SPECIAL ARTICLE

Diagnostic Criteria for Parkinson Disease

Douglas J. Gelb, MD, PhD; Eugene Oliver, PhD; Sid Gilman, MD

The clinical diagnosis of Parkinson disease (PD) is based on the identification of some combination of the cardinal motor signs of bradykinesia, rigidity, tremor, and postural instability, but few attempts have been made to develop explicit diagnostic criteria. We propose a clinical diagnostic classification based on a comprehensive review of the literature regarding the sensitivity and specificity of the characteristic clinical features of PD. Three levels of diagnostic confidence are differentiated: Definite, Probable, and Possible. The diagnoses of Possible and Probable PD are based on clinical criteria alone. Neuropathologic confirmation is required for the diagnosis of Definite PD in patients with the clinical diagnosis of Possible or Probable PD. Criteria for histopathologic confirmation of PD are also presented. *Arch Neurol. 1999;56:33-39*

Although neurologists generally agree that the clinical diagnosis of Parkinson disease (PD) requires identification of some combination of the cardinal motor signs of bradykinesia, rigidity, tremor, and postural instability, few have attempted to develop rigorous diagnostic criteria that can be applied consistently and assessed for reliability.[1-5] Widely accepted diagnostic standards are particularly important at this time of rapidly developing diagnostic and therapeutic modalities. Currently, only about 75% of clinical diagnoses of PD are confirmed at autopsy,[6-10] largely because the cardinal signs can also occur in conditions other than PD; they are then termed "extrapyramidal signs," "parkinsonian features," or "parkinsonism." The goal of this communication is to propose diagnostic criteria that reliably distinguish PD from other conditions with parkinsonian features.

We have surveyed the clinical features that may have diagnostic utility in PD and reviewed the published literature regarding the sensitivity and specificity of these features individually and in combination. This literature has several limitations that preclude a rigorous statistical analysis. Many clinical features have not been studied systematically. The pertinent studies that do exist vary with respect to the population from which the patients were obtained, the procedures for evaluating patients and identifying clinical features, and the methods of analysis (especially retrospective vs prospective).

In most of the relevant studies, the final diagnosis of PD has been made on clinical grounds, so the frequency with which a particular feature was observed could have depended on the degree to which that feature was required for diagnosis. For this reason, the most reliable information comes from studies in which autopsy confirmation was required for diagnosis. Unfortunately, only a few autopsy studies have been published, and they generally have involved only small numbers of patients. In the largest series of patients with autopsy-proven PD, the clinical evaluations were not standardized, and they were performed by a large number of different clinicians.[3,8,9,11]

Despite these limitations, the clinical features of PD are usually straightforward. Herein, we define a core set of clini-

From the Department of Neurology, University of Michigan, Ann Arbor (Drs Gelb and Gilman); and the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Md (Dr Oliver).

cal criteria to identify patients for whom the diagnosis of PD can be made with confidence, and a less restrictive set of criteria for identifying patients for whom the diagnosis is likely but less certain. We reaffirm the role of autopsy confirmation as the essential diagnostic criterion standard even in patients with typical clinical features of PD.

INDIVIDUAL CLINICAL FEATURES

Cardinal Signs

Tremor. The characteristic tremor of PD is a 3- to 6-Hz distal resting tremor, but patients with PD may have a resting tremor, an action tremor, or both, and the character of the tremor may change during the course of the illness.[12-14] The proportion of patients with PD who have tremor ranges from 79% to 90% in clinical series,[15-17] and from 76% to 100% in 3 series of patients with autopsy-proven PD.[9,18,19] The proportion of patients with resting tremor ranged from 69% to 100% in the 3 autopsy-based series.[9,18,19]

Although tremor, particularly resting tremor, is more common in PD than in other diseases with parkinsonian features, it is not rare in the other disorders. For example, in 1 series of patients with autopsy-diagnosed multiple system atrophy (MSA), 80% of patients had tremor, and resting tremor was explicitly noted in 34% of patients.[20] In 2 other series of patients with autopsy-proven MSA, tremor was reported in 13% to 31% of patients.[21,22] In a series of 12 patients with autopsy-proven progressive supranuclear palsy (PSP), 2 patients (17%) had a resting tremor.[23] Postural tremor is even more common, occurring in 8 (47%) of 17 patients with pathologic findings of PSP.[24] A postural or action tremor is present in 57% to 79% of patients with cortical-basal ganglionic degeneration (CBGD),[25,26] and 2 (29%) of 7 patients in 1 series[25] had a resting tremor. In several series of patients who were assigned the histopathologic diagnosis of dementia with Lewy bodies (DLB), the proportion of patients with tremor ranged from 25% to 76%,[18,27-30] and rest tremor was specifically noted in the records of 27% of 30 patients in one series[30] and 55% of 20 patients in another.[18]

