 1967a) is that data can be recorded without coding, i.e., time is saved, and coding and punching errors are avoided. Boxes are already printed on forms, each box associated with a particular sign or symptom and marked with a pencil or left open. The pencil marks are then detected by an optical reader. (Photo cells detect the different reflections of light; see IBM 1968.) The reader is used off line (i.e., without direct access to the computer), simply for storing information on punched cards or tape; or it is used on line as a direct input device. Computerized plausibility controls allow detection and rejection of incorrectly or incompletely marked sheets A wide range of data can be recorded on a single sheet (Ehlers, 1967a; Ehlers et al., 1968).

In some fields standardized data have to be supplemented by free text. This free text can be recorded on the same sheet, but it has to be punched onto cards later. The simplicity of the off line procedure of optical mark reading makes it suitable for multicenter studies. Individual groups do not need computer facilities; processing can be done centrally. However, this centralization has the disadvantage that delays are encountered in the handling of incorrectly marked sheets. This can be particularly troublesome in intensive patient care.

The optical mark reader system is now used in numerous fields of medicine (Poser et al., 1974b). However, it is important to remember that well-designed questions and precise definitions are required if the system is to be successful. Two groups of psychiatrists succeeded in designing an optical mark reader documentation system for multicenter use (see Angst et al., 1969; Spitzer et al., 1971). The system stood up well in several therapeutic trials (Berner et al., 1971; Angst et al., 1971; Bente et al., 1974). It allows the recording of data from the patient's case history as well as physical and mental findings.

Optical mark reader systems have already been used for recording case histories in other fields of medicine (internal medicine: Giere et al., 1972; surgery: Grund-Krehl, 1973). Several attempts have been made to tailor questions about case history to each individual patient by using a computer-aided questionnaire. This modern method has also been suggested for physical examinations (Reichertz, 1973).

2.2 Choice of Documentation Method for Multiple Sclerosis

A first approach to standardized documentation of MS patients was made in the Department of Neurology of Göttingen University. Between 1963 and 1968 data from 625 inpatients were recorded on punching documents (Bauer et al., 1978). The form was developed in connection with the German Ministry of Labor's study on the feasibility of rehabilitation for MS patients already receiving compensation. In this investigation 22 of 80 items concerned working capacity; neurologic findings were recorded briefly in terms of disability only.

The present attempt to correlate clinical and laboratory data required more detailed documentation of neurologic signs and symptoms. As mentioned above, the optical mark reader system was considered suitable for this purpose. It soon became evident to us that we should consider only those signs and symptoms most frequently observed in MS.

The recording of all available neurologic findings had proved to be time consuming and tiresome (Poser et al., 1976a). Thus, the first aim here was

to design a single documentation sheet containing the data most relevant to the research groups concerned.

2.2.1 Development of the Documentation Sheet for Multiple Sclerosis

A preliminary sheet was used in a pilot study (Poser, 1974). After discussion with the participating physicians about the difficulties that arose, modifications were made in the sheet. The standard examination was not followed exactly; and it became evident, for example, that reflexes were inconveniently placed on the sheet, and that there were too many details about sensory signs and symptoms.

The final documentation sheet (see Fig. 1 inside back cover) was divided into three main parts:

1. Personal data of the patient and hospital identification.
2. Case history, CSF findings, diagnostic classification, complicating and unrelated diseases.
3. Present neurologic findings.

A survey of the main items is given on Figure 2.

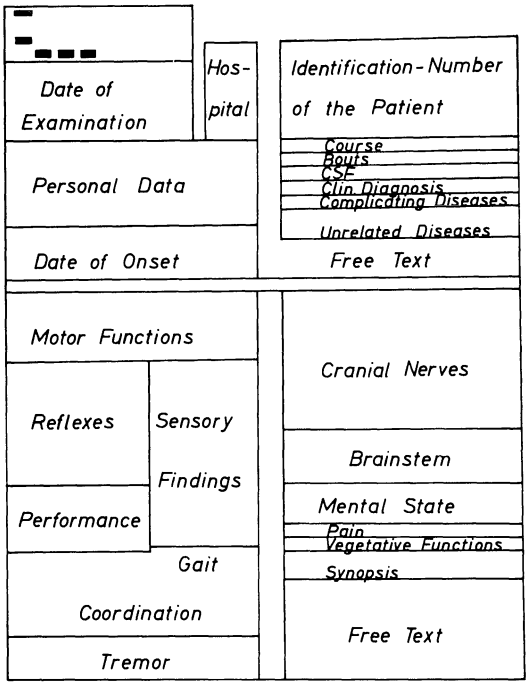

Fig. 2. Layout of the main items on the documentation sheet

The first part was arranged in a similar way to sheets already being used in other hospitals of Göttingen University. This made sharing of a common plausibility program possible.

Part 2 gave the date of birth and time of onset of the first symptoms (left side); and the course of the disease, a summary of CSF findings, diagnostic classification, and complicating and unrelated diseases (right side). Quantitative details of the CSF findings would have taken too much space and were therefore omitted on this first sheet.

The arrangement of clinical findings on the lower part of the form followed the usual pattern of a neurologic examination. A summary of clinical findings was given at the end. Additional data could be written as free text in the lower right hand corner.

A form-filling guide was added to each sheet. This contained technical instructions and explanations of abbreviations as well as definitions of terms used on the sheet.

2.2.2 Handling of the Sheet

Members of participating hospitals and institutions met during the first workshop of the *DFG-Schwerpunktprogramm* in December 1971 in order to become familiar with the new system. The documentation procedure was demonstrated during examination of a patient. Since January 1972, seventeen hospitals have joined in the program. A central secretary's office was responsible for the organization and coordination of the program. Monthly reports were made on the state of the data-pool and on problems arising.

2.3 Quality Control of the Data

Analysis of errors is particularly important in medical documentation (Proppe et al., 1956; Immich, 1964; Wagner, 1964; Nacke et al., 1964). In the present study plausibility programs were used to prevent the storage of incomplete data; incorrectly or incompletely marked sheets were automatically rejected. Examination and documentation of the same patient by different physicians was used in a test for validity. Each of 25 patients was examined in the Neurology Department of Göttingen University by two or more physicians within a 2-day period. The results of these 65 examinations were compared with the help of a computer program and the differences analyzed (see Sect. 3.2.4).

A number of patients were examined repeatedly by the same physician over a longer period. However, it was not possible to test the reliability of these data, since the signs and symptoms of MS can change rapidly.

2.4 Management of the Forms

2.4.1 The Process of Registration

Incoming sheets were registered in the central office. An index card containing personal data, the date of examination, and the name of the examining physician was set up for each patient, who was given a number. The forms were then sent to the computing center. The information was automatically transferred from the documentation sheet to three punched cards by an IBM optical mark reader 1232 and then transferred onto a magnetic tape and fed into a Siemens 4004/35 computer.

2.4.2 Description of the Program

A computer program is a sequence of instructions that enables the computer to solve specific, usually repetitive tasks. Lange et al. (1972) developed a universal program, MARBEL, for plausibility control and storage of data on optical mark reader sheets. By means of a program written by Mr. Wegener and Mr. Brauns, EDP Department, Göttingen, MARBEL was adapted to our problem. The plausibility controls had to be individually defined for each item (see Poser, 1974). A detailed description of the program for data analysis is given in an earlier paper (Poser et al., 1974b).

2.4.3 Access to the Data

Each user of the system was able to select data which interested him. The field numbers corresponding to the particular items were transferred to a punching document (see Fig. 3) and then were transferred manually from

Fig. 3. Punching document on which the field numbers are filled in.

135, age at onset		15, 15 years 16, 16 years etc.
ϕ15, course of disease		1, remitting 2, remitting and progressive 3, progressive from onset
$\phi\phi$9, sex of patient		1, male 2, female
138–149 152 117	clinical signs or symptoms	2, present
ϕ26, clinical diagnosis		1, definite 2, probable 3, possible
ϕ74, ability to work ϕ77, ability to walk		1, normal 2, slightly disturbed 3, severely disturbed 4, lost

see Fig. 4

Siemens-Datenverarbeitung

Ablochschema-Auswertung

MB Ø1 - Neurologie

Programm NEUGRU, NEUAUS

Bearbeiter Poser

Datum 20.2.74

Blatt 1

KA	PARA 1 Feld	Wert	PARA 2 F	W	PARA 3 F	W	PARA 4 F	W	PARA 5 F	W	PARA 6 F	W	PARA 7 F	W	PARA 8 F	W	PARA 9 F	W	PARA 10 F	W	PARA 11 F	W	PARA 12 F	W	PARA 13 F	W	PARA 14 F	W	PARA 15 F	W	FREI
//	JOB																														
//	EXEC NEUGRU																														
//	EXEC NEUAUS																														
//	MEND																														
0	135	15	135	16	135	17	135	18	135	19	135	20	135	21	135	22	135	23	135	24											
/	*																														
E	Ø15	1	Ø15	2	Ø15	3	ØØ9	1	ØØ9	2	138	2	139	2	14Ø	2	143	2	145	2	146	2	147	2	148	2	152	1	149	2	
E	117	1	Ø26	1	Ø26	2	Ø26	3	Ø74	1	Ø74	2	Ø74	3	Ø74	4	Ø77	1Ø	Ø77	2Ø											
/	*																														

Key For KA Zero=Ø

E=Counting Of Items

O=Selection Of Alternative Items

U=Combination Of Items

the punching document to punched cards and then fed into the computer for analysis. The results were printed out as shown in Figure 4. These print-outs gave the field numbers, together with the number of patients exhibiting the particular feature. Further analysis of the results (calculation of mean values, standard deviation, and percentages) was performed on a Hewlett-Packard 9820 desk-computer.

2.4.4 Correction of Errors

The mark reader sheets were returned to the central office. Forms accepted by the computer were filed; incompletely or incorrectly marked sheets were returned to the physicians, together with a list of particular errors made. Corrected sheets were returned via the central office to the EDP Department.

2.5 Analysis of the Data

Patients were registered according to the above-mentioned sheet until July 1973. The file was then closed and a pair of new forms was introduced (see Sect. 2.7). The computer program enabled us to group the patients according to sex, age at onset, month of onset, duration and course of disease, disability, working ability, probability of diagnosis, CSF findings, and individual signs and symptoms. Different signs and symptoms could then be correlated with various groups and subgroups.

A selection of patients for special investigations or therapeutic procedures was also possible. The relationship between certain symptoms and the course of the disease could be determined by comparing different groups of patients. The program allowed selection of patients for future tests for correlation between laboratory results and clinical findings. Clinical data of a particular patient could not be obtained in text form from the original closed file. However, a print-out is already in use in the new two-sheet system (see Sects. 5.6 and 2.7).

2.6 Distribution of the Data

Initially, only the author and programer handled the data directly. They then had continuous access to the data while checking and correcting the program. Other members of the project had indirect access to the data;

```
EVALUATION  OPTICAL  MARK  READER   FORM  01     -  NEUROLOGY  -                  02/28/1974                    PAGE   1

PUNCHED  CARD  CONTENT

01351513516135171351813519135201352113522135231352 4

PATIENT  NO.
0000019
0000027
0000035
0000051
0000094
0000108
0000124
0000167
0000175
0000280
0000337
0000353
000040X
000047X
0000485
0000531
0000582
0000590
0000639
000071X
0000728
0000752
0000760
0000817
000085X
0000892
0000949
```

```
EVALUATION  OPTICAL  MARK  READER   FORM  01     -  NEUROLOGY  -                  02/28/1974                    PAGE   6

FIELD 135  FIELD 135  FIELD 135  FIELD 135  FIELD 135  FIELD 135  FIELD 135  FIELD 135  FIELD 135  FIELD 135
VALUE  15  VALUE  16  VALUE  17  VALUE  18  VALUE  19  VALUE  20  VALUE  21  VALUE  22  VALUE  23  VALUE  24


NO OF CASES COUNTED      :  912

OF THESE APPLICABLE HERE :  218

SIGNIFICANCE OF THE FIELD NUMBER, SEE KEY LIST



EVALUATION  OPTICAL  MARK  READER   FORM  01     -  NEUROLOGY  -                  02/28/1974                    PAGE   1

PUNCHED  CARD  CONTENT
E0151 0152 0153 0091 0092 1382 1392 1402 1432 1452 1462 1472 1482 1521 1492

FIELD 015  FIELD 015  FIELD 015  FIELD 009  FIELD 009  FIELD 138  FIELD 139  FIELD 140  FIELD 143  FIELD 145
VALUE  1   VALUE  2   VALUE  3   VALUE  1   VALUE  2   VALUE  2   VALUE  2   VALUE  2   VALUE  2   VALUE  2

      123          79          16          66         152         121         159         174         177         201

FIELD 146  FIELD 147  FIELD 148  FIELD 152  FIELD 149
VALUE  2   VALUE  2   VALUE  2   VALUE  1   VALUE  2

      150          77          43         107         132                          NO OF CASES COUNTED :  218



PUNCHED  CARD  CONTENT
E1171 0261 0262 0263 0741 0742 0743 0744 0771007720

FIELD 117  FIELD 026  FIELD 026  FIELD 026  FIELD 074  FIELD 074  FIELD 074  FIELD 074  FIELD 077  FIELD 077
VALUE  1   VALUE  1   VALUE  2   VALUE  3   VALUE  1   VALUE  2   VALUE  3   VALUE  4   VALUE  10  VALUE  20

       50         159          49           8          27          80          52          49          49          67

                                                                                NO OF CASES COUNTED :  218
```

Fig. 4. Computer print-out of the data that had been requested on the punching document (for the meanings of field numbers, see Fig. 3)

they could send in a request for a particular analysis and later receive the results in a computer print-out in tabulated form. All participants have direct access to the new open file.

2.7 The New Set of Documentation Sheets

An extended version of the documentation system was introduced in 1973 and the data stored in a new file. The basic documentation sheet I (*Grunddokumentationsbogen I* = GD I; see Fig. 5 inside back cover) was elaborated by a commitee[2] after frequent discussions with the participating clinicians and research-workers. The additional section is largely devoted to the preceding course of the disease (Poser et al., 1973b).

The second part *Grunddokumentationsbogen II* (GD II; see Fig. 6 inside back cover) was designed in cooperation with H. Hauptvogel. Graphic representation of the body facilitates the recording of clinical findings. The most important definitions are printed on the back of both sheets. The original sheets are sent to the EDP Department; a copy of each sheet is filed in the medical record.

The personal data of patients are recorded on a separate form, the *Stammdatenbogen* (see Fig. 7 inside back cover). Plausibility controls for this new set of sheets were defined for each item as before. In the new sheets it is possible to indicate that details from the previous history are unknown by marking "yes" and "no" simultaneously (see instruction in the upper right-hand corner of Fig. 5).

2.8 Statistical Methods

2.8.1 Significance Tests

Frequency distributions were compared using 2-I-tests (Kullback et al., 1951). Unlike the Chi-square-test, they provide for analysis of contingency tables with small numbers (Sachs, 1968, p. 475 ff.). The coefficient of constriction was calculated using the method of Lienert (1973). It is similar to the correlation coefficient and can vary between 0 and ± 1. The age at onset

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[2] H. Angstwurm, München; W. Grüninger, Würzburg; H. Hauptvogel, Göttingen; U. Patzold, Hannover; S. Poser, Göttingen; D. Przuntek, Würzburg; W. Weinrich, Hannover.

and duration of the disease were each given as the mean ± the standard deviation.

Analysis of variance revealed that not all numerical data were normally distributed, whereupon distribution-free significance tests were used. Wilcoxon's rank test was used for comparison of two independent samples, the H-test of Kruskal and Wallis for comparison of more than two independent samples (Sachs, 1968, pp. 302–306). The null hypothesis was assumed to be wrong if $p < 0.05$. These significance tests were performed on a PDP 12 computer (Digital Equipment Maynard, USA).

2.8.2 Graphic Presentation

When symptoms or disability were to be considered graphically as functions of time, a weighted mean was used (averages taken over 5-year periods). Short-term irregularities were thereby eliminated (Pfanzagl, 1966).

3. Results

3.1 Size of the Study

In this study, 1125 examinations of 947 patients were recorded from November 1, 1971 until July 19, 1973. Thirty-two physicians in 17 hospitals participated. When the data file was closed in August 1973, only 990 examinations of 812 patients were available for analysis. The other 135 sheets were still being corrected. The latest results are based on 831 patients (state of file in January 1974). For practical reasons it was not always possible to include all 812 patients in all tests (see details below).

3.2 Comments on the Method

3.2.1 Analysis of Errors

Details on the frequency of errors during different periods of time cannot be given; the optical mark reader rejected sheets that were incompletely or incorrectly marked. The sheets were returned to the physician; unfortunately, statistics on this procedure were not collected. Before the plausibility program was working, the quality of the marking was checked manually. During this period the rate of errors fell from 30 to a final level of 10–15 per 100 sheets.

At the end of the study, when the plausibility program was used, it was found that 4 out of 47 sheets were not correctly marked. The following errors were made:

1. Incorrect registration of patient identification numbers.
2. Contradiction in the description of symptoms by marking "no disturbance" and "sensory symptoms present" in the same field.
3. Misunderstanding of the definitions given.
4. Simple omission and incomplete erasing

A particularly frequent source of error was omission of zeros at the end of a number, whereupon a special reminder was printed on the new sheets (see Fig. 5, upper right-hand corner). Sensory signs and symptoms and disturbances of cranial nerves were sometimes completely ignored, perhaps because these fields were easily overlooked. There were sometimes inconsistencies between the summary at the end and the main body containing more detailed information. Refusals were often the result of technical problems, e.g., if the surface of the paper was damaged by erasing or if a mark was not sufficiently clear.

