# New Diagnostic Criteria for Multiple Sclerosis: Guidelines for Research Protocols

Charles M. Poser, MD,[1] Donald W. Paty, MD,[2] Labe Scheinberg, MD,[3] W. Ian McDonald, FRCP,[4] Floyd A. Davis, MD,[5] George C. Ebers, MD,[6] Kenneth P. Johnson, MD,[7] William A. Sibley, MD,[8] Donald H. Silberberg, MD,[9] and Wallace W. Tourtellotte, MD[10]

Several schemes for the diagnosis and clinical classification of multiple sclerosis (MS) have been advanced [1]. The best known is that published by Schumacher et al [3]. The criteria for this scheme were established in order to select patients for participation in therapeutic trials, and pertain only to what might be called definite MS. No provision was made for incorporating supportive laboratory data into the diagnostic criteria.

As no reliable specific laboratory test for the diagnosis of MS has been discovered, the diagnosis remains a clinical one, and there is still a need for clinical diagnostic criteria. However, several laboratory and clinical procedures have been developed within the last decade which aid greatly in demonstrating neurological dysfunction attributable to lesions, and even the lesions themselves.

One problem with the various published diagnostic classifications is their discrepant terminology: what is considered "probable" in one is called "definite" in another. Another problem is that all the proposed schemes require much subjective judgment, a difficulty which cannot be completely overcome but can be diminished by adding to the clinical evaluation the results of laboratory, neuroimaging, neuropsychological, and neurophysiological procedures. Today there is a need for more exact criteria than existed earlier in order to conduct therapeutic trials in multicenter programs, to compare epidemiological surveys, to evaluate new diagnostic procedures, and to estimate the activity of the disease process in MS.

## Method and Procedure

On April 26 and 27, 1982, the following persons participated in a Workshop on the Diagnosis of Multiple Sclerosis, held in Washington, DC, for the purpose of establishing new diagnostic criteria for MS: Bruce Becker (National Naval Medical Center), Jerry Blaivas (Columbia), Keith Chiappa (Harvard), Floyd Davis (Rush), Burton Drayer (Duke), George Ebers (Western Ontario), Andrew Eisen (British Columbia), Robert Herndon (Rochester, NY), Kenneth Johnson (Maryland), Ian McDonald (National Hospital, London), Dale McFarlin (NINCDS), Donald Paty, Co-chairman (British Columbia), Janis Peyser (Vermont), Charles Poser, Chairman (Boston), David Regan (Dalhousie), Daniel Sax (Boston), Labe Scheinberg, Co-chairman (Albert Einstein), Simon Sears (Texas-Houston), William Sibley (Arizona), Donald Silberberg (Pennsylvania), Robert Slater (National MS Society), Emanuel Stadlan (NINCDS), Wallace Tourtellotte (Wadsworth VA/UCLA), and Byron Waksman (National MS Society). Dr Robert Daroff (Case–Western Reserve) made many useful suggestions. The disciplines represented included neurology, neuropsychology, urology, immunology, neuroradiology, neuroophthalmology, clinical neurophysiology, and neuropathology.

The participants reviewed in detail historical and clinical symptomatology in MS; immunological observations; cerebrospinal fluid (CSF) tests; neurophysiological procedures including visual, brainstem auditory, trigeminal, and somatosensory evoked potential measurements; the evoked blink reflex; a variety of physiological and psychophysiological procedures; neuropsychological assessment; tissue imaging procedures such as computer assisted tomography (CT scanning) and nuclear magnetic resonance (NMR); and urological studies of bladder, bowel, and sexual dysfunction. This re-

[1]Department of Neurology, Boston University School of Medicine, Boston, MA, [2]Division of Neurology, Vancouver General Hospital, University of British Columbia, Vancouver BC, Canada, [3]Multiple Sclerosis Center, Albert Einstein College of Medicine, Bronx, NY, [4]National Hospital, Queen Square, London, England, [5]Department of Neurological Sciences, Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL, [6]Division of Neurology, University of Western Ontario, London, Ont, Canada, [7]Department of Neurology, University of Maryland School of Medicine, Baltimore, MD, [8]Department of Neurology, University of Arizona School of Medicine, Tucson, AZ, [9]Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, PA [10]Wadsworth VA Medical Center, University of California School of Medicine, Los Angeles, CA.

view resulted in formulation of guidelines for the performance of these procedures and for evaluation of the results that will be published with recommendations regarding their usefulness in the diagnosis of MS [2]. The diagnostic criteria presented here represent the views of the majority of the workshop participants.