Rigidity. The frequency with which rigidity occurs in PD has been reported explicitly in only a few series, with values ranging from 89% to 99%.[9,15-18] Rigidity is a prominent feature of a wide variety of movement disorders and is not specific to PD. Indeed, even patients with uncomplicated essential tremor may demonstrate cogwheeling.[12]

Bradykinesia. Depending on how it is defined, bradykinesia is present in 77% to 98% of patients with PD.[9,16-18] The specificity of bradykinesia as an isolated clinical sign also depends on how it is assessed and the population under study, but bradykinesia is certainly not unique to PD. It can occur as a result of normal aging, depression, and Alzheimer disease, as well as more obviously parkinsonian diseases such as PSP, MSA, CBGD, and DLB.

Postural Instability. Although many authors consider postural instability to be a cardinal feature of PD, it does not usually occur early in the disease. In fact, the defining feature of stage III disease on the Hoehn and Yahr scale[15] for grading disability in PD is early postural instability. These investigators found that only 37% of patients with a disease duration of 5 years or less had reached stage III. In contrast, postural instability and falls are the most common initial symptoms of PSP,[31] and their presence within a year of disease onset has been considered a diagnostic requirement for that condition.[31] Postural instability has limited diagnostic specificity because it can result from a variety of problems in afferent pathways, efferent pathways, central processing, and even musculoskeletal mechanical function.

Asymmetric Onset

Symptoms begin unilaterally in most patients with PD. There have been few quantitative assessments of the reliability of this rule, but exceptions certainly exist. For example, stage I of the Hoehn and Yahr[15] scale is defined as unilateral involvement only, yet Hoehn and Yahr observed that "not infrequently, Stage I is skipped and the onset is bilateral or generalized." In 2 series of patients with pathologically proven PD, symptoms began asymmetrically in 72% to 75% of patients.[9,21]

Symptoms can also begin asymmetrically in other movement disorders. Hughes et al[3] found the initial symptoms to be asymmetric in 42% of a group of patients who had neuropathologic diagnoses other than PD. The percentage of patients with asymmetric symptom onset ranged from 19% to 50% in 2 series of patients with autopsy-proven PSP[21,23] and from 27% to 56% in 2 series of patients with autopsy-confirmed MSA.[21,22]

Thus, asymmetric onset is neither sensitive nor specific as a marker for PD. Even so, when Hughes et al[3] reviewed the autopsy findings of 89 patients who met strict clinical criteria for the diagnosis of PD, 65 of whom had pathologic changes diagnostic of PD and 24 of whom did not, asymmetric symptom onset was 1 of only 2 clinical features that was statistically different between the 2 groups.

Levodopa Responsiveness

Although there are documented cases of patients with autopsy-proven PD who did not respond to levodopa,[32] they are not common. In those series of patients where the diagnosis was confirmed at autopsy, 94% to 100% of patients with PD responded to levodopa.[9,18,21,33] A response to levodopa is not specific to PD, however. Between 22% and 35% of patients with PSP respond to levodopa, at least temporarily.[21,23,24,34] Levodopa responsiveness was reported in 69% to 75% of patients with autopsy-confirmed MSA,[21,35] and a good or excellent response was noted in 43% to 45% of patients.[20,35] The response diminished over time in most patients, but 7% to 35% of patients remained at least partially responsive to levodopa until the time of death.[20,35] Among patients with DLB who presented with parkinsonian features, 70% to 87% responded to levodopa.[18,36]

Other Motor Features

Festination, blink rate, micrographia, the phenomenon of "freezing" while walking, and blepharospasm may help differentiate PD from other movement disorders, but these features have not been investigated systematically. Patients with PD have distinctive speech abnormalities that can be used to differentiate them from patients with other movement disorders,[37] but the distinctions can be subtle and difficult to appreciate.

Nonmotor Clinical Features

Dementia. Cognitive impairment develops in a subset of patients with PD, but estimates of the size of this subset vary widely depending on the definition of impairment, the duration of follow-up, and the inclusion criteria for the series. The best estimates derived from consideration of the literature as a whole suggest that dementia occurs in 25% to 40% of patients with PD.[38-41]

Considerable efforts have been made to identify particular cognitive deficits that are characteristic of the dementia of PD and other subcortical diseases, but the results have been inconclusive.[42-44] Cognitive deficits appear later and are less prominent than motor abnormalities in most patients with PD, but there are exceptions.[45,46]

Depression. In clinical series in which psychiatric manifestations were not the principal subject of interest, significant depression was noted in fewer than 5% of patients.[15,16] In contrast, when depression has been a focus, it has been found in about 40% of patients with PD,[47,48] though only about 8% of patients meet criteria for major affective disorder.[48]