The plausibility controls were not general enough to check all types of data. There was not always enough room to record "no", "yes", or "un-

known" for each item separately. For example, control over micturition, bowel function, sexual function, and circulatory and trophic regulations had to be considered together as vegetative disturbances (see Fig. 1, lower right-hand part). If one of these symptoms was marked, there was no way to check whether the examiner had asked for any of the others. For instance, sexual disturbances were often not discussed at all. They were apparently more common in men than in women (see below), although it is possible that more men than women talk about this problem spontaneously.

3.2.2 The Precision of Recording

The quality of recording varied between the two extremes shown in Figures 8 and 9. The items were marked by crossing the boxes with a ballpoint pen on the sheet of Figure 8; in this form the sheet could not be read at all. The neat record seen on Figure 9 was made by a physician working in a busy hospital for MS patients. She participated in this survey regularly and had the least number of errors despite a considerable work load. Some doctors could be recognized by their specific and recurring pattern of errors. The number and kind of errors thus seem to depend on the individual physician.

3.2.3 Free Text

Free text was added frequently; in the beginning, 35% of the sheets contained additional findings, later 30%. Usually, the free text included CSF findings or comments on other diseases. Technical comments appeared in 10% of the sheets at the beginning and in 3% later.

Documentation difficulties were often found in the *Romberg* and *Gang* (gait) fields; unfortunately, the sheet did not allow for a "not possible to examine" comment. It was also difficult to record slight differences in reflexes, in spasticity, or in disturbances not directly related to MS. All these objections were considered in the planning of the new set of sheets.

3.2.4 Validity of the System

Twenty-five patients were examined by two or more physicians within two days: 13 patients twice, 9 patients three times, 2 patients four times and 1 patient five times. The results of these 65 examinations were compared with the aid of a computer[3].

[3] Program written by Mr. Kerscher, EDP-Department, Göttingen University.

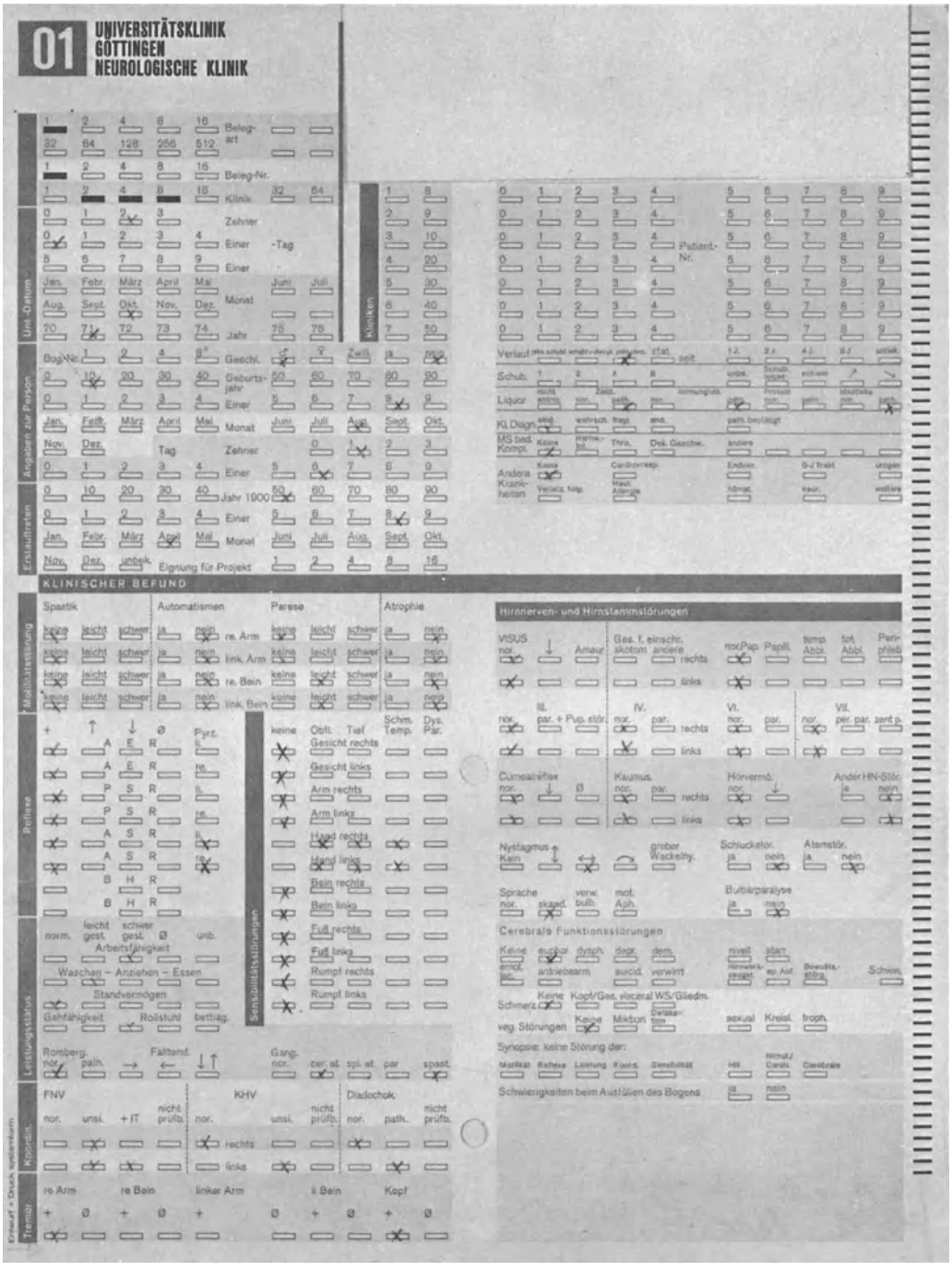

Fig. 8. Example of a sheet that could not be read by the computer

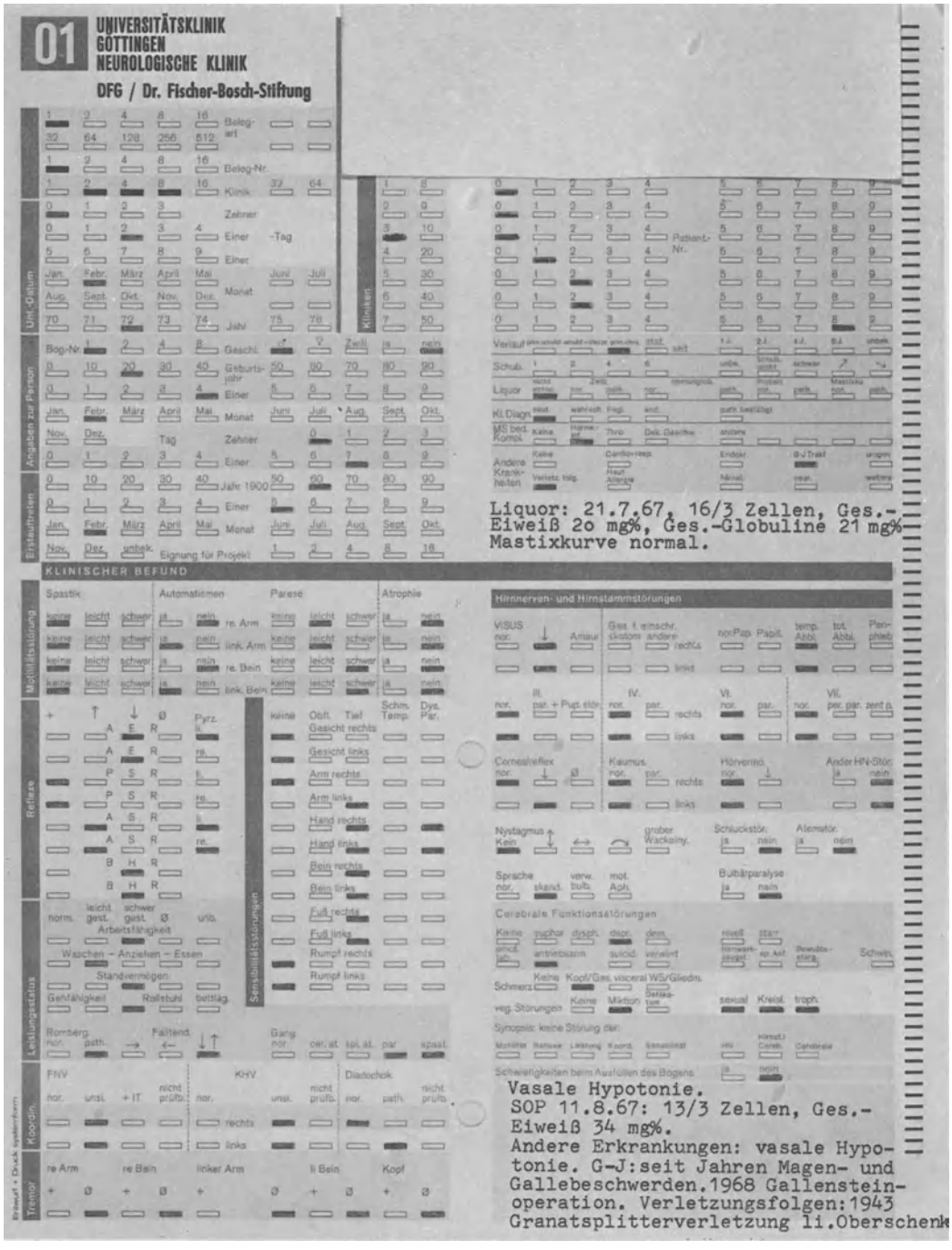

Fig. 9. Example of a neatly marked sheet

Figure 10 shows an example of three examinations of one patient given by different physicians. Each number indicates how many of the three physicians marked that particular part of the sheet. Thus, the number 3 means that there was perfect agreement, whereas the numbers 2 and 1 indicate disagreement. The number of discrepancies increased, as is to be expected, with increasing frequency of a disturbance and with more refined grading of a sign or symptom (see Fig. 11).

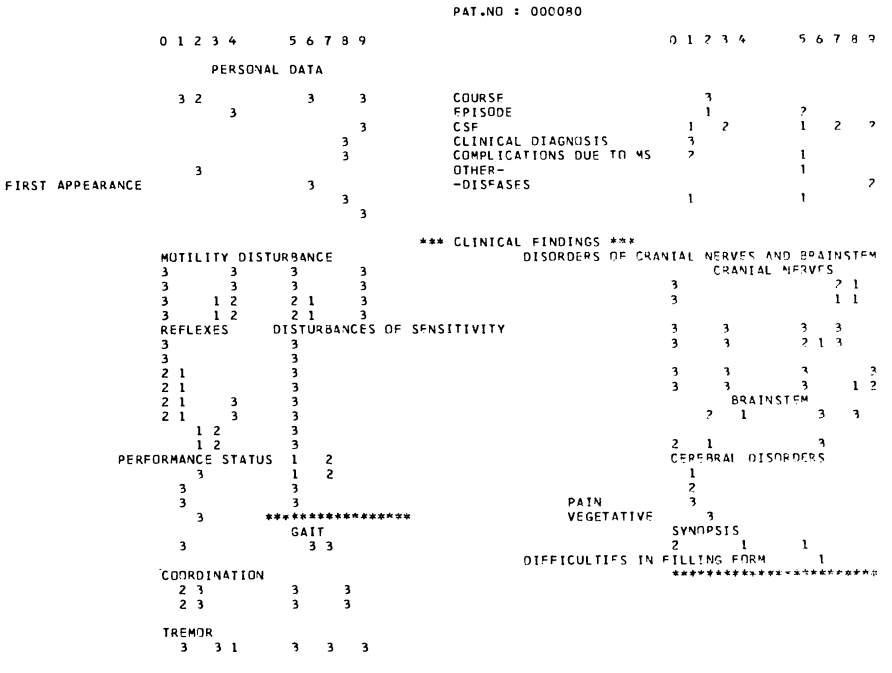

Fig. 10. Summary of three examinations of one patient given by three physicians.
3, item marked by all three physicians
2, item marked by two of the three physicians
1, item marked by one of the physicians

It is known that discrepancies of this kind can often be prevented by clearly defining the criteria to be applied (Fletcher, 1963; Gill et al., 1973). These multiple examinations, made early in the project, enabled us, after discussions with the physicians concerned, to design a suitable glossary. This was printed on the back of the new sheets, so that the physicians did not need to refer to a separate glossary. Unfortunately, it was not possible to repeat the multiple examination check after the glossary was in use.

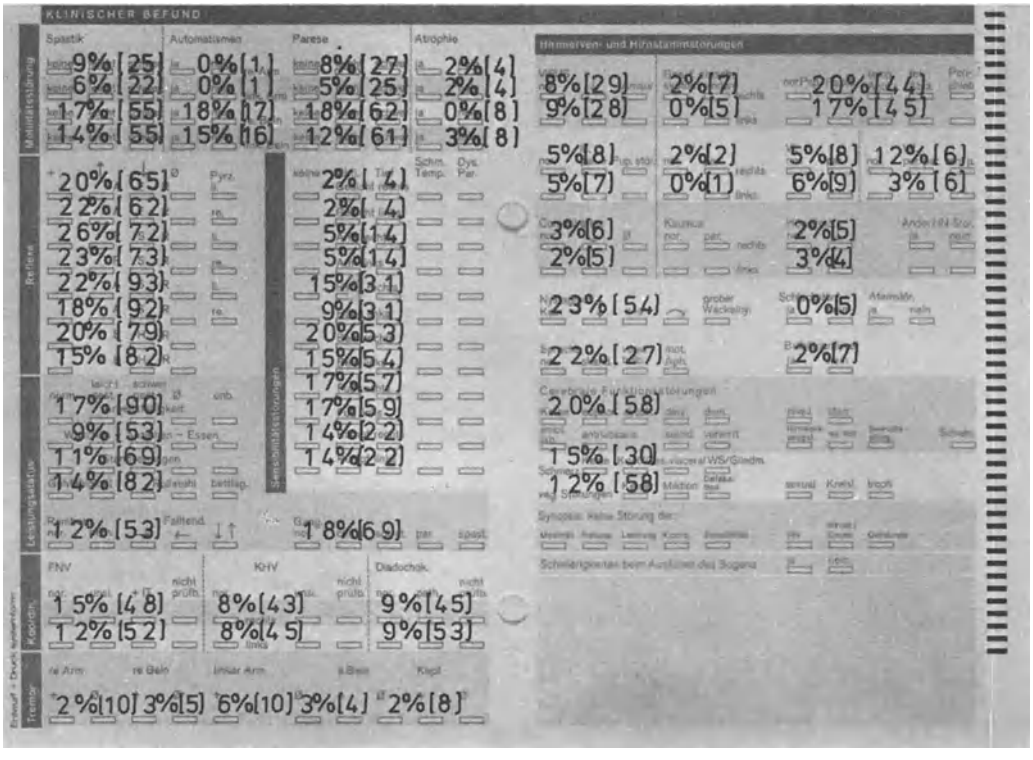

Fig. 11. Discrepancies among different examiners given as a percentage of 65 multiple examinations. Frequency of occurrence of the item in the whole group (N = 812) is given in brackets

3.3 Documentation of Disease Course

The data of the 178 follow-up examinations were not analyzed by the computer. It became evident that the clinical findings could not be recorded in sufficient detail, because variations were usually small during the course of this project. It therefore did not seem worthwhile comparing the repeated examinations by computer.

3.4 Analysis of All Examinations Performed

Some of the data here refer to all examinations performed, as did those of Kurtzke (1970). The frequency of cranial nerve disturbances and bulbar symptoms refer to 990 examinations of 812 patients in our project; a com-

parison with the data of Kurtzke is shown in Table 1. Repeated examinations of a patient with a rare symptom can give misleading statistical results; the value of analyzing all examinations is therefore limited. Discrepancies among data from different samples are perhaps to be expected if repeated examinations are included.

Table 1. Brain stem symptoms in MS. Data from all examinations (N = 990) compared with the Army series of Kurtzke (1970)

	Pool N = 990	Army series N = 1999 (%)
Diplopia	195 (20%)	19.1
Altered facial sensation	60 (6%)	4.6
Jaw weakness	2 (0%)	0.3
Facial weakness	103 (10%)	2.6
Dysarthria	256 (26%)	19.9
Dysphagia	51 (5%)	4.4
Bulbar palsy	8 (1%)	0.8
Vertigo	91 (9%)	4.7

3.5 Analysis of First Examinations

The data presented in the following sections refer to the documentation of 812 examinations on sheet No. 1. Altogether, 812 patients with definite, probable, or possible diagnosis of MS were included, irrespective of the duration and previous course of the disease. Different kinds of hospitals participated: special hospitals for MS patients, neurology departments of general and university hospitals, and two outpatient departments. There was, therefore, a wide range of symptoms and of severity of MS. The number of patients recorded in a particular hospital depended on the availability and motivation of the staff. It was therefore possible that the selection of patients was biased.

In an attempt to test for possible bias, 226 patients from the epidemiologic area of Lower Saxony were examined and compared with the main group of 812 patients. In the epidemiologic study all known patients were recorded. It was hoped that the control group of 226 patients was typical, i.e., not biased itself.

3.5.1 Month of Onset

In a retrospective study, Wüthrich et al. (1968) and Rudin (1968) found that onset of MS was significantly less likely during the summer and autumn months. In our sample, too, the first bouts were less likely to occur in summer and in autumn (see Fig. 12; the precise onset was known in only 472 cases). However, deviation from the expected number of bouts was not significant. Other authors (Limburg, 1950; Poskanzer et al., 1966; Panelius, 1969) confirm our finding. The difference found by Caselmann (1968) was not significant when we reassessed his data by means of the 2-I-test.