## Definitions

1. *Attack (bout, episode, exacerbation):* The occurrence of a symptom or symptoms of neurological dysfunction, with or without objective confirmation, lasting more than 24 hours constitutes an attack. This may be completely subjective and anamnestic, e.g., the patient reports having had double vision for three days but did not consult a physician; or numbness and tingling of a leg caused a visit to a physician who was unable to demonstrate objective changes; or the patient was hospitalized because of severe ataxia and was found to have signs of cerebellar dysfunction, bilateral Babinski signs, and left facial weakness. Individual symptoms, however, may last for considerably less time than that: e.g., a Lhermitte sign (which is really a symptom) or vertigo may last for only seconds; these manifestations cannot be considered attacks in this context.

2. *Historical information:* The description of symptoms by the patient. The example just cited (under the definition of attack) of the episode of diplopia would be historical, and so would the leg numbness, although medical corroboration would strengthen the latter. Ideally, medical records which confirm anamnestic information should be obtained.

3. *Clinical evidence of a lesion: Signs* of neurological dysfunction demonstrable by neurological examination. Such neurological signs are acceptable even if no longer present, provided that they were elicited and recorded in the past by a competent examiner.

4. *Paraclinical\* evidence of a lesion:* The demonstration by means of various tests and procedures of the existence of a lesion of the central nervous system (CNS) which has not produced *signs* of neurological dysfunction but which may or may not have caused *symptoms* in the past. Such tests and procedures include the hot bath test, evoked response studies, tissue imaging procedures, and reliable, expert urological assessment, provided that these tests and procedures follow the guidelines and are interpreted according to the newly established criteria to be published [2]. These diagnostic procedures represent various options, all of which may not be available and some of which may not be deemed suitable or reliable enough by individual neurologists.

5. *Typical of MS:* MS is known to involve certain parts of the CNS much more frequently than others, and thus certain signs and symptoms are more frequently noted. Gray matter lesions occur rarely enough in MS that they should not be considered in establishing the diagnosis. Lesions of the peripheral nervous system, except when accounted for by their intramedullary course (e.g., oculomotor, trigeminal, or facial nerves), may not be counted. Complaints such as headaches, convulsive seizures, depression, or alterations of the state of consciousness are too nonspecific to be considered in the diagnostic construct.

6. *Remission:* A definite improvement of signs, symptoms, or both that has been present for at least 24 hours is called a remission for the purpose of these guidelines. A remission must last at least one month to be considered significant.

7. *Separate lesions:* Separate signs or symptoms cannot be explainable on the basis of a single lesion; simultaneously occurring internuclear ophthalmoplegia, facial weakness, and signs of involvement of the corticospinal tracts could have been caused by a single lesion (e.g., brainstem infarction) and thus would not be acceptable. Optic neuritis involving both eyes occurring simultaneously, or the second eye becoming involved within 15 days of the first (provided that compression of the chiasm by tumor or aneurysm has been ruled out), is considered to represent a single lesion. Only lesions that involve distinctly different parts of the CNS are called separate lesions.

8. *Laboratory support:* The term is applied here only to the examination of CSF for oligoclonal bands and increased production of immunoglobulin G (IgG). All other laboratory procedures, such as evoked responses or tissue imaging techniques, are considered to be extensions of the clinical examination.