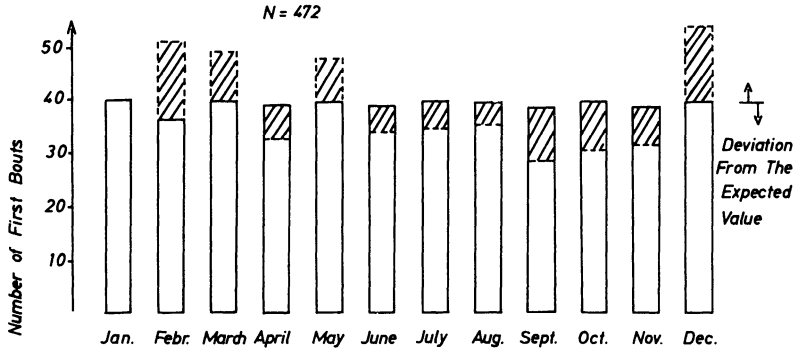

Fig. 12. Occurrence of first bouts related to the time of year

3.5.2 Age at Onset, Present Age, and Differences Between Males and Females

The present age of patients and age at disease onset are shown on Figure 13 and 14. The present age was compared to the age distribution of males and females of the normal population in 1971 (*Statistisches Jahrbuch*). The deviations observed between MS patients and the normal population reflect that first, MS is a rare disease in children; secondly, that MS patients do not usually reach old age. In Figure 14 the age at onset is given for the whole sample as well as for males and females separately; there were no significant differences between the two groups. The mean age at onset was 31.1 years, but the scatter was slightly higher for females than for males (see Table 2). The lower age at onset for females mentioned in the literature (see Discussion) was not confirmed in our study.

The disease lasted longer in females than in males. The significant difference of 1.3 years could be responsible for the differences found between the frequency of pareses (77% for females, 67% for males, $p = 0.0034$) and limb ataxias (84% for females, 78% for males, $p = 0.0305$). However, sen-

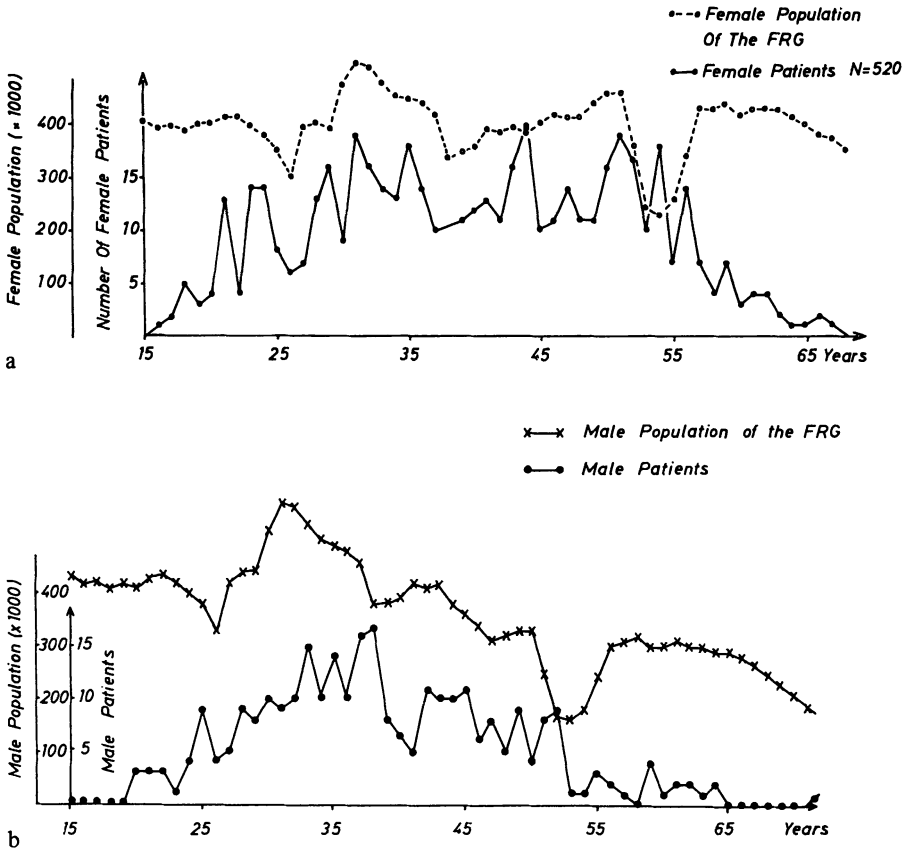

Fig. 13. (a) Present age of female MS patients compared with that in the normal female population. (b) Present age of male MS patients compared with that in the normal male population

sory signs and symptoms depend on disease duration only slightly, so that differences found between men and women cannot be explained in this way (see Sect. 3.6.2).

Disturbances of sexual function were recorded in 5% of the women and 23% of the men ($p < 0.0001$). However, as mentioned above, in the plausibility control we did not check whether this item was specifically asked for, and it is possible that men are more likely than women to complain of sexual disturbances spontaneously. Bladder infections occurred more frequently in females than in males, possibly for anatomic reasons. No significant differences between men and women were found either in the remaining signs and symptoms or in performance.

The preponderance of females having MS (64% females, 36% males) in our study confirms the findings of other authors (McIntyre et al., 1943;

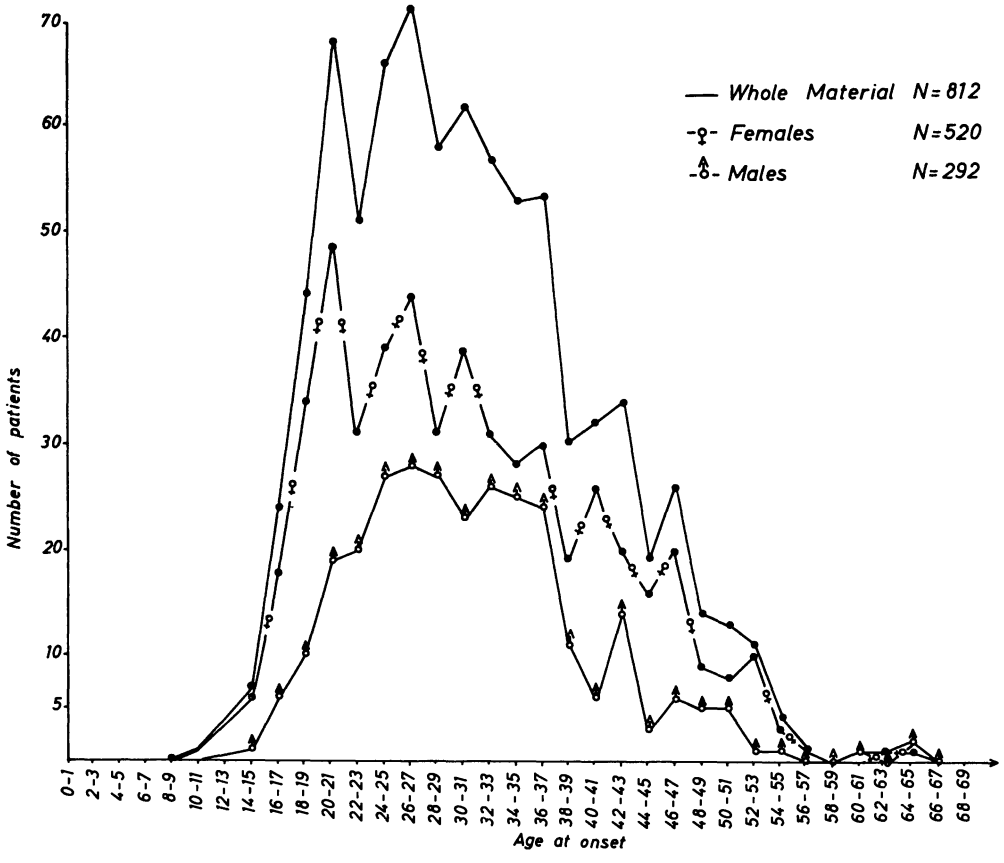

Fig. 14. Age of MS patients at disease onset

Alexander et al., 1958; H. R. Müller, 1961 and 1966; Stazio et al., 1964; Panelius, 1969; Gudmundsson, 1971; Dassel, 1973; Lhermitte et al., 1973). However, the actual ratios varied (see Table 15).

3.5.3 Disturbances of the Functional Systems

Disturbances of different functional systems are summarized and compared with the findings of R. Müller (1949) and Kurtzke (1961) in Table 3. The only striking difference among the three sets of findings concerns mental changes. We found cerebral signs or symptoms in 56% of the patients, Kurtzke in 20%. R. Müller did not give the corresponding figure; however, he found dementia in 28% of his patients (4% in our sample; see Sect. 4.1.3).

Table 2. Symptomatology in MS compared for men and women (N = 812)
n. s. = not significant

	Men N = 292 (36%)	Women N = 520 (64%)	Level of significance
Age at onset (years)	31.1 ± 8.5	31.1 ± 9.95	n. s.
Duration of disease (years)	7.8 ± 7.2	9.1 ± 8.3	$p = 0.017$
Course: Remitting	133 (46%)	212 (41%)	n. s.
Course: Rem. + progressive	117 (40%)	207 (40%)	
Course: Progr. from onset	42 (14%)	101 (19%)	
Paresis of limbs	197 (67%)	401 (77%)	$p = 0.0034$
Spasticity	182 (62%)	340 (65%)	n. s.
Hyperreflexia	273 (93%)	482 (93%)	n. s.
Sensory disturbances	222 (76%)	429 (83%)	$p = 0.0261$
Ataxia of limbs	227 (78%)	436 (84%)	$p = 0.0305$
Ataxic gait	129 (44%)	217 (42%)	n. s.
Urinary dysfunct.	135 (46%)	264 (51%)	n. s.
Sexual dysfunct.	66 (23%)	27 (5%)	$p < 0.0001$
Visual disturb.	180 (62%)	311 (60%)	n. s.
Diplopia	69 (24%)	99 (19%)	n. s.
Brainstem symptoms	191 (65%)	305 (59%)	n. s.
Euphoria	72 (25%)	120 (23%)	n. s.
Depression	29 (10%)	65 (13%)	n. s.
Ability to work: Normal	29 (10%)	56 (11%)	n. s.
Ability to work: Slightly dist.	114 (39%)	195 (38%)	
Ability to work: Severely dist.	78 (27%)	129 (25%)	
Ability to work: Lost	71 (24%)	139 (27%)	
Ability to walk: Normal	51 (17%)	93 (18%)	n. s.
Ability to walk: Slightly dist.	112 (38%)	176 (34%)	
Ability to walk: Severely dist.	67 (23%)	117 (23%)	
Ability to walk: Lost	62 (21%)	134 (26%)	
Infection of urinary tract	39 (13%)	102 (20%)	$p = 0.0204$

Table 3. Signs and symptoms in the pool material compared with the series of R. Müller and J. F. Kurtzke
? = no comparable data

Signs and Symptoms	Pool N = 812	R. Müller (1949) N = 582	J. F. Kurtzke (1961) N = 408
Pyramidal tract dysfunct.	757 (93%)	?	93%
Paresis of limbs	598 (74%)	436 (75%)	?
Impairment of coordination	?	?	87%
Balance disturb.	343 (42%)	287 (49%)	?
Sensory disturb.	651 (80%)	?	65%
Figure-writing	?	359 (81%)	?
Bowel and bladder dysfunct.	413 (51%)	?	53%
Bladder sympt.	399 (49%)	290 (50%)	?
Bowel complaints	158 (19%)	145 (25%)	?
Visual impairment	289 (36%)	?	40% (N = 93)

Table 3 (continued)

Signs and Symptoms	Pool N = 812	R. Müller (1949) N = 582	J. F. Kurtzke (1961) N = 408
Other cranial nerve/brainstem disturb. (excl. trigeminal involvement)	562 (69%)	382 (66%)	81%
Cerebral signs and symptoms	451 (56%)	?	20% (N = 93)
Euphoria	192 (24%)	102 (18%)	?
Dementia	35 (4%)	164 (28%)	?

3.5.4 Selection of Certain Groups

3.5.4.1 Therapeutic Procedures

Patients with spasticity were selected for special therapy. Their motor performance was assessed on a special mark reader sheet and appropiate treatment given (Lowitzsch, 1973). Patients with a severe tremor were selected for another special therapy. Riechert (1973) suggested that stereotactic operations should be considered for patients whose main symptom was an incapacitating tremor of the arms. We found 51 patients to be suitable candidates for stereotactic surgery (26 right-sided, 25 left-sided tremor). Each of these patients showed intention tremor of one arm, full power or only slight paresis of the same arm, and full dependence on help for washing, eating, and dressing.

3.5.4.2 Patients with Epileptic Seizures

The frequency of epileptic fits in patients with MS is reported to vary between 1% and 6% (Hopf et al., 1970). In the present study 9 out of 812 patients had seizures. With the help of extra, more detailed, medical records from the various hospitals it was possible to analyze the occurrence of epilepsy with MS (Ritter et al., 1974). In four cases epilepsy appeared first and MS years later; in three cases this was reversed. In two cases only one of the diagnoses was satisfactorily clear-cut. The prevalence rate of epilepsy is 0.5%–5%, that of MS 0.05% for a normal population. Thus, there does not appear to be a syntropism of the two syndromes.

3.5.4.3 Familial Cases

Although the incidence of MS among immediate relatives of MS patients is known to be 15 to 20 times that normally expected (see McAlpine et al.,

1972), the role of heredity remains unclear. Bertrams et al. (1972) and Jersild et al. (1972, 1973a) found a correlation between a certain pattern of histocompatibility antigens and MS. This supported the concept that genetic factors might be involved. Investigations of the histocompatibility antigens of "MS families" should be particularly interesting in this context. Analysis of the genetic background of four pairs of twins (one identical and three nonidentical) and 39 other familial cases is in progress (Zander et al., 1976).

3.5.5 Statistical Analysis of Symptoms

The statistics on signs and symptoms of MS that are currently available are mostly based on retrospective data or on small samples. The value of a certain symptom or of a pattern of symptoms in the diagnosis of a disease can only be assessed after long-term analysis of a large sample (Griesser, 1965). It is also necessary to study other diseases with similar symptoms, particularly in the context of a planned, computer-assisted diagnosis.

The frequency of disturbances of motor performance, of reflexes, of sensory functions, and of coordination is given in Table 4. Separate analysis of arms and legs showed the well-known preponderance of disturbances in the lower extremities.

Table 4. Symptoms in MS (N = 812)

	Total	Upper limbs	Lower limbs
Spasticity	522 (64%)	254 (31%)	507 (62%)
Paresis	598 (74%)	289 (36%)	578 (71%)
Atrophy	94 (12%)	39 (5%)	78 (10%)
Hyperreflexia	755 (93%)	568 (70%)	724 (89%)
Ataxia of limbs	663 (82%)	340 (42%)	424 (52%)
Tremor	114 (14%)	93 (11%)	44 (5%)
Involuntary spasms	156 (19%)	9 (1%)	154 (19%)
Sensory disturb.	651 (80%)	340 (42%)	582 (72%)

Table 5 shows the exact location of pareses in our survey and in those of R. Müller (1949) and Kurtzke (1970). The different kinds of sensory signs and symptoms and their combinations are shown in Figure 15; disturbances of cranial nerves and brainstem symptoms are seen in Figure 16 and in Table 6. Dysphoric and depressive patients are combined into one group in a graphic representation of mental changes in Figure 17. Out of 812 patients, 451 showed signs of mental impairment, predominantly an affective disorder (382 patients). Of these, 192 were recorded to be euphoric, 190 depressive-dysphoric. The pattern of other mental changes in combination with euphoria or depression is shown in Figure 17.

Table 5. Pattern of motor symptoms by limbs involved (3 series compared)

Limb involvement	Pool N = 812	Müller (1949) N = 582	Kurtzke (1970) N = 2019
None	214 (26%)	211 (36.1%)	37.7%
One upper	19 (2%)	7 (1.2%)	3.6%
One lower	102 (13%)	30 (5.2%)	7.8%
Two upper	1 (1%)	1 (0.2%)	0.9%
Two lower	207 (25%)	176 (30.2%)	22.8%
Two upper-lower	49 (6%)	21 (3.6%)	9.7%
Three	94 (12%)	64 (11.0%)	4.0%
Four	126 (16%)	73 (12.5%)	13.4%

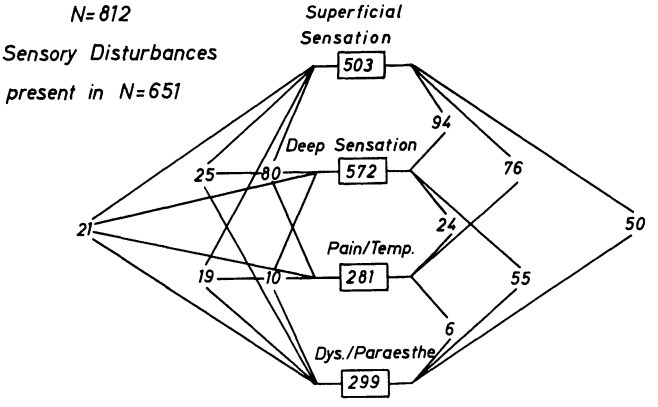

Fig. 15. Sensory signs and symptoms and their combinations in MS patients

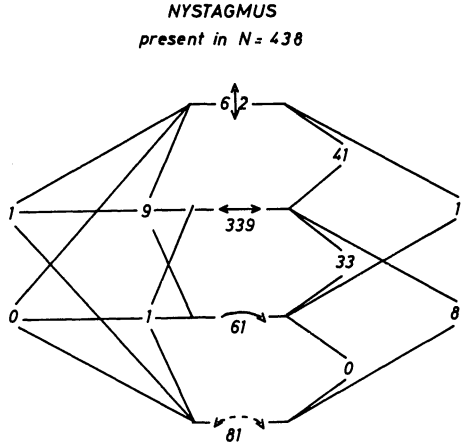

Fig. 16. Different forms of nystagmus and their combinations in MS patients. ↕ = vertical. ↔ = horizontal. ↷ = rotary. ⇜ = jellylike

Table 6. Involvement of cranial nerves and brainstem in MS (N = 812)

No. of nerve involved				
II	491 (60%)	Vision impaired		291 (36%)
		Amaurosis		23 (3%)
		Scotomas		56 (7%)
		Atrophy	temporal	311 (38%)
			total	92 (11%)
		Papillitis		40 (5%)
		Periphlebitis		8 (1%)
III	96 (12%)	Diplopia		74 (9%)
		Disturb. of pupillary reactions		28 (3%)
IV	17 (2%)			
V	101 (12%)	Hypaesthesia		29 (4%)
		Pain/paraesth.		41 (5%)
		Corneal reflex ↓		73 (9%)
		Jaw weakness		2 (< 1%)
VI	97 (12%)			
VII	90 (11%)	Peripheral palsy		23 (3%)
		Central palsy		67 (8%)
VIII	127 (16%)	Hearing loss		52 (6%)
		Vertigo		85 (10%)
Speech	222 (27%)	Scanning		159 (20%)
		Disarticulated		85 (10%)
		Aphasia		2 (1%)
				26 (3%)
Dysphagia	38 (5%)			
Disorder of respiration	2 (< 1%)			
Bulbar palsy	7 (1%)			
Triad of Charcot	89 (11%)			

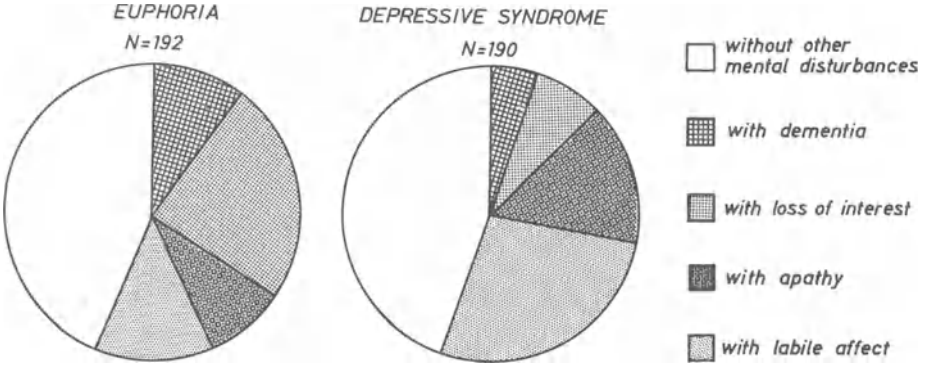

Fig. 17. Combination of euphoria and depressive syndrome with other mental disturbances in MS patients

The difference between left- and right-sided reflex-abnormalities and pareses found by Morsier (1971) could not be confirmed in our study (see Fig. 18). A difference between left- and right-sided symptoms was only registered in dysdiadochokinesis ($p = 0.0011$); the higher left-sided frequency could easily be due to the clumsiness of the left hand in right-handed people.

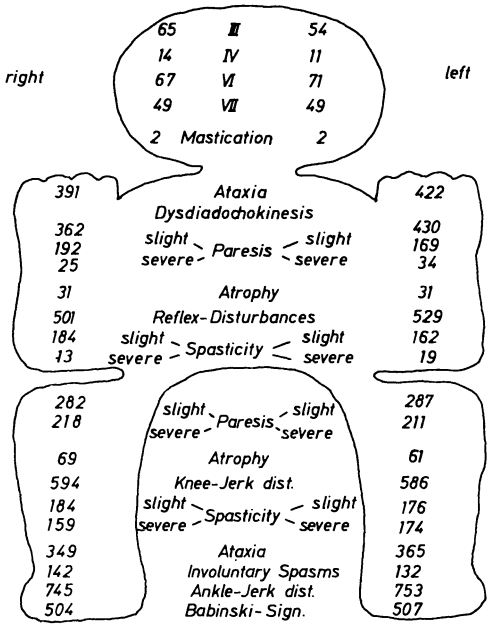

Fig. 18. Regional distribution of symptoms (N = 812)

3.6 Correlations

3.6.1 Correlation between Mental Changes and Other Disturbances

Psychopathologic phenomena are particularly difficult to record. Those related to MS in the literature vary widely, depending on the sample examined and on the method applied. The simplified classification scheme on our sheet does not allow a detailed analysis. Six categories of mental disturbances were defined according to Payk (1973). Correlation with other parameters (see Table 7) showed that patients with any kind of mental changes had a longer and more severe course of MS than patients without mental impairment. Patients with intellectual deterioration and disturbances of

Table 7. Mental disturbances in relation to other symptoms and to clinical characters in MS

	N	Severe paresis	Ataxia of limbs	Ataxic gait	Miction disorder	Completely helpless	Age at onset	Duration of disease	Course		
									Rem.	Rem. and progr.	Progr. from onset
No mental impairment	342	56 (16%)	240 (70%)	122 (36%)	120 (35%)	3 (1%)	30.7 ± 9.5	6.7 ± 7.7	205 (60%)	91 (27%)	46 (13%)
Euphoria	192	84 (44%)	179 (93%)	92 (48%)	111 (58%)	13 (7%)	30.8 ± 9.0	9.9 ± 7.3	46 (24%)	104 (54%)	42 (22%)
Depressive syndrom	183	73 (40%)	162 (89%)	86 (47%)	114 (62%)	15 (8%)	31.6 ± 9.5	9.7 ± 7.9	60 (33%)	84 (46%)	39 (21%)
Labile affect	110	40 (36%)	97 (88%)	58 (53%)	69 (63%)	8 (7%)	31.2 ± 9.9	9.4 ± 8.1	41 (37%)	52 (47%)	17 (15%)
Dementia	169	88 (52%)	156 (92%)	76 (45%)	117 (69%)	19 (11%)	31.6 ± 9.1	10.7 ± 8.0	35 (21%)	89 (53%)	45 (27%)
Disturb. of consciousness	6	3 (50%)	6 (100%)	5 (83%)	6 (100%)	1 (17%)	28.8 ± 11.7	11.8 ± 6.4	0	5 (83%)	1 (17%)
		$p < 0.0001$	$p < 0.0001$	$p = 0.0023$	$p < 0.0001$	$p < 0.0001$	not significant	$p < 0.01$	$p < 0.0001$		

consciousness were found to be those most seriously ill. According to some authors, euphoria is typical for the cerebellar form of the disease. Unlike Poeck (1973), we (Poser et al., 1974a) found from our data that the statement "The Person who shakes can laugh" is a clinical impression rather than a proven correlation.

3.6.2 Duration of Disease and Symptoms

The influence of the duration of the disease on different signs and symptoms is seen in Figures 19–21. With increasing duration of the disease, patients were more likely to develop spasticity, pareses, disturbances of micturition (with bladder infections as a sequel), and euphoria. The same was true for ataxia (not included in the figures). Regarding affective disorders, it can be assumed that euphoria becomes increasingly frequent as a result of a build-up of organic lesions. On the other hand, depression, as a reactive disorder, is relatively independent of the duration of the disease (see Fig. 21).

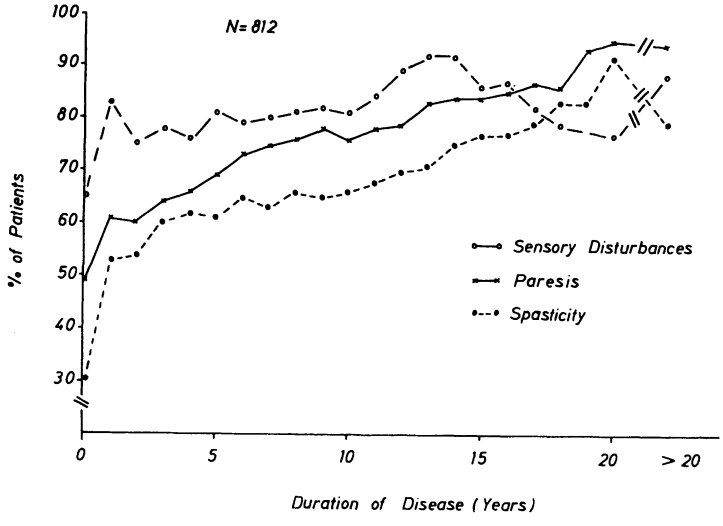

Fig. 19. Frequency of sensory disturbances, paresis, and spasticity in relation to the duration of MS (averages taken over 5-year periods)

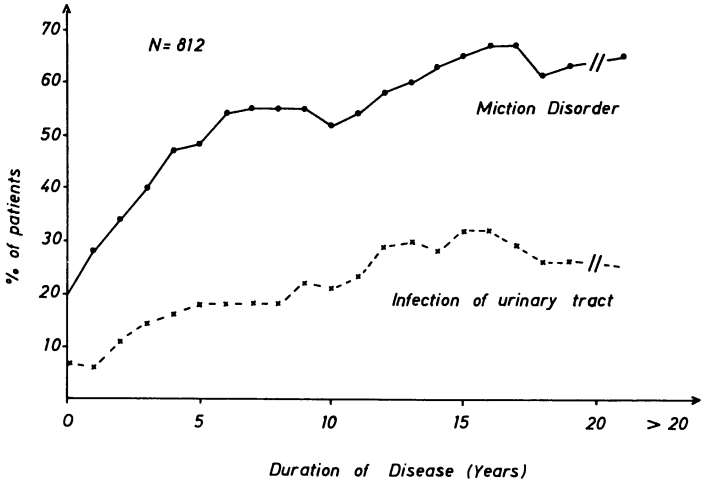

Fig. 20. Frequency of micturition disorders and of bladder infections in relation to the duration of MS (averages taken over 5-year periods)

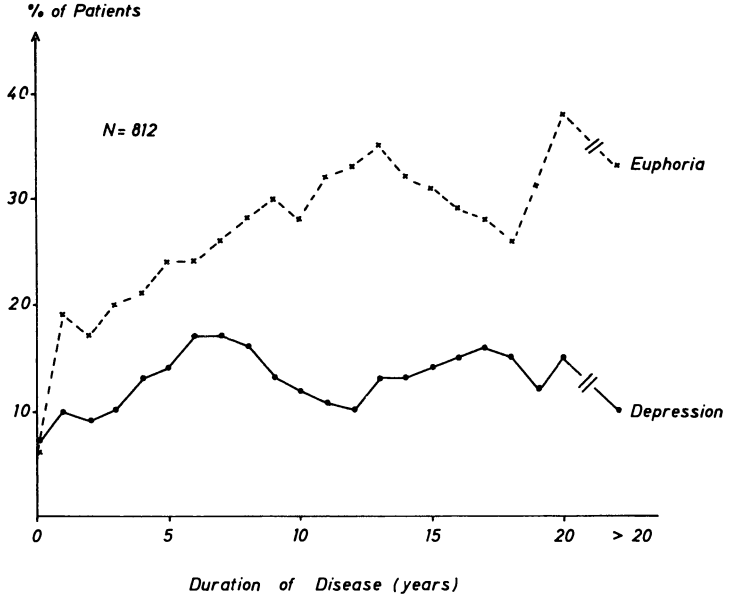

Fig. 21. Frequency of euphoria and depression in relation to the duration of MS (averages taken over 5-year periods)

3.6.3 Duration of Disease and Performance

Single signs and symptoms are only of limited value in predicting the overall performance of a patient. In our study the degree of disability was therefore assessed by the ability to work and to walk. As seen in Figure 22, the

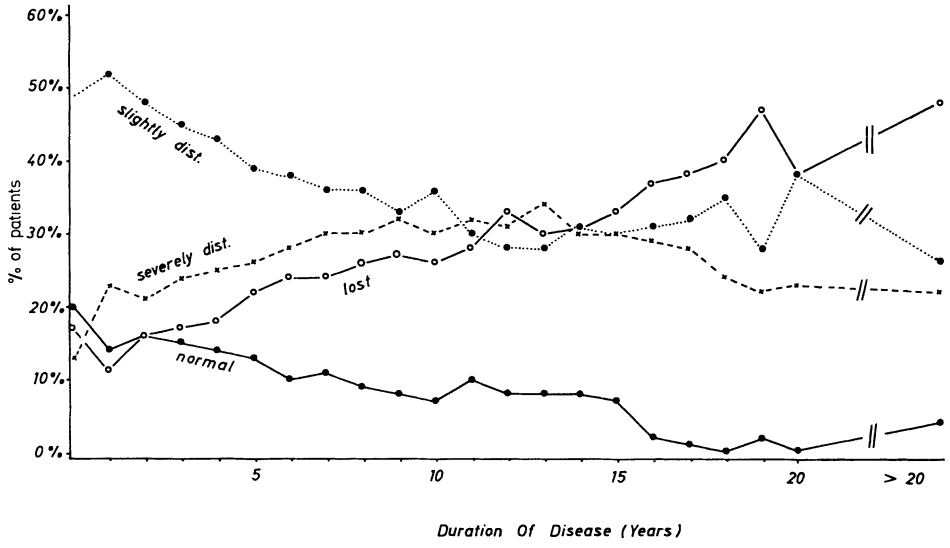

Fig. 22. Ability to work in relation to the duration of MS in 812 MS patients (averages taken over 5-year periods)

number of patients still able to work decreased with increasing duration of the disease, and the number of patients with severely disturbed working ability or complete loss thereof increased. However, after 20 years duration of MS, about 30% of the patients were still not seriously restricted in their ability to work. The ability to work is not only limited by physical handicaps (mainly spastic pareses, ataxia, and bladder disturbances; see Bauer et al., 1963); it also depends on the sex of the patient, on his profession, on the tolerance of his employer, on future prospects, and on the local employment situation.

The ability to walk, which is not influenced by these factors, tended similarly to decrease with increasing duration of the disease. The particular kind of ambulatory disturbance does not seem to be important. As shown in Table 8, patients with cerebellar ataxia, spinal ataxia, or gait disturbance due to spastic paresis are equally incapacitated.

Table 8. Different kinds of gait disturbances in correlation to the ability to work
n. s. = not significant

Gait disturbance due to	N	Ability to work normal	Ability to work slightly dist.	Ability to work severely dist.	Ability to work lost
Cerebellar ataxia	N = 227	6 (3%)	77 (34%)	84 (37%)	60 (26%)
Spinal ataxia	N = 181	6 (3%)	79 (44%)	54 (30%)	42 (23%)
Paresis/Spasticity	N = 404	13 (3%)	174 (43%)	131 (32%)	86 (21%)
Level of significance		n. s.	n. s.	n. s.	n. s.

The correlation between the ability to work and the ability to walk was analyzed by the coefficient of constriction, which assumed a value of 0.38, suggesting that 38% of the ability to work depends on the ability to walk. In the following sections each statement on prognosis is made on the basis of the ability to work and the ability to walk.

3.6.4 Age at Onset and Performance

Several authors have attempted to identify groups of patients with a particularly benign or malignant course. R. Müller (1949, 1951) and Leibowitz et al. (1964a, b, 1970, 1973) found that the age at onset of disease did influence the prognosis. The patients in our sample were grouped according to their age at onset to test this idea. Comparison of the groups showed differences in the frequency of occurrence of single signs and symptoms (spasticity, bulbar symptoms), but no important differences in the ability to work or to walk (see Table 9).

Since the duration of the disease was sometimes related to the age at onset, various grouping procedures were used in an attempt to eliminate the influence of disease duration. Patients with different ages at onset but similar duration of MS were compared (see Fig. 23). It was found that the ability to work und to walk did not depend on age at onset, except in 1 out of the 16 groups (original data; see Poser, 1974). After calculating the mean age at onset for patients with a particular sign or degree of disability, no significant deviation from the mean age at onset of the total sample (31.1 years) could be found (see Table 10).

Table 9. Comparison of clinical parameters in patients with different ages at onset

Age at onset	15–24	25–34	35–44	45–65	Level of sign.
N	218	316	186	84	
Mean duration of disease (in years)	10.3 ± 9.1	9.3 ± 8.0	7.5 ± 6.6	4.7 ± 4.4	$p < 0.001$*
Sex: Females	152 (70%)	183 (58%)	118 (63%)	61 (73%)	$p = 0.0118$**
Sex: Males	66 (30%)	133 (42%)	68 (37%)	23 (27%)	
Course: Remitting	123 (56%)	130 (41%)	65 (35%)	22 (26%)	$p < 0.0001$**
Course: Rem. + progr.	79 (36%)	138 (44%)	73 (39%)	31 (37%)	
Course: Progr. from onset	16 (7%)	48 (15%)	48 (26%)	31 (37%)	
Diagnosis: Definite	159 (73%)	202 (64%)	109 (59%)	33 (39%)	$p < 0.0001$**
Diagnosis: Probable	49 (22%)	87 (28%)	66 (35%)	36 (43%)	
Diagnosis: Possible	8 (4%)	24 (8%)	10 (5%)	14 (17%)	
Paresis of limbs	159 (73%)	222 (70%)	146 (78%)	65 (77%)	$p = 0.1816$
Spasticity	121 (56%)	210 (66%)	130 (70%)	55 (65%)	$p = 0.0153$
Sensory disturbances	177 (81%)	254 (80%)	151 (81%)	70 (83%)	$p = 0.9437$
Coordination dist.	201 (92%)	282 (89%)	176 (95%)	79 (94%)	$p = 0.1431$
Micturition dist.	107 (49%)	152 (48%)	99 (53%)	36 (43%)	$p = 0.5566$
Visual impairment	150 (69%)	199 (63%)	93 (50%)	42 (50%)	$p = 0.0004$
Diplopia	77 (35%)	124 (39%)	74 (40%)	34 (40%)	$p = 0.7403$
Other cranial nerve dist.	43 (20%)	71 (22%)	44 (24%)	10 (12%)	$p = 0.1031$
Bulbar symptoms	132 (61%)	198 (63%)	121 (65%)	38 (45%)	$p = 0.0169$
Euphoria	50 (23%)	81 (26%)	42 (23%)	17 (20%)	$p = 0.7082$
Depress. syndrome	63 (29%)	91 (29%)	64 (34%)	24 (29%)	$p = 0.5566$
Ability to work: Normal	27 (12%)	36 (11%)	16 (9%)	6 (7%)	$p = 0.5549$**
Slightly dist.	80 (37%)	124 (39%)	64 (34%)	37 (44%)	
Severely dist.	62 (28%)	73 (23%)	51 (27%)	21 (25%)	
Lost	49 (22%)	83 (26%)	54 (29%)	20 (24%)	
Ability to walk: Normal	48 (22%)	60 (19%)	25 (13%)	10 (12%)	$p = 0.1483$**
Slightly dist.	67 (31%)	115 (36%)	68 (37%)	35 (42%)	
Severely dist. or lost	103 (47%)	141 (45%)	93 (50%)	39 (46%)	

* H-test according to *Kruskal* and *Wallis*.
** k × m-field-2I-test.