## General Considerations

The acceptable age of onset for research purposes is between 10 and 59 years inclusive. The manifestations of the disease offered in evidence must be shown to be characteristic of MS and not attributable to another condition. Such a decision must be made by a physician who is experienced in clinical neurology. It is strongly recommended that the diagnosis of MS be established only by a competent neurologist. Although extended and expensive investigations are not encouraged, other illnesses capable of producing signs and symptoms of multiple lesions of the CNS must be considered. More important, clinical observation over several weeks or months may obviate the need for much laboratory investigation. A steadily progressive disease from onset, without reliable evidence of exacerbations or remissions, with manifestations reflecting a single lesion, and without paraclinical evidence of a lesion elsewhere in the CNS is not to be classified as MS for research

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*\*Webster's Third New International Dictionary,* unabridged, 1971, gives the following definitions for para-: 1a. beside, alongside of; 1d. associated in a subsidiary or accessory capacity. *Paraclinical* would appear more suitable than *subclinical.*

| Category | Attacks | Clinical Evidence | | Paraclinical Evidence | CSF OB/IgG |
|---|---|---|---|---|---|
| A. Clinically definite | | | | | |
| CDMS A1 | 2 | 2 | | | |
| CDMS A2 | 2 | 1 | and | 1 | |
| B. Laboratory-supported definite | | | | | |
| LSDMS B1 | 2 | 1 | or | 1 | + |
| LSDMS B2 | 1 | 2 | | | + |
| LSDMS B3 | 1 | 1 | and | 1 | + |
| C. Clinically probable | | | | | |
| CPMS C1 | 2 | 1 | | | |
| CPMS C2 | 1 | 2 | | | |
| CPMS C3 | 1 | 1 | and | 1 | |
| D. Laboratory-supported probable | | | | | |
| LSPMS D1 | 2 | | | | + |

OB/IgG = oligoclonal bands *or* increased IgG.

purposes, even in the presence of oligoclonal bands or increased IgG production in the CSF. Most neurological clinicians will regard such patients as probable cases of MS; nevertheless, they should not be enrolled in research protocols.

## Classification of Multiple Sclerosis

The proposed classification of MS for use in research protocols consists of two major groups, definite and probable, each with two subgroups, clinical and laboratory supported (Table). The traditional possible MS group is not included because patients so labeled would not be acceptable for research studies.

A. *Clinically definite MS (CDMS)*
  1. Two attacks and clinical evidence of two separate lesions
  2. Two attacks; clinical evidence of one lesion and paraclinical evidence of another, separate lesion

COMMENT. The two attacks must involve different parts of the CNS, must be separated by a period of at least one month, and must each last a minimum of 24 hours.

Certain historical information may be substituted for clinical evidence of one of the two lesions (in category A1) if it fulfills the following conditions: the information is reliable, is adequate to localize a lesion typical of MS, and has no other explanation. Examples include a Lhermitte sign in any person under the age of 50 years who does not have radiologically demonstrable evidence of cervical spine disease; a useless hand due to severe impairment of position sense causing severe stereoanesthesia; a typical optic neuritis occurring be-

fore the age of 50 with loss of vision and with pain on motion of the eye or, if no substantial loss of vision has occurred, with description of visual field defect or alteration of color vision; transient paraparesis with paresthesias; oscillopsia; typical diplopia (in the absence of thyroid disease or a prior history of orbital trauma) that is abolished by closing either eye; and trigeminal neuralgia with onset before the age of 40. Extreme caution must be exercised in making such a substitution. If possible, confirmation by a relative or friend should be obtained if the attack was not observed and recorded by a physician.

Many individuals have become quite familiar with the symptoms of MS from articles published in lay magazines and other easily available sources of information. MS Munchausens are known to exist, and establishment of the diagnosis of MS may be of advantage to some individuals in some circumstances.

Paraclinical evidence of CNS lesions may be elicited by a variety of means, including induced hyperthermia, evoked potential studies, CT and NMR scans, or special urological studies. Neuropsychological evaluation by an expert examiner that indicates definite cognitive impairment in a patient under the age of 50 may be suggestive and helpful but not yet specific enough to be fully diagnostic. No other explanation for these lesions must be evident. Use of the procedures and evaluation of results must follow the guidelines, which will be published shortly [2].

B. *Laboratory-supported definite MS (LSDMS)*
  The laboratory support consists of demonstration in CSF of IgG oligoclonal bands (OB) or of increased CNS synthesis of IgG. Oligoclonal bands must not

be present in the patient's serum, and the serum IgG level must be normal. This assumes that other conditions causing CSF changes, such as syphilis, subacute sclerosing panencephalitis, sarcoidosis, collagen vascular disease, and similar disorders, have been ruled out.