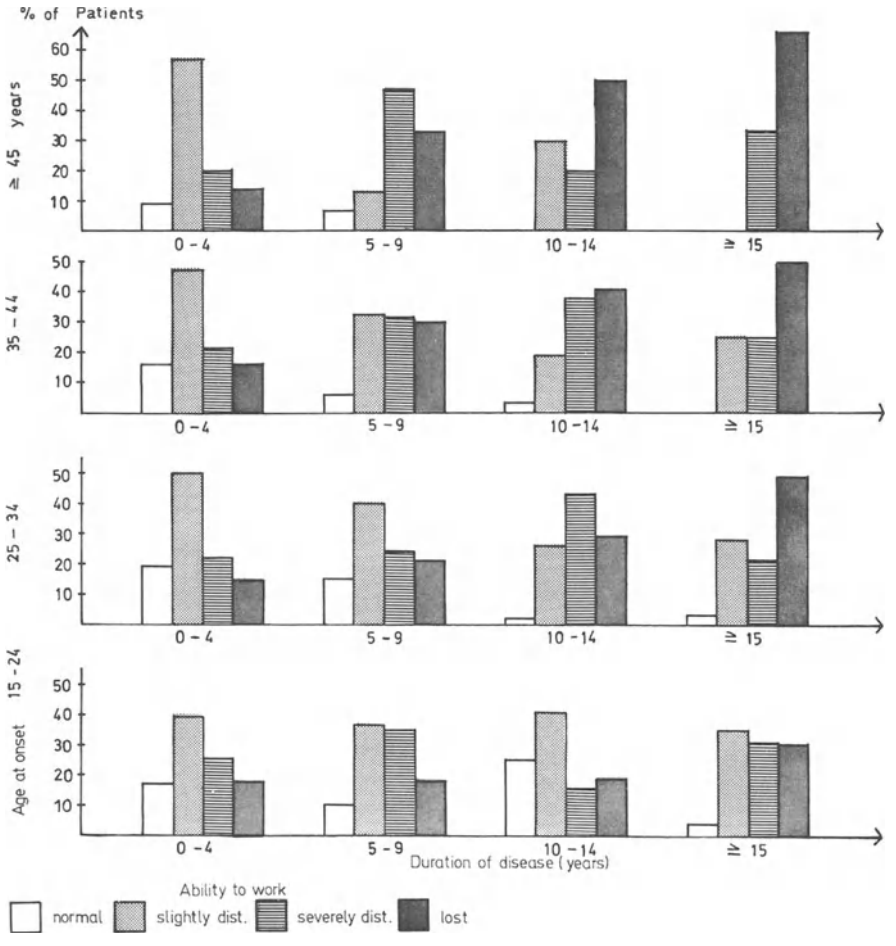

Fig. 23. Ability to work in patients of different age at onset and with similar duration of MS

Table 10. Mean age at onset of patients with a given symptomatology

Disturbance	N	Mean age at onset in years
Spasticity/paresis	669	30.6 ± 11.4
Severe paresis	251	31.3 ± 9.4
Ataxia of limbs	660	30.5 ± 10.5
Ataxic gait	343	30.6 ± 9.1
Sensory dist.	651	31.2 ± 9.5
Micturition dist.	399	31.1 ± 9.4
Impairment of vision	491	29.3 ± 9.8
Diplopia	168	30.8 ± 8.5
Ability to walk: Slightly dist.	288	31.8 ± 9.1
Severely dist.	184	32.2 ± 10.2
Lost	196	30.8 ± 9.3
Ability to work: Slightly dist.	309	31.1 ± 9.6
Severely dist.	207	31.3 ± 9.7
Lost	210	31.8 ± 9.4

3.6.5 Disease Course and Performance

The patients were divided into three groups according to the course of the disease: (1) Patients with bouts and full remissions, (2) Patients with transition into a chronic-progressive stage after a phase of bouts and remissions, and (3) Patients with a chronic-progressive course from the beginning. The frequency of certain parameters was found to be different in the three groups (see Table 11). The lower incidence of disturbances in group 1 (remitting course) could perhaps be the result of a shorter duration of the disease or a lower age at onset. Grouping patients according to the duration of their disease revealed significant differences again among the three groups (see Fig. 24).

Table 11. Comparison of clinical parameters in patients with different course of MS

Course	Remitting N = 345	Rem. and progr. N = 324	Progr. from onset N = 143	Level of significance
Mean age at onset (in years)	28.6 ± 8.9	31.2 ± 8.8	36.8 ± 9.8	$p < 0.001$
Mean duration of disease (in years)	6.1 ± 7.2	11.7 ± 8.0	8.0 ± 6.8	$p < 0.001$
Sex: Females	212 (61%)	207 (64%)	101 (71%)	$p = 0.1493$
Sex: Males	133 (39%)	117 (36%)	42 (29%)	
Diagnosis: Definite	190 (55%)	248 (77%)	72 (50%)	$p < 0.0001$
Diagnosis: Probable	121 (35%)	64 (20%)	54 (38%)	
Diagnosis: Possible	30 (9%)	10 (3%)	16 (11%)	
Paresis	182 (53%)	290 (90%)	126 (88%)	$p < 0.0001$
Spasticity	147 (43%)	263 (81%)	112 (78%)	$p < 0.0001$
Sensory dist.	266 (77%)	269 (83%)	116 (81%)	n. s.
Ataxia of limbs	245 (71%)	291 (90%)	124 (87%)	$p < 0.0001$
Ataxic gait	128 (37%)	161 (50%)	37 (26%)	$p < 0.0001$
Micturition dist.	103 (30%)	219 (68%)	77 (54%)	$p < 0.0001$
Impairment of vision	184 (53%)	225 (69%)	82 (57%)	$p = 0.0002$
Other cranial nerve dist.	117 (34%)	135 (42%)	59 (41%)	n. s.
Bulbar symptoms	179 (52%)	229 (71%)	88 (62%)	$p < 0.0001$
Mental dist.	140 (41%)	233 (72%)	97 (68%)	$p < 0.0001$
Ability to walk: normal	138 (40%)	3 (1%)	3 (2%)	$p < 0.0001$
Slightly dist.	132 (38%)	104 (32%)	52 (36%)	
Severely dist.	42 (12%)	100 (31%)	42 (29%)	
Lost	33 (10%)	117 (36%)	46 (32%)	
Ability to work: normal	78 (23%)	5 (2%)	2 (1%)	$p < 0.0001$
Slightly dist.	172 (50%)	90 (28%)	47 (33%)	
Severely dist.	53 (15%)	108 (33%)	46 (32%)	
Lost	42 (12%)	120 (37%)	48 (34%)	

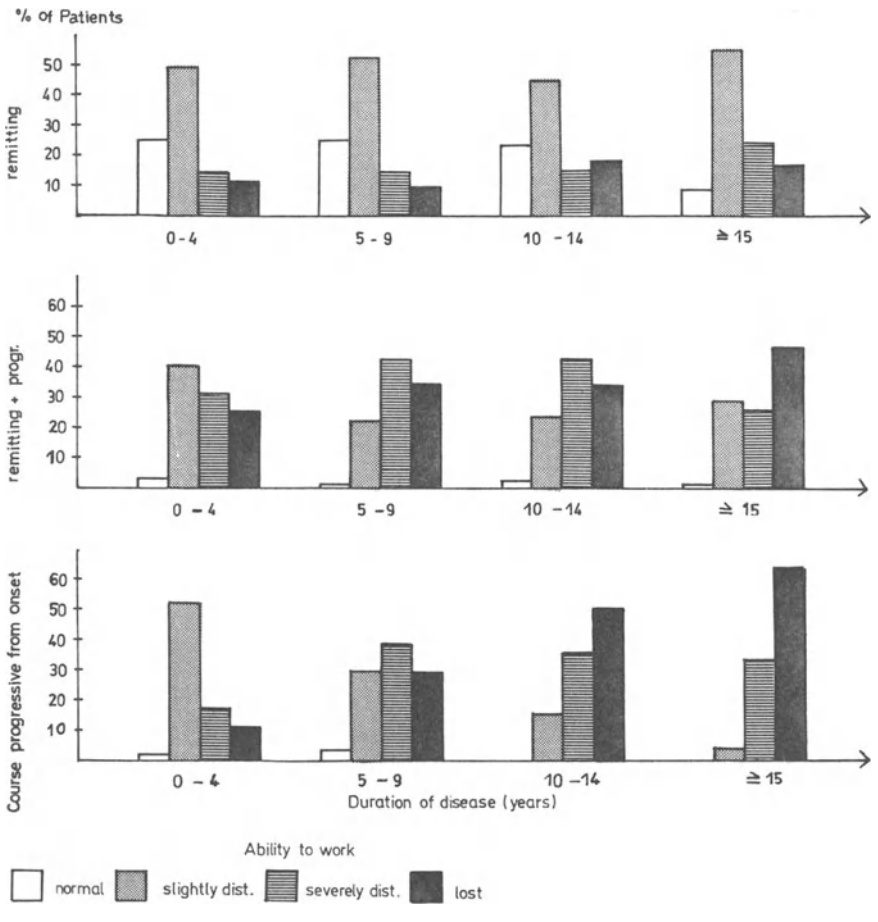

Fig. 24. Ability to work in patients with different course but with similar duration of MS

To test for the possible influence of age at onset, each of the three groups of patients was divided into eight subgroups (onset before or after the age of 30 and duration of disease up to 4, 9, 14 or more years). A significant difference in favor of patients with lower age at onset was found in one group only (see Table 12; group 1, duration of disease 10–14 years). The difference found in another group (group 2: duration of disease 0–4 years), however, was in favor of patients with higher age at onset. No clear differences were found in the remaining ten groups when patients with the same course and duration but with different age at onset were compared. Patients of similar age at onset and with similar duration, but with different course of disease, differed significantly in their performance (for levels of significance, see Poser, 1974).

Table 12. Comparison of ability to work and walk in patients with different course of MS (grouping according to age at onset and duration of disease; for level of significance, see Poser, 1974)

N = 802 Course / Age at onset	N	Remitting		Rem. and progr.		Progr. from onset	
		< 30	> 30	< 30	> 30	< 30	> 30
Duration of disease 0–4 years	315	94	92	23	44	10	52
Ability to work:							
Normal		25 (27%)	22 (24%)	0	2 (5%)	0	1 (2%)
Slightly dist.		48 (51%)	43 (47%)	1 (4%)	26 (59%)	6 (60%)	27 (52%)
Severely dist.		11 (12%)	16 (17%)	14 (61%)	7 (16%)	2 (20%)	15 (29%)
Lost		10 (11%)	11 (12%)	8 (35%)	9 (20%)	2 (20%)	9 (17%)
Ability to walk:							
Normal		47 (50%)	40 (43%)	1 (4%)	2 (5%)	0	1 (2%)
Slightly dist.		30 (32%)	33 (36%)	4 (17%)	27 (61%)	6 (60%)	27 (52%)
Severely dist.		11 (12%)	12 (13%)	10 (43%)	8 (18%)	2 (20%)	15 (29%)
Lost		6 (6%)	7 (8%)	8 (35%)	7 (16%)	2 (20%)	9 (17%)
Duration of disease 5–9 years	196	55	22	38	47	8	26
Ability to work:							
Normal		14 (25%)	5 (23%)	0	1 (2%)	0	1 (4%)
Slightly dist.		30 (55%)	10 (45%)	5 (13%)	14 (30%)	4 (50%)	6 (23%)
Severely dist.		7 (13%)	4 (18%)	22 (58%)	14 (30%)	2 (25%)	11 (42%)
Lost		4 (7%)	3 (14%)	11 (29%)	18 (38%)	2 (25%)	8 (31%)
Ability to walk:							
Normal		24 (44%)	7 (32%)	0	0	0	1 (4%)
Slightly dist.		20 (36%)	9 (41%)	7 (18%)	18 (38%)	4 (50%)	7 (27%)
Severely dist.		6 (11%)	2 (9%)	16 (42%)	13 (28%)	2 (25%)	9 (35%)
Lost		5 (9%)	4 (18%)	15 (39%)	16 (34%)	2 (25%)	9 (35%)
Duration of disease 10–14 years	116	25	14	21	36	4	16
Ability to work:							
Normal		8 (32%)	1 (7%)	1 (5%)	0	0	0
Slightly dist.		12 (48%)	5 (36%)	6 (29%)	7 (19%)	0	3 (19%)
Severely dist.		3 (12%)	3 (21%)	8 (38%)	16 (44%)	2 (50%)	5 (31%)
Lost		2 (8%)	5 (36%)	6 (29%)	13 (36%)	2 (50%)	8 (50%)
Ability to walk:							
Normal		12 (48%)	2 (14%)	0	0	0	0
Slightly dist.		11 (44%)	6 (43%)	6 (29%)	12 (33%)	0	5 (31%)
Severely dist.		0	5 (36%)	7 (33%)	11 (31%)	2 (50%)	6 (38%)
Lost		2 (8%)	1 (7%)	8 (38%)	13 (36%)	2 (50%)	5 (31%)

Table 12 (continued)

N = 802 Course / Age at onset	N	Remitting		Rem. and progr.		Progr. from onset	
		< 30	> 30	< 30	> 30	< 30	> 30
Duration of disease ⩾ 15 years	175	30	7	68	43	12	15
Ability to work:							
Normal		3 (10%)	0	0	1 (2%)	0	0
Slightly dist.		14 (47%)	6 (86%)	23 (34%)	8 (19%)	0	1 (7%)
Severely dist.		8 (27%)	0	20 (29%)	8 (19%)	4 (33%)	5 (33%)
Lost		5 (17%)	1 (14%)	25 (37%)	26 (60%)	8 (67%)	9 (60%)
Ability to walk:							
Normal		3 (10%)	2 (29%)	0	0	0	1 (7%)
Slightly dist.		15 (50%)	5 (71%)	21 (31%)	8 (19%)	1 (8%)	2 (13%)
Severely dist.		6 (20%)	0	19 (28%)	15 (35%	4 (33%)	2 (13%)
Lost		6 (20%)	0	28 (41%)	20 (47%)	7 (58%)	10 (67%)

The influence of duration of the disease was eliminated by the grouping procedure. Consequently, differences in the ability to work and to walk seen in patients with different disease courses could not be explained by different duration or by different age at onset of MS.

Grouping patients according to the course and duration of the disease in 1 year steps (see Fig. 25) confirmed the above findings that the disease course has an important influence on prognosis. Most patients with bouts and remissions were not severely disabled, even after a long disease duration; whereas patients with a transition into a chronic-progressive course developed considerable disability during the first 5 years, and not much change was seen afterward. Patients with a chronic-progressive course from the beginning showed steadily progressing disability throughout the years.

3.6.6 Analysis of Bouts

In patients with transition into a progressive course, a mean of 2.9 ± 2.5 bouts occured, in comparison to 2.6 ± 2.1 bouts in patients without progression. The timing of individual bouts was not entered on the sheet, so it was impossible to conclude from this analysis how many bouts occur on an average, before patients enter the progressive stage. Similarly, the influence of bouts on prognosis could not be evaluated, because the relation of bouts to loss of performance was not registered on the sheet.

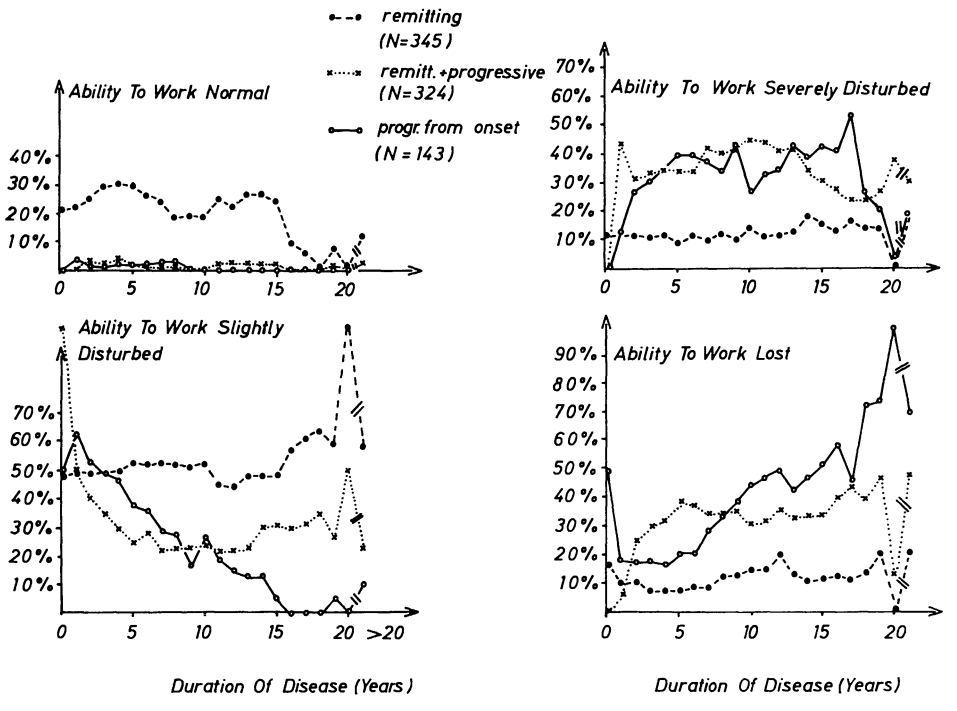

Fig. 25. The relation of the ability to work and the course of MS to the duration of MS (averages taken over 5-year periods, N = 812)

3.7 Diagnostic Classification

The clinical diagnosis was classified as "definite" in 510 patients, as "probable" in 239, and as "possible" in 56 cases (it was unknown in 7 cases). The different frequency of some parameters in the three diagnostic groups (definite, probable, possible) found earlier in a smaller sample (Poser et al., 1973a) was confirmed in this study. It is difficult to decide whether possible cases should be included in statistics on MS or not. Leibowitz et al. (1973) suggested that exclusion of the possible cases would lead to a biased sample, whereas Kurtzke et al. (1969) have the opposite view. Since we particularly wanted to reexamine the statement of Leibowitz et al. (who did include possible cases), that the age at onset has an important influence on prognosis, the possible cases were included in our study, too.

3.8 Laboratory Results

3.8.1 CSF Findings

A lumbar puncture was performed on 435 out of 812 patients during the present investigation. Abnormalities were found in 367 patients (84%). The frequency of occurrence of pathologic CSF findings is given for the whole sample as well as for the three groups showing different courses in Figure 26. More CSF examinations were made and the frequency of pleocytosis was higher in patients with bouts and remissions. The value of this finding is limited for two reasons: Firstly, a lumbar puncture was not done in all patients; secondly, the present documentation sheet only allowed for a rather crude classification.

It would be possible to record quantitative CSF findings on a special optical mark reader sheet like that of Hauptvogel and Poser (1974), so that direct correlation with clinical symptomatology could be made. In the con-

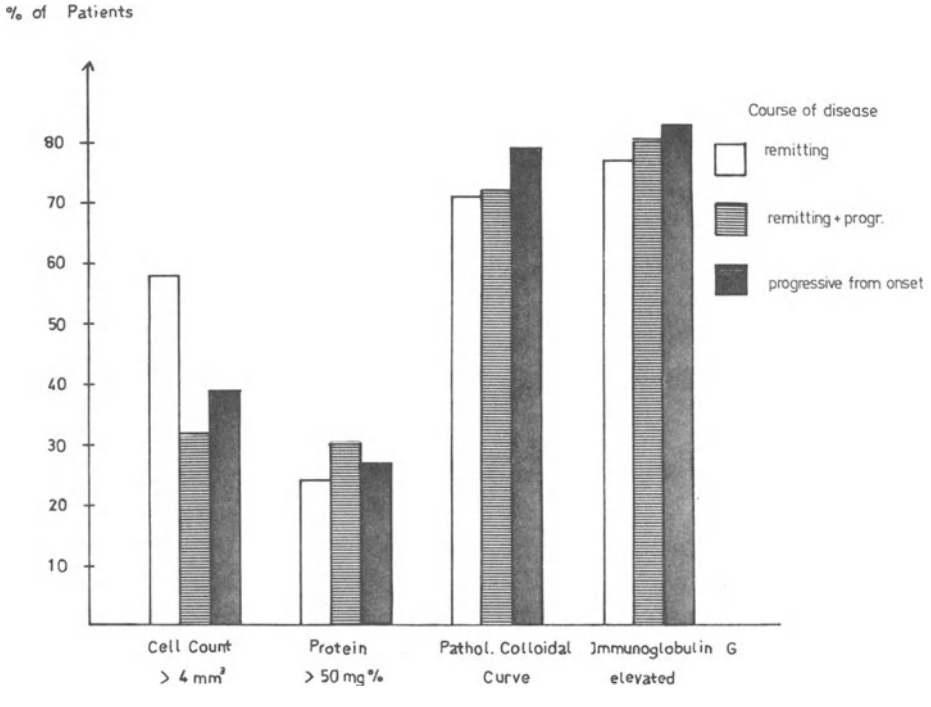

Fig. 26. CSF findings in patients with different course of MS

text of these CSF findings, the current documentation sheet was only used to select patients for reexamination; for example, in 1973 a search was made for patients with signs of acute disease in their CSF during the preceding year, and 217 patients were found.

3.8.2 Serologic Studies

In 1972 an infectious agent related to group-1 parainfluenza virus was isolated from the cultured brain cells of two MS cases (ter Meulen et al.). A study of specific immune reactions of other patients was planned in an attempt to relate this virus to MS. Serologic studies in two groups of patients were started: first, patients in this survey who had signs of acute disease in the CSF during the preceding year (see Sect. 3.8.1); secondly, patients from the epidemiologic area of Lower Saxony. The patients of this second group were examined, the findings recorded on the new documentation sheets, and a blood sample was taken. They were interviewed about social factors and previous infections. A control group consisted of normal siblings or close friends not more than three years older or younger than the patients. So far, 226 patients and 21 controls have been screened in the same way.

3.9 Different Samples

3.9.1 The Epidemiologic Study

A manual analysis was made of clinical data from the patients in Lower Saxony. These data comprised age at onset, duration of disease, sex, course of disease, diagnostic classification, ability to walk, and a disability scale. We could not include any more parameters, because no computer program for the new documentation sheets was then available.

A comparison with the data of the 812 patients was made. Patients from the epidemiologic area had a longer disease duration (see Table 13) but were less restricted in their ability to walk. The interpretation of this difference can only be tentative; one would expect there to be more patients with a benign course in the epidemiologic study. Some of these patients had not seen a doctor for many years and came only on request for an examination. These patients might account for the higher proportion of "possible" cases in the epidemiologic sample (see Table 13).

A test like that in Section 3.6.4 was made to see whether or not the age at onset, duration, and course of disease had an influence on the progno-

Table 13. Comparison of patients from the documentation pool and from the epidemiologic area in respect to clinical parameters. n. s. = not significant

	Pool N = 812	Epidemiol. study N = 226	Level of significance
Mean age at onset (years)	31.1 ± 9.5	31.8 ± 9.4	n. s., no dif. in distrib.
Mean duration of dis. (years)	8.7 ± 7.9	13.0 ± 9.4	$p < 0.0001$
Sex: Males	292 (36%)	80 (35%)	n. s.
Sex: Females	520 (64%)	146 (65%)	
Course: Remitting	345 (42%)	97 (43%)	n. s.
Course: Rem. and progr.	324 (40%)	99 (44%)	
Course: Progr. from onset	143 (18%)	30 (13%)	
Diagnosis: Definite	510 (63%)	145 (64%)	$p = 0.0086$
Diagnosis: Probable	239 (29%)	50 (22%)	
Diagnosis: Possible	56 (7%)	28 (12%)	
Ability to walk: Normal	144 (18%)	56 (25%)	$p = 0.0306$
Ability to walk: Slightly dist.	288 (35%)	60 (27%)	
Ability to walk: Severely dist.	184 (23%)	54 (24%)	
Ability to walk: Lost	196 (24%)	56 (25%)	

sis. The ability to walk and the disability scale (Kurtzke, 1961) were used as measures of performance. Similar results were obtained from the presumably selection-free sample of patients from Lower Saxony as well as from the patients in the present study (for the original data, see Poser, 1974). These results can be summarized as follows:

1. The degree of disability depends on the course of MS.
2. With longer duration of the disease, patients with a remitting course are less disabled than patients with the progressive form.
3. The age at onset in itself has no influence on the prognosis.

3.9.2 Subgroups

The locations of hospitals participating in the program can be seen in Figure 27. They were grouped according to available facilities: firstly, university hospitals (1, 4, 5, 6, 10, 12, 13, 15); secondly, neurology departments of general hospitals (8, 9, 11, 14, 16, 17); and thirdly, special hospitals for MS patients (2, 3, 7). Selected items from these three groups are shown in Table 14. The majority of patients in special hospitals had a chronic-progressive course; 74% of them were unable to work or were severely handi-

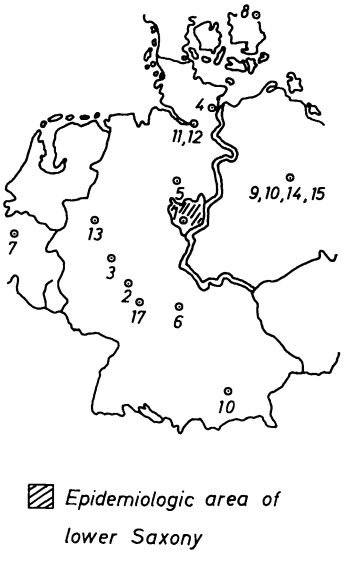

Fig. 27. Geographic distribution of hospitals participating in the documentation program

Table 14. Clinical parameters compared for patients from different institutions (N = 831)

		University hospitals N = 421	Neurol. depart. of gen. hosp. N = 221	Special instit. for MS patients N = 189
Sex	Females	271 (64%)	137 (62%)	122 (65%)
	Males	150 (36%)	84 (38%)	67 (35%)
Mean duration of disease (in years)		7.1 ± 6.8	11.0 ± 10.0	11.2 ± 6.9
Course	Remitting	214 (51%)	100 (45%)	25 (13%)
	Rem. and progr.	146 (35%)	80 (36%)	116 (61%)
	Progr. from onset	61 (14%)	41 (19%)	48 (25%)
Diagnosis	Definite	258 (61%)	142 (64%)	150 (79%)
	Probable	132 (31%)	68 (31%)	33 (17%)
	Possible	31 (7%)	11 (5%)	6 (3%)
Ability to work	Normal	67 (16%)	20 (9%)	0
	Slightly dist.	190 (45%)	65 (29%)	49 (26%)
	Severely dist.	94 (22%)	44 (20%)	75 (40%)
	Lost	70 (17%)	92 (42%)	65 (34%)
Ability to walk	Normal	102 (24%)	33 (15%)	3 (2%)
	Slightly dist.	171 (41%)	61 (28%)	58 (31%)
	Severely dist.	96 (23%)	59 (27%)	57 (30%)
	Lost	52 (12%)	68 (31%)	71 (38%)
Completely helpless		7 (2%)	23 (10%)	12 (6%)

capped. In the neurology departments 62% of the patients were unable to work or were severely handicapped; the greatest proportion of completely helpless patients were seen in these departments.

Patients in university hospitals were usually less disabled than patients from the other institutions. Cases with remitting course without progression and possible cases were more often admitted to university hospitals. But a few patients with chronic progression and clinically definite diagnosis were also hospitalized there. This latter group could probably be better treated in special hospitals. There has long been a need for aftercare facilities (Bauer et al., 1965), particularly for MS patients (Heier, 1973).

4. Discussion

4.1 Clinical Questions

4.1.1 Prognosis

For neurologists concerned with MS in clinical practice, the question of prognosis inevitably arises. The physician's attitude toward the disease can have a strong influence on the patient indirectly, if not directly. Individual personal experience concerning prognosis is often limited. Opinions are often contradictory in the literature. The data gathered with our documentation system have made it possible to reexamine this problem. The present status and the previous course of the disease were analyzed in a large number of cases; individual follow-up examinations were not included.

Prospective studies naturally give the most reliable statements on prognosis, since all patients are studied from the very beginning of their disease. However, this method presents particular problems in analyzing MS. Many patients do not see a doctor when the first slight and transient symptoms appear. In addition, misdiagnoses often occur in the beginning (Sällström, 1942; Kolb, 1950; v. Büren et al., 1972; Käppeli et al., 1972). These early stages are not only important for diagnostic reasons; McAlpine (1964) was able to show that patients who were hospitalized during the early phase actually had a more benign course of the disease later. He wrote: "The period of rest in the early active stage of the disease, the advice given as to future mode of living, and the stress laid on rest in bed during a relapse may have played a part in modifying the course of the disease".

Early drug treatment might also influence the subsequent course of the disease. In particular, an immunosuppressive therapy can reduce the frequency of bouts, although it has no influence on preexisting progression (Frick et al., 1971; Grüninger et al., 1973).

The prospective method has not yet been used in a large representative sample of MS patients. Kurtzke et al. (1968, 1969) followed up 527 US Veterans, including 234 early-onset cases, but it is doubtful whether his sample is representative. First, only young males were recorded; and secondly, the data were not obtained in a standardized form, but reconstructed from traditional records. It will be several years before the results of the detailed prospective study on 93 patients by Broman et al. (1972) are available. Thygesen (1949) and McAlpine (1961, 1964) reported on early cases; however, a systematic follow-up was not made. Because large scale prospective studies are so difficult to carry out in MS, other methods have been used to gather information on disease course and prognosis.

Several authors followed up a sample of patients over many years. In most cases the numbers were small, and the patients did not participate in the study from the disease onset (McIntyre et al., 1943; Millar, 1949; Allison,

1950; Panelius, 1969; Fog et al., 1970). Alexander et al. (1958) used a quantitative scoring system with standardized definitions to register the course of 554 patients. This study was designed from a therapeutic point of view; therefore the average time of observation (3 years) was too short to give a long-term prognosis. A variety of retrospective studies have appeared in the literature. The results concerning factors which influence prognosis often differ. This could perhaps be expected, because the selection of patients, the methods of registration, and the criteria applied in diagnosis and prognosis vary widely.

A survey of the most important studies is given in Table 15. Number and selection of patients, method of recording, criteria applied for prognosis, and the results obtained are included. In addition, statistical analyses are mentioned, for they seem to be important. For example, Thygesen (1949) suggested that the course of MS is more favorable in patients with late disease onset. However, statistical analysis of his data shows no significant difference in ability to work among patients of different age at onset (2-I-test applied to the data of his Table 6).

There was possibly no respresentative sample in our study. Not all inpatients from the participating hospitals could be included (see Sect. 3.5), and outpatients were recorded in only 2 of the 17 institutions. The registration of all patients in a certain area should result in a relatively unbiased sample, because no internal selection is made, but such registration requires organization and effort. Firnhaber (1969) received help in registration from all family doctors, internists, ophthalmologists and neurologists in a defined area. He then examined all the MS patients personally.

Preliminary results from 226 patients (those from Firnhaber's study, together with those from new patients) in the epidemiologic area were given in Section 3.9.1 and compared with the corresponding data in our main study of 812 patients in Table 13. No deviations were found regarding sex ratio, age at onset, and desease course. The differences in disease duration, in diagnostic classification, and in the ability to walk seem to indicate that the percentage of patients with a benign course is higher in the epidemiologic group (see Sect. 3.9.1). The prognosis is apparently better in the epidemiologic group than in our group of patients, which is the type of group normally studied.

4.1.1.1 Age at Onset and Prognosis

R. Müller made a detailed study in 1949 and found that patients with lower age at onset of their disease have a better prognosis. He also found that patients with progressive bouts do worse than patients with remittent bouts. He did not attempt to correlate age at onset with disease course. However, Leibowitz et al. (1964a, b, 1973), who confirmed the findings of Müller,

Table 15. Survey of the literature on the prognosis of MS

Author	Place	Year	Sample	N	♀	♂	Method of Investigation
Brain	London	1936	3 different samples	171	?	?	Retrosp. data coll.
Henner et al.	Prague	1939	Outpat. and inpat.	178	95	83	Retrosp. data coll.
McIntyre et al.	Cincinnati/ USA	1943	?	55	34	21	Follow-up study
Millar	Belfast	1949	Outpat. and inpat.	91	41	50	Retrosp. and reexam.
R. Müller	Stockholm	1949	Outp. and inp. from dif. instit.	810	453	357	Retrosp. and reexam.
Thygesen	Copenhagen	1949	Inpat. only	110	59%	41%	Retrosp. and prosp. data coll.
Carter et al.	New York	1950	Dead inpat.	46	22	24	Retrosp. data coll. from autopsy cases
Kolb	Baltimore	1950	Inpat. only	176	45%	51%	Retrosp. and reex. of a group
Lazarte	Rochester	1950	Pat. from the Mayo Clinic	342	173	169	Retrosp. data coll.
Allison	Belfast	1950	Pat. from epid. area	40	25	15	Follow-up study
McLean et al.	Rochester	1951	Pat. from the Mayo Clin. (remit. course)	418	226	192	Retrosp. data coll.
McAlpine et al.	London	1952	Mainly inpat.	840	65%	35%	Retrosp. and follow-up
Abb et al.	Würzburg	1956	Inpat.	1725	51%	49%	Retrosp. and reexamin.
Alexander et al.	Boston	1958	?	554	352	202	Follow-up study
Hyllested	Denmark	1961	Pat. dead from MS	854	452	402	Retrosp. data coll.
H. R. Müller	Switzerland	1961 1966	Pat. dead from MS	111	73	38	Retrosp. data coll.
Bauer et al.	Hamburg	1963 1965	War-veterans and inpat.	797	14%	86%	Retrosp. and reexam.
Stazio et al.	Winnipeg	1964	Pat. from epid. area	128	88	40	Retrosp. and reexam.
Leibowitz et al.	Israel	1964 1973	All pat. from Israel	266	141	125	Retrosp. and reexam.
Poeck et al.	Freiburg	1964	Inpat.	220	130	65	Retrosp. and reex. of 17 pat.
Kurtzke et al.	Washington	1968 1969	US-veterans	527	–	527	Follow-up from med. records
Panelius	Finland	1969	Pat. from epid. area	146	90	56	Retrosp. and reexam.
Fog et al.	Copenhagen	1970	Outpat. and inpat.	73	39	34	Follow-up study
Riser et al.	Toulouse	1971	Inpat.	203	108	95	Retrosp. and follow-up
Gudmundsson	Iceland	1971	All pat. from Iceland	104	63	41	Retrosp. and reexam.
Dassel	Netherlands	1973	Pat. dead from MS 1950–58	3788	2121	1667	Mortality statistics
Lhermitte	Paris	1973	Inpat.	245	69%	31%	Follow-up study
Poser	Germany	1974	Inpat. and outpat.	812	520	292	Retrosp. and reexam.