1. Two attacks; either clinical or paraclinical evidence of one lesion; and CSF OB/IgG

COMMENT. The two attacks must involve different parts of the CNS and be separated by a minimum of one month, each having lasted at least 24 hours. One of the episodes must involve a part of the CNS distinct from that demonstrated by the clinical or paraclinical evidence.

2. One attack; clinical evidence of two separate lesions; and CSF OB/IgG
3. One attack; clinical evidence of one lesion and paraclinical evidence of another, separate lesion; and CSF OB/IgG

COMMENT. Historical information cannot be substituted for the clinical evidence. Whether the evidence is clinical or paraclinical, both lesions must not have been present at the time of the first examination and must be separated by at least one month. This separation in time is designed to reduce the possibility of including a case of acute disseminated encephalomyelitis. In a patient with the so-called progressive form of MS, i.e., without remissions and exacerbations, evidence of clinical or paraclinical optic nerve involvement, for example, should not have been present at the time the paraparesis first appeared. Under those circumstances, and only if steady progression has taken place for at least six months, may such a case be accepted as MS.

C. *Clinically probable MS (CPMS)*
    1. Two attacks and clinical evidence of one lesion

COMMENT. The two attacks must involve separate parts of the CNS. Historical information cannot be considered as a substitute for the clinical evidence.

2. One attack and clinical evidence of two separate lesions
3. One attack; clinical evidence of one lesion and paraclinical evidence of another, separate lesion

COMMENT. See under B3.

D. *Laboratory-supported probable MS (LSPMS)*
    1. Two attacks and CSF OB/IgG

COMMENT. The two attacks must involve different parts of the CNS, must be separated by a minimum of one month, and must each have lasted at least 24 hours.

Discussion
The main reason for establishing these criteria is to restrict therapeutic trials and other research protocols to patients with definite MS; the category of probable is designed for the purpose of prospectively evaluating new diagnostic methods. The introduction of the categories of laboratory-supported definite and probable MS extends the limits of the diagnostic criteria, thus making available a larger reservoir of patients for investigative purposes. Naturally, investigators retain the prerogative of availing themselves of this additional group of patients or restricting their choice on the basis of the classic clinical criteria.

The guidelines may appear unduly complicated to the neurological practitioner. They are not meant to deter the clinician in the effort to establish a diagnosis of MS. They will not replace the intuitive feelings derived from subtle indices that so often lead an experienced physician to the solution of the problem; rather, they should help guide the diagnostic investigation in the right direction. To a physician, the distinction between definite and probable MS may matter very little. To a patient, the end of uncertainty is important. If the guidelines result in diminution of the patient's (and the family's) search for alternative or confirmatory opinions, they will be worthwhile.

A major concern in establishing diagnostic criteria for MS is differentiation of the disease from acute disseminated encephalomyelitis (ADEM) with its multiple separate lesions. With rare exceptions, ADEM is a monophasic illness, all its lesions occurring within a couple of weeks in most instances. Patients with ADEM may also have CSF oligoclonal bands or increased CNS production of IgG. The problem of steadily progressive myelopathy is equally difficult to resolve, and a prolonged period of observation may be necessary. The need to make the diagnostic criteria fairly rigid for the intended purposes means that some types of patients will not fit any of the proposed categories despite the fact that many neurologists would consider them to have definite MS; for example, a young woman who during the course of an employment physical examination is found to have monocular optic atrophy, sustained nystagmus on left lateral gaze, and a right Babinski sign but who denies ever having had symptoms referable to the CNS will almost certainly be so diagnosed, as will a young man who, following an automobile accident, is found to have several separate, contrast-enhancing periventricular lesions on CT scan. The former patient in fact may well have had a single episode of ADEM that manifested itself only as a cou-

ple of days of headache, malaise, and slight nausea, a constellation of symptoms hardly suggestive of MS. It can be argued that such asymptomatic patients should not be included as subjects for therapeutic trials.

The Schumacher criteria have served us well, but presently available reliable and productive ancillary procedures must be incorporated into more up-to-date guidelines. These diagnostic criteria were developed to delineate groups of patients whose diagnosis will be accepted by a wide range of investigators worldwide for inclusion in various studies and protocols.

## References

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