Criterion applied	Stat. anal.	Sex Infl.?	Quality	Age at onset Infl.?	Quality	Infl. of symptoms At onset	Later	Course Infl.?	Quality
Duration of dis., disability	No	?		Yes	Old better	Yes	Yes	Yes	?
Ability to walk	No	Yes	♀ Worse	Yes	Old better	Yes	?	?	
Dur. of dis., symptomatol.	No	?		?		?		Yes	Rapid progr. unfavorable
Dur. of dis.	No	No		Yes	Young better	Yes		Yes	Monosymptomatic better
Mortality, incapacity	Yes	Yes	♂ Worse	Yes	Young better	Yes		Yes	Progr. bouts unfavorable
Disability, working capacity	No	?		Yes	Old better	Yes		Yes	Progr. from onset unfavorable
Dur. of dis.	No	?		Yes	Old better	Yes		Yes	According to clin. symptomatol.
Working cap.	No	?		No		Yes		?	
Dur. of dis. incap.	No	Yes	♀ Worse	Yes	Old better	Yes		Yes	Chron. progr. + acute forms unfav.
Dur. of dis., disability	No	?		?		Yes	Yes	Yes	Oligosymptomatic better
Incap. (ability to walk or to work)	No	?		?		?		Yes	As long as ambulatory fav.
Dur. of dis., disability	Yes	No		No		Yes	Yes	Yes	Chron. progr. unfav.
Dur. of dis., work. ability	No	?		?		?	Yes	Yes	Oligosympt. better, cerebell. worse
Neurologic deficit score	No	No		No		?		Yes	Progr. worse
Dur. of dis., mortality	No	Yes	♂ Worse	No		?	?	Yes	?
Dur. of dis., work. ability	Yes	Yes	♂ Worse	Yes	Yg. bet. for ♀	?	?	?	
Working ability	No	?		?		?		Yes	Remitting better
Disability	No	No		Yes	Young better	?	?	?	
Disability	Yes	Yes	♀ Worse	Yes	Young better	Yes	No	Yes	Progr. worse
Dur. of dis.	No	No		No		Yes	?	Yes	Progr. from onset unfavorable
Dur. of dis., disability	No	?		No		Yes	Yes	Yes	?
Dur. of dis., disability	Yes	Yes	♂ Worse	Yes		Yes	Yes	Yes	Depending on numb. of bouts
Neurologic deficit score	No	?		Yes		Yes	Yes	Yes	Depending on progr.
Dur. of dis., abil. to walk	No	?		Yes	Young better	Yes		Yes	Chronic progr. worse
Disability	Yes	No		No		Yes	Yes	?	
Mortality	Yes	Yes	♀ Worse	?		?		?	
Frequency of bouts	No	?		No		?		Yes	Depending on no. of bouts
Ability to work and to walk	Yes	No		No		?	?	Yes	Progressive worse

suggested that age at onset clearly determines the prognosis and influences the disease course.

An analysis of the results given in Leibowitz' book on Table 3.16, page 38, shows that there is no statistically significant deviation in the age at onset in the group of severely handicapped patients ($p > 0.05$). However, a difference was found in the course of the disease in this group ($p < 0.05$). Leibowitz grouped the patients according to "degree of malignancy" and found only then that the age at onset was the most relevant factor for prognosis. The results of Leibowitz et al. could be biased by selection. All his patients were immigrants to Israel and there is no way to find out if the severity of the disease influenced their decisions to emigrate. Dean et al. (1976) also encountered the problem of biased population. It is possible that young patients with an unfavorable course were underrepresented in the sample. After a mean disease duration of 11.5 years, 63% of Leibowitz' patients had a remitting course without progression, possibly another indication of a sample with a particularly high number of benign cases. Our corresponding figures are: a remitting course in 42% of the patients in our main pool sample with mean disease duration of 8.7 years, and a remitting course in 43% of patients in the epidemiologic sample with a mean disease duration of 13.0 years.

R. Müller (1949) made a great effort to get a representative sample. He gathered information from 810 patients registered in different institutions around Stockholm during the previous 25 years and reexamined 582 of them. Results were obtained from the whole group of 582 patients as well as from three subgroups individually. These subgroups were defined according to the place of registration (outpatient departments, private practice, and internal neurology departments of several hospitals). There were no important differences in results from the various subgroups and also none between the subgroups and the whole sample; the latter was thus regarded as representative. As regards prognosis, the sample was divided into patients with remittent and with progressive bouts. R. Müller gave neither the number of patients without progression, nor the number of those with primary progression at the time of examination. This makes a comparison of his results with ours difficult.

The frequency of clinical signs and symptoms are similar to those in other studies (see Table 3), whereas the duration of the disease was longer (15 years), and the age at onset lower (26 years; taken from Fig. 1 on p. 63 of his book). More than half of his patients (411 out of 810) were registered as ill before the age of 24, the corresponding figure in our material being 218 out of 812 (27%). These differences suggest that perhaps his method of registration (examination of survivors) resulted in overrepresentation of patients with low age at onset having a benign course. Young patients with an unfavorable course could have died of MS in the meantime.

The mean age at onset of 31 years in our study is similar to that found recently by Leibowitz et al. (1973) and Gudmundsson et al. (1974). Older statistics often give a lower age at onset. Gudmundsson et al. (1974) pointed out a significant rise of the mean age at onset during the last decades (from 26.5 to 31.6 years). A similar trend was mentioned by Broman et al. (1972). The mean age at onset recorded in a prevalence study of patients in and around Göteborg in 1960 was 29 years; it was 32 years in the same area in 1972 (incidence material). If this rise in the mean age at onset can be confirmed by long-term prospective studies, it would be of great interest to test for correlations with other factors (antibody titers, age during measles infection, etc.). It might be possible to find clues about pathogenesis from such a study. A difference in age at onset between males and females has been reported by some authors (survey: see McAlpine et al., 1972; Firnhaber, 1973), but could not be confirmed by others (Panelius, 1969; Tavolato, 1974; present study). Again, prospective studies might explain these discrepancies.

4.1.1.2 Disease Course and Prognosis

Significant differences were found in the degree of disability among patients with different disease courses. These differences were similar for the pool sample and for the epidemiologic group. Comparable degrees of disability were recorded in patients of different ages at onset, but with the same disease course. That is, our results seem to indicate that loss of performance depends on the disease course rather than on age at onset. However, the chronic-progressive form is seen more often in older patients; therefore, old age at onset seems to bear an unfavorable prognosis. Bouts and remissions do occur in older patients, but in these cases the prognosis is as good as for younger patients.

In common with the findings of R. Müller (1949), McAlpine (1961), and Bauer et al. (1965), our results suggest that a progressive course from disease onset or transition into a chronic-progressive course after initial bouts and remissions indicate a poor prognosis. Poeck et al. (1964) arrived at the same conclusion in a different way. They showed that the mean life expectancy was greater than 20 additional years for patients with a remittent course and of different age at onset. Patients with a progressive course from the beginning had only 15 more years to live on the average (again, regardless of age at onset).

McAlpine (1961) distinguished three types of disease course. The first type, the "remittent" course, is characterized by full remissions between bouts. In the second type, "remittent and progressive", a remittent phase is followed by a chronic progression. A chronic progression is present from the beginning in the third type, "progressive from onset". In the literature

the differences in the type of onset and the development of the disease have usually been regarded as variations of the same basic process. Different manifestations have been assumed to reflect a different immunologic status of patients. There is a malignant form with rapid progression and possible death within a few months (Brain 1936; McIntyre et al. 1943), and a benign course with little disability over many years or decades (McAlpine, 1961; Mackay et al., 1967; Lehoczy et al., 1963; Bonduelle, 1969), and a variety of forms in between. Some authors stress the peculiarities of the primary progression (Friedman et al., 1945; Leibowitz et al., 1967) and separate it from other forms of the disease (Glatzel et al., 1968).

Fog et al. (1970) divided the course of MS into three phases: a hypothetical incubation period (phase I), a prephase (phase II) characterized by an intermittent course, and a progressive phase (phase III). They suggested that all patients go through these three phases, although MS is not diagnosed in some patients until they are in the progressive phase. This model reflects the apparent predilection of the progressive course for older ages. Its relevance, however, must be confirmed by large prospective studies.

4.1.1.3 Duration of the Disease and Prognosis

There is general agreement in the literature that in most patients the degree of disability increases with time, i.e., with duration of the disease. However, the speed of this deterioration varies widely in the different studies. The results of major papers are given in Table 16. The proportion of patients with little or no disability after 8–15 years is shown to facilitate comparison.

Some of the discrepancies can be explained by different selection of the patients; for example, MacLean et al. (1951), who recorded remarkably good performances, studied only ambulatory patients with a remittent course.

Table 16. Influence of duration of MS on the performance of patients; survey of the literature

Author	Year	After n years	Percentage	Criterion applied
MacLean et al.	1951	> 10	42%	Ability to walk and to work preserved
McAlpine	1961	10–14	42%	No disability
Abb et al.	1956	> 10	41%	Ability to work preserved
R. Müller	1949	15	34%	No invalidity
Bauer et al.	1963	15	32%	Ability to work fully or partly preserved
H. R. Müller	1966	11–15	27%	
Thygesen	1949	8–15	25%	
Kolb	1950	15	–	Ability to work preserved

Percy et al. (1971) confirmed this favorable prognosis; two-thirds of the patients from the Mayo Clinic were still able to walk after 25 years of illness.

The criteria applied for prognosis may have an influence on the results. For instance, the ability to work is not only dependent on physical or on mental findings, but also on social factors (see Sect. 3.6.3). On the other hand, the ability to walk, which is taken as a parameter for "disability" (McAlpine) or "invalidity" (R. Müller), does not completely determine performance. For instance, an incapacitating tremor of the arms can be found in connection with a preserved ability to walk.

In our study, prognosis is considered in terms of both the ability to work and the ability to walk. After 15 years of illness, 30% of our patients showed little or no disturbance in their ability to work; the corresponding figure for the ability to walk was 39%.

This is in general agreement with other studies (see table 16).

4.1.1.4 Sex and Prognosis

Male patients with MS often appear to have a less favorable prognosis than females (R. Müller, 1949; H. R. Müller, 1966; Panelius, 1969). However, according to Henner et al. (1939), Lazarte (1950), Leibowitz et al. (1973), and Dassel (1973), males have a better prognosis. Dassel based his results on mortality data, which are probably of limited value for statements on prognosis (Stazio et al., 1964). A statistical analysis was not made by Henner et al. or by Lazarte. There was no significance in the data of Leibowitz et al. In several other studies, including ours, no difference in prognosis between males and females could be found (McAlpine et al., 1952; Alexander et al., 1958; Poeck et al., 1964; Gudmundsson, 1971).

4.1.1.5 Symptomatology and Prognosis

The symptoms of MS have often been related to prognosis. Classifying patients according to symptomatology (Oppenheim, 1911; Carter et al., 1950; Kurtzke et al., 1968) can reveal different prognosis for the different groups. However, the pattern of symptoms can vary widely during the course, which means that a permanent reassessment of the classification is needed.

We were unable to include systematic follow-up studies in the present investigation and were therefore unable to correlate symptomatology to the course and prognosis of disease.

4.1.2 The Problem of Diagnosis

Computer-assisted diagnosis has attracted the interest of numerous investigators (survey: see Pirtkien, 1971; Jacques, 1972). In other fields it has already proved to be a valuable aid to the clinician (Horrocks et al., 1972; Hirschfeld et al., 1974; Levi et al., 1976).

It would be tempting to develop a similar tool for the diagnosis of MS. In the Scandinavian countries preliminary work in this direction is now in progress (Bergmann et al., 1965; Broman et al., 1969). Markov et al. (1969) reported on the successful use of a computer for differential diagnosis, i. e., in differentiating between MS and acute allergic encephalomyelitis.

The reliability of clinical diagnosis was defined in our study as: definite, probable, or possible. In the beginning it was not necessary to set down rigid criteria in order to decide among these categories. The study of C. M. Poser (1965) showed that the age, experience, and nationality of a neurologist have little influence on his ability to make a correct diagnostic classification of MS. However, it is necessary to have standardized criteria for the development of a computer-assisted study. These criteria were given on the new set of data sheets (see Fig. 5; Bauer, 1972). The symptomatology of patients with different certainty of diagnosis of MS and those with other similar diseases should now be recorded in a standardized manner. Hopefully, analysis of such data will allow computer-assisted diagnosis in the future, in spite of the warning of J. K. Kurtzke (1967): "caveat computator".

Several authors had tried to construct a diagnostic classification system independently (Allison et al., 1954; Gilland, 1965; Schumacher et al., 1965), but up to now no general agreement has been reached. This still makes a comparison of prevalence and incidence data in epidemiologic studies very difficult. Even if similar diagnostic criteria are applied, there is the problem of deciding whether or not possible cases should be included. The same is true for statistics on symptomatology. For instance, Leibowitz et al. (1973) included possible cases and suggested that bias of selection would increase if they were excluded. Patients with a progressive course from disease onset and spinal cases would be lost, because they do not fulfill the classic criteria (Leibowitz et al., 1973). Kurtzke et al. (1969) and Panelius (1969), on the other hand, did not include the possible cases. As long as different diagnostic criteria are applied and the selection of patients varies widely, a comparison of data from different studies is difficult. A first step has been made in this direction by the construction of a standardized multicenter recording system.

4.1.3 Statistics on Signs and Symptoms

For the reasons mentioned above (see Sect. 1.3) it did not seem worthwhile comparing the frequencies of single signs and symptoms with those in the literature, particularly with data gained in retrospect from traditional medical records (Sällström, 1942; Abb et al., 1956; Kurtzke, 1970; Morsier, 1971). Even for samples recorded in a similar semi-prospective way, comparison is difficult. The signs and symptoms registered by R. Müller (1949) are listed in Table 3. Only data concerning general disturbances of functional systems were recorded in the study of Kurtzke (1961). These were not mentioned by Müller, who preferred to record more detailed findings. This made comparison difficult; but where a comparison was possible, no obvious deviations were noticed, except for cerebral (= mental) symptoms. Exact registration of mental status during a neurologic examination is almost impossible. Knowledge of the patient's personality before the onset of the disease and psychological tests would be desirable, but are rarely available.

Consistency in the frequency of other signs and symptoms in Table 3 does not necessarily mean that these statistics are representative for MS. Results from large, strictly prospective studies, where data are always recorded from the very beginning of the disease, are not yet available. The data collection in the present investigation is an attempt to solve this problem, but success depends on the early registration of all cases, as well as on long-term follow-up examinations.

4.1.4 Follow-Up Examinations

A total of 178 follow-up examinations were recorded on the original sheet. It was found that the symptomatology could not be registered in sufficient detail. This disadvantage does not apply to the new documentation system. A detailed clinical status can be recorded on GD II (see Fig. 6), including small changes seen during the course of the disease. Follow-up studies in the literature were mostly based on "disability" or on other rating scales. Unfortunately, the original findings were not presented. Records of original findings, such as neurologic symptomatology, always contain more information and are more easily reproducible than a summary or a general grading system (Hall et al., 1976).

4.2 Critical Comments on the Method

It is doubtful whether the documentation method developed here can be applied to all the special projects, as originally planned. Although the need

for more detailed information was felt by all members of the study, active participation decreased, and the error rate increased after introduction of the new documentation system. It is hoped that familiarity with the sheets will reduce these difficulties. However, good motivation is necessary for successful cooperation, particularly when busy physicians are involved.

One improvement in this direction has been the development of a printed record, which is sent back to the physician (see Fig. 28: program written by Mr. Kerscher, EDP-Department, Göttingen University). The time usually needed for dictating and writing a medical record can then be used for the documentation process. Another way of maintaining the clinician's interest in the program is to give him access to the data store. This idea is now being developed, and every effort is being made to facilitate the handling of data. Even physicians with no computer experience should be able to address their questions directly to the EDP department and obtain answers in an appropiately designed print-out. A good design was developed by Wingert (1972) and has already been applied to the correlation of EEG findings to cerebral tumors by Patzold et al. (1973) and Haller et al. (1973).

The optical mark reader sheet was found to have an added advantage; because it could be read without computer equipment, this project was not interrupted at times when the EDP department was too busy to work for us. Analysis of findings concerning the 226 patients from the epidemiologic area was only possible by a manual process. In the daily routine of patient care, the copy sheets are useful, too; it was some time before the printed text was returned.

Regardless of the quality of computer facilities in the future, there will always be a personnel problem. The computer staff have many other duties and differing appreciation of medical problems, while the physicians have limited time and differing attitudes toward the use of computers in medicine. In our program the physicians were interested in problems of MS and participated voluntarily. Some of the above difficulties were encountered when all members of the regular staff had to participate in the testing of the documentation program; a particularly high error rate in form-filling resulted; also, some patients were not recorded at all. Baird et al. (1965), Ehlers (1970), and Penin et al. (1972) had similar experiences with optical mark reader systems. When planning medical computing systems, these problems must be kept in mind. Although optical mark reader sheets seem to be of limited value in everyday clinical documentation, they are certainly a valuable tool for multicenter studies, when computer analysis is required.

ANAMNESTIC DATA AND CLINICAL FINDINGS IN DISSEMINATED ENCEPHALOMYELITIS (DFG FOCAL POINT PROGRAM) FORM 1

PATIENT NO : 2222221 DATE OF EXAMINATION : 09/19/74

COURSE OF DISEASE	: EPISODIC / CHRONIC PROGRESSIVE
CERTAINTY OF THE CLINICAL DIAGNOSIS	: DEFINITE
FIRST APPEARANCE	: 1963
INITIAL SIGNS AND SYMPTOMS	: PARESIS, SENSITIVITY DISTURBANCES
NUMBER OF EPISODES IN THE FIRST YEAR	: 1
NUMBER OF EPISODES IN THE FURTHER COURSE	: 5
DISORDERS WHICH APPEARED IN THE COURSE	: SPASTICITY/BABINSKI, PARESIS, SENSITIVITY, OPTIC, TRIGEMINAL/FACIAL, VEGETATIVE
DEFECT SINCE (MORE THAN)	: 4 YEARS
PROGRESSIVE SINCE (MORE THAN)	: 2 YEARS
DISORDERS AS PRESENT DEFECT	: SPASTICITY/BABINSKI, PARESIS, OPTIC, VEGETATIVE

/// FINDINGS IN THE PRESENT EXAMINATION ///

EPISODE	: NO
WASHING, DRESSING, EATING	: SERVERELY DISTURBED
ABILITY TO WALK	: SERVERELY DISTURBED, WHEELCHAIR, BEDRIDDEN
ABLE TO PRACTISE PROFESSION	: NO
ABLE TO WORK	: NO
RETIRED	: YES
DISABILITY (KURTZKE SCALE)	: 6
COMPLICATIONS	: NONE
PAIN	: NONE
CSF (TAKEN EARLIER)	: YES CELL NO : UNKNOWN MASTIX CURVE :UNKNOWN IMMUNOGLOBULIN : UNKNOWN
CSF (TAKEN AT EXAMINATION)	: NO
OTHER DISEASES	: UROGENITAL, SKIN/ALLERGY ,ENDOCRINOLOGICAL, LOCOMOTOR APPARATUS, SEQUELAE OF INJURIES, NEUROLOGICAL, PSYCHIATRIC

ANAMNESTIC DATA AND CLINICAL FINDINGS IN DISSEMINATED ENCEPHALOMYELITIS (DFG FOCAL POINT PROGRAM) FORM 1

***** /// IF FORM 2 IS AVAILABLE FOR THIS EXAMINATION, THEN PASS OVER THE FOLLOWING EXPRESSION /// *****

/// PRESENT CONDITION ///

SPASTICITY/BABINSKI	: RIGHT ARM, RIGHT LEG, LEFT LEG
PARESIS	: RIGHT ARM, RIGHT LEG, LEFT LEG
SENSITIVITY DISTURBANCE	: RIGHT TRUNK/LEG
VISUAL DISTURBANCE	: ATROPHY RIGHT, ATROPHY LEFT
DISORDER OF OCULAR MOTILITY	: ---
TRIGEMINAL-FACIAL DISORDER	: ---
DISORDER OF BRAINSTEM/CEREBELLUM	: ---

Fig. 28. Print-out of data recorded on the documentation sheet

4.3 The Contribution of the New Documentation System to MS Research

The success of any documentation system depends on careful planning of criteria and definitions to be applied. It was sometimes difficult to come to a general agreement, and extra definitions had to be included in the new documentation system for the most controversial items. The work involved in building up this mutually acceptable system has now been rewarded. Patients from a variety of institutions in different parts of the country (see Fig. 27) can be included; a data pool can be established on a large scale and used for many purposes.

The sample was large enough to give clear results when analyzed statistically. Questions previously open to discussion in the literature could be answered (see, for example, Sect. 3.6.4). All members of the study have permanent access to the data pool. Selection and analysis of certain cases or of a group can be made in a few days. Statistics on signs and symptoms will be of value in any future computerized diagnostic system. An attempt to correlate laboratory results with clinical findings is now being made (Hauptvogel et al., 1974). On the whole, the new documentation system has lived up to our expectations, and although revisions were made as various weaknesses came to light, there is still room for improvement.

5. Outlook

Projects affiliated with this program that are now taking advantage of the new documentation system are summarized in the following sections.

5.1 Neuropathology

Characteristic morphologic features of MS have long been recognized. Attempts to correlate pathologic findings with clinical symptomatology were made as early as 1868 (Charcot). These efforts have been continued up to the present time (Fog, 1965b; H. Strötker, 1968; S. Strötker, 1969; Lumsden, 1970). Morphologic changes can be analyzed in great detail. For instance, Fog (1965b) applied a technique of serial sections and called the specific localization of typical plaques around small vessels "periphlebitis cerebrospinalis et retinalis." Lumsden (1970) confirmed the findings of Fog and observed clear-cut, reproducible changes in the tissue, although the intensity, extent, and speed of this process vary.

In contrast to the large number of sophisticated methods and results available in pathology, clinical findings were usually not sufficiently detailed. Thus, correlations could only be made for small samples (H. Strötker, 1968; S. Strötker, 1969). A continous follow-up of the clinical course is now needed for future correlation of morphologic findings with symptomatology; this could reveal new information about pathogenesis (Lumsden, 1970).

Recent clinical findings concerning a particularly interesting patient (record No. 957/72) were recorded on the documentation sheets, which also included information on the dynamics of the final process. Subsequent electron microscopic studies revealed two types of virus particles; nucleocapsid-like structures and particles similar to the papovavirus (Bauer et al., 1975). Similar structures have been seen by other authors (Narang et al., 1973; Barbosa et al., 1973; Prineas, 1972; Raine et al., 1974). Whether they are relevant to the etiology or pathogenesis of MS remains to be seen.

5.2 Virology

Ter Meulen et al. (1972) were able to isolate a virus from MS brain tissue. This was exciting news, but the significance of this so-called 6/94 virus is still unclear. Further cultures and analysis of results gained by other methods are still necessary (Iwasaki et al., 1973). The early sterile autopsy, which is considered the most practical way of obtaining tissue for cultures and ultrastructure studies (Bauer et al., 1975), present problems. Good communication between clinicians and research groups of the DFG-pro-

gram facilitates the inclusion of cases and data that would otherwise be lost because of organizational problems.

The determination of antibody titers against the isolated virus might also give information about the virus and its relevance. Two groups of patients seemed particularly interesting in this context: first, patients who exhibited CSF activity during the preceding year (their selection has been mentioned above; see Sect. 3.8.1); and secondly, patients from the epidemiologic area. Blood was taken from 226 patients, and a clinical examination was made at the same time. Data on previous childhood infections, on vaccinations, and on infectious diseases later in life are known for all the patients as well as for the following control groups (Poser et al., 1976b):

1. Relatives or friends who had lived with or close to them during childhood and who were born within 3 years of the patient.
2. Psychiatric patients aged 30–60 years.
3. Patients with disc lesions aged 30–60 years.

Antibody titers of measles virus were also determined in all these persons.

The role of measles virus in MS is still unclear. Elevated antibody titers were found by most authors in serum and/or CSF specimens of MS patients (for a survey of the literature until 1972, see McAlpine et al., 1972; Anonymous, 1974; for recent papers see Panelius et al., 1973; Salmi, 1973; Salmi et al., 1973; Salmi et al., 1974; Cendrowski et al., 1974; Nemo et al., 1974; Norrby et al., 1974a, b; Woyciechowska et al., 1974; Vandvik et al., 1975). The decreased serum/CSF antibody ratios support the hypothesis that local production of measles antibodies takes place in the central nervous system of some MS patients, in certain patients with optic neuritis (Link et al., 1973; Nikoskelainen et al., 1975a, b), as well as in a particular group of patients with chronic myelopathy (Link et al., 1976). Haire et al. (1973, 1974) were able to demonstrate high titers of specific anti-measles IgG and IgM antibodies in the serum of MS patients and of IgG (but not of IgM) in the CSF. These observations are suggestive of continuing active systemic infection by the measles virus (Anonymous, 1974), but they are by no means conclusive (Anonymous, 1976). The older interpretation of elevated measles antibodies as an anamnestic or nonspecific response (Brody et al., 1971; Daniel, 1972) was based on the finding of raised serum antibodies against several other viruses, most of which could not be confirmed by more specific methods.

There are several discrepancies in the results of published antibody studies, probably for methodologic reasons. The tests applied vary considerably (e.g., hemagglutination inhibition and hemolyzing inhibition of nucleocapsid complement-fixing antibodies differ in their specifities; see Salmi et al., 1973). There is also the usual problem of selecting the right persons as controls. The observation that in cases of acute neurosyphilis, spe-

cific measles antibodies can be detected in the CSF could support the hypothesis that measles virus is ubiquitous and can be reactivated by any kind of immunologic process (ter Meulen, 1976).

Investigation of a cell-mediated immunologic mechanism in MS showed an anergy toward measles in the study of Utermohlen et al., 1973. However, Cunningham-Rundles et al. (1975) and Bartfeld et al. (1976) could not confirm this finding. The observation that MS patients acquire measles later in life than controls (Alter, 1976) was based on the retrospective data of 30 MS patients (Alter et al., 1976).

In future studies it will be necessary to correlate the nature and titer of serum and of CSF antibodies and of cell-mediated mechanisms with clinical findings, including the history of previous infections. The standardized documentation system is an invaluable tool in this context.

5.3 Immunology

Further immunologic studies are planned with patients from the pool and from the epidemiologic area. The genetically determined histocompatibility (HL-A) antigens show different patterns in MS patients and in controls (Bertrams et al., 1972; Jersild et al., 1972; 1973a, b; Naito et al., 1972). It is important to know whether or not the HL-A antigens have an influence on the course of the disease. A correlation between the HL-A pattern and clinical findings was observed by Jersild et al. (1973b) and by Bertrams et al. (1974a). In the Danish study (Jersild et al., 1973b) detailed data concerning the course and symptomatology were given, but the same sample was small (28 patients). Bertrams et al. (1974a) reported on a larger group, but they did not give detailed information about clinical findings.

These results should now be confirmed and specified by making HL-A typings on a large number of patients whose clinical data are recorded in sufficient detail. The pool material here should be useful in this context, too.

It is still debatable whether there is a correlation of HL-A antigens and antibody titers to measles virus in MS patients. Jersild et al. (1973c) found high-titer antibodies to measles in 13 out of 57 MS patients carrying the HL-A antigens known to be increased in MS, but in only 2 out of 45 MS patients lacking these particular antigens. These findings were confirmed by Cazzullo et al. (1974), but not by Bertrams et al. (1973).

Antibody titer to measles virus and detailed clinical information are already available from patients from the epidemiologic area. An analysis of the HL-A antigens in these patients and in their relatives is planned. The HL-A pattern of the relatives should be interesting for two reasons: firstly,

to obtain more knowledge of HL-A pecularities of MS patients themselves (Bertrams et al., 1974b); and secondly, to elucidate the frequent occurrence of familial cases (Zander et al., 1976).

Lymphocyte-defined determinants have shown an even higher correlation to MS than the serologically determined HL-A antigens (see Jersild et al., 1975; Bertrams, 1976).

A 100% association of MS with alloantigens, which are exclusively located on B-lymphocytes (so called Ag 7a), has recently been reported (Winchester et al., 1975).

Immunological phenomena associated with experimental allergic encephalomyelitis, an animal model for MS, have been investigated in MS patients (Bornstein, 1972; survey: see Nilsson, 1972). The role of serum induced demyelination (Raine et al., 1973) is still unclear. Follow-up studies of individual patients and close correlation with the clinical course promise an insight into the pathogenetic mechanisms involved. Our documentation system provides clinical data in a practical way and will be used by others (Bornstein, 1976) in this context.

5.4 Relevance of CSF Findings

An increase of the γ-globulin fraction (mainly IgG) has proved to be the only result of diagnostic value so far obtained from analysis of the CSF of MS patients (Bauer et al., 1969; Olsson et al., 1973). It is still debatable whether or not this increase is correlated with the existence of auto-aggressive or protective antibodies or even whether or not it is related to pathogenesis. The determination of γ-globulin fractions presents no problems; special methods are already available (Bauer et al., 1969; Olsson et al., 1973; Iwashita et al., 1974).

However, the diagnosis of MS cannot be made from CSF findings alone without knowledge of the clinical picture. The combination of a non-computer-compatible form with an optical mark reader sheet makes a computerized correlation of CSF with clinical findings possible (Hauptvogel et al., 1974).

Follow-up studies of MS patients should give useful information on the dynamics of the clinical course and corresponding CSF changes.

5.5 Epidemiology

Information on environmental and social factors concerning MS patients were gained together with clinical and serologic findings. Analysis and

correlation of these data by a computer program (written by Mr. Brauns, EDP Department, Göttingen University) is now in progress. A preliminary survey confirms the findings of Firnhaber (1969); it was not possible to find any association between environmental factors and the frequency of occurrence of MS. We were mainly interested in the social factors. It soon became evident that, although medical care seems to be sufficient, the social needs of MS patients are met very poorly.

The close contact between physicians and patients in the epidemiologic area should be valuable in future prevalence and incidence studies. In our investigation the prevalence rate in the epidemiologic area increased as the methods of finding and documenting patients improved. This observation had already been made by Broman (1976).

There is no evidence at the moment that MS is really becoming more frequent, except in some special areas (Bird et al., 1975).

Cooperation with a Japanese research group should reveal new epidemiologic findings. Reported differences between MS patients in Western countries and in Japan in the context of clinical symptomatology (Kuroiwa et al., 1973) will be reassessed after recording the data on our documentation sheets in both countries.

5.6 The Standardized Medical Record

The printed version of the data which originally appeared on the documentation sheet has two advantages: First, it saves time, because the traditional method of writing or dictating the medical record can be replaced; secondly, it can be requested by any member of the program who wants full information on individual patients and their follow-up examinations. Numerous other applications of the documentation system are possible and have already been discussed. Only a few of them will be realized immediately, but others should gather momentum as new data accumulate.

Summary

A variety of new findings in multiple sclerosis research has yielded clues to its etiology and pathogenesis. One reason why some of the results remain inconclusive or even contradictory, and why the final solution of the problem is still pending, is the lack of communication among the different branches of research, as well as their isolation from the patient and his clinical symptomatology. The DFG (Deutsche Forschungsgemeinschaft)program "Ätiologie and Pathogenese der Multiplen Sklerose und verwandter Erkrankungen" was started in 1970 with a view to creating better exchange of information among immunologic, virologic, neuropathologic, biochemical, and epidemiologic investigators. Clinical findings were also regarded as an essential part of all research activities.

Because data recorded in traditional medical records are often found to be incomplete and disorganized, a standardized documentation method has been developed. The optical mark reader system was adapted to the problem and proved to be particularly appropiate for this multicenter program, in which 17 hospitals and 8 research institutions participated. The data of 947 MS patients were recorded on optical mark reader sheets and fed into a Siemens 4004/35 computer for analysis from January 1972 to August 1973. Incompletely or incorrectly marked data sheets were refused with the help of a plausibility control program, which also produced a protocol of the errors made. The initial error rate of 20%–30% was reduced to 10%–15%. Different features of MS, as well as statistical information on signs and symptoms, were gained by correlation and selection of data from the 812 first examinations.

The results can be summarized as follows:

The mean age at disease onset was 31.1 years, the mean duration of the disease 8.7 years, and the sex ratio 64% females to 36% males. Differences between the sexes were found in single signs and symptoms (pareses, ataxia, sensory and sexual disturbances), but not in general performance or in the ability to walk and to work, and also not in the age at disease onset. With very few exceptions (e.g., mental disturbances), the frequency of signs and symptoms was found to be in good agreement with that in the literature.

The ability to walk and to work, used as a parameter for prognosis, was compared in different groups of patients. Both the duration and course of MS had a significant influence on the disability, but the age at onset in itself was found to be less important.

The correlation of clinical parameters with the duration of the disease provided information about the dynamics of certain signs and symptoms and about the ability to walk and to work over the years. A detailed analysis of certain signs and symptoms was performed, keeping any future computer program for diagnostic help in view. Certain groups of patients were selected for special therapeutic (e.g., stereotactic surgery) and research procedures (e.g., antibody determinations). In an attempt to test for possible bias in the selection of our patients, the data of a group of 226 patients from an epidemiologic area were compared with our results and found to be very similar in respect of the above statements.

The experience gathered with the aid of the first documentation sheet was helpful in the development of two new sheets that allow for the registration of more details. With increasing amount of data, there is inevitably an increase in common interests and goals and improvement in communication among the fields of biochemistry, virology, immunology, epidemiology, and neuropathology. Clinicians should profit from the computerized medical record developed from the new documentation sheets. The optical mark reader documentation method has limitations, but it is suitable for multicenter research studies.

Acknowledgments. This study was supported by the *Deutsche Forschungsgemeinschaft* in the frame of the *Schwerpunktprogramm: Ätiologie und Pathogenese der Multiplen Sklerose und verwandter Erkrankungen.* I would like to thank Professor Bauer, who initiated the program, and all members who participated in the data collection.

Miss Jane Houchin was most helpful in the revision of the English text, Mrs. Ingrid Karstens in typing parts of the manuscript.

Participating hospitals:

1 Neurologische Universitätsklinik, Göttingen
2 Taunusklinik, Falkenstein
3 Kamillusklinik, Asbach
4 Neurologische Klinik der Med. Akademie, Lübeck
5 Neurologische Klinik der Med. Hochschule, Hannover
6 Neurologische Universitätsklinik, Würzburg
7 Centrum voor Multiple Sclerose, Melsbroek
8 Kommunehospitalet, Kopenhagen
9 Karl-Bonhoeffer-Nervenklinik, Berlin
10 Nervenklinik der Universität, München
11 Allgemeines Krankenhaus St. Georg, Hamburg
12 Neurologische Universitätsklinik, Hamburg
13 Neurologische Klinik der Hochschule, Essen
14 Schloßparkklinik, Berlin
15 Neurologische Universitätsklinik, Berlin-Steglitz
16 Rudolf-Virchow-Krankenhaus, Berlin
17 Neurologische Klinik der Städtischen Krankenanstalten, Darmstadt

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