Psychotic Features. Hallucinations occur in about 20% of patients with PD who receive dopaminergic agents,[49] but psychotic features are not common manifestations of the disease itself, particularly in the early stages. Only 2% to 6% of patients with PD experienced hallucinations unrelated to medications in 2 series.[50,51]

Autonomic Dysfunction. Patients with PD frequently demonstrate impaired cardiovascular response to postural changes on laboratory testing, but they are usually asymptomatic.[9,21,52] In contrast, orthostatic hypotension is one of the hallmarks of MSA.[20,53,54] Patients with PD can develop abnormal thermoregulation, gastrointestinal or urinary tract dysfunction, or impotence,[52,53,55] but prominent autonomic symptoms are more characteristic of MSA.[20]

Oculomotor Abnormalities. Patients with PD exhibit abnormalities of both the saccadic and pursuit oculomotor systems,[56,57] but they are minor compared with the supranuclear vertical gaze palsy and slowing of vertical saccades that are hallmarks of PSP. Some patients with pathologic features of PSP never exhibit a supranuclear gaze palsy, however, and are misdiagnosed as having PD.[23,24,58] Furthermore, oculomotor abnormalities are not useful in differentiating PD from MSA[57] or PD from DLB.[18]

Other Nonmotor Features. Characteristic abnormalities of olfactory and visual perception have been described in patients with PD, but the techniques required to demonstrate these abnormalities are not commonly available in standard clinical practice. Sensory symptoms and pain are often reported by patients with PD, but the value of these symptoms in differentiating PD from other diseases has not been determined.

COMBINATIONS OF CLINICAL FEATURES

Two clinicopathologic studies have explicitly assessed the diagnostic accuracy achieved when 2 or more cardinal features are required for the diagnosis of PD. Ward and Gibb[2] found that only 69% to 75% of patients with the postmortem diagnosis of PD had at least 2 of 3 cardinal parkinsonian features (tremor, rigidity, and bradykinesia). Moreover, 21% to 25% of patients who *did* manifest at least 2 cardinal features had pathologic findings of diseases other than PD. In fact, 13% to 19% of patients who demonstrated all 3 cardinal features had pathologic diagnoses other than PD.

Over a 22-year period in their movement disorder clinic, Rajput et al[7] reviewed all 59 patients with parkinsonian syndromes who had had satisfactory autopsies. All of these patients had been seen by a single neurologist, and the diagnosis of idiopathic PD was made when patients had at least 2 of the 3 nonpostural cardinal signs (bradykinesia, rigidity, and resting tremor), no identifiable cause of parkinsonism, and no clinical evidence of widespread central nervous system lesions. The final clinical diagnosis was idiopathic PD in 41 patients, and this was confirmed at autopsy in 31 (76%) of them.

In another series,[10] autopsy confirmed the diagnosis in 489 (84%) of 580 patients thought to have PD on clinical grounds, although the criteria for assigning a clinical diagnosis were not specified. In a series of 100 patients with the clinical diagnosis of idiopathic PD, the diagnosis could be confirmed histologically in only 76 patients.[8] Eighty-nine of the 100 patients satisfied the United Kingdom Parkinson's Disease Society Brain Bank clinical criteria for idiopathic PD,[1] which require that patients have bradykinesia and at least 1 of the other 3 cardinal features (rigidity, rest tremor, and postural instability), none of 16 exclusion criteria, and at least 3 of 8 supportive features (relating to asymmetric onset and progression, levodopa responsiveness, and chronic progression of clinical features). Autopsy confirmed the diagnosis in 73 (82%) of these 89 patients. Diagnostic specificity could be increased further by requiring all 3 cardinal features (tremor, rigidity, and bradykinesia) for the diagnosis of PD, but at the expense of reduced sensitivity—only 65% of patients with a pathologic diagnosis of PD would qualify for the diagnosis clinically if these were the criteria.[3]

Studies of diagnostic criteria for several other movement disorders have included patients with PD in control groups. Colosimo et al[21] considered 5 clinical features thought to be typical of MSA and calculated the total number of features demonstrated by each patient. All of the patients with MSA had at least 2 features and none of the patients with PD had more than 3 features, but there

was still overlap: 9 of the patients with MSA had 3 features and 4 of them had 2 features, while 2 patients with PD had 3 features and 2 had 2 features. There was no statistically significant difference between the patients with PD and those with MSA with respect to symmetry of symptoms at onset, presence of resting tremor, or response to dopaminergic drugs.

Litvan et al[59] evaluated 4 combinations of diagnostic features to determine how well they distinguished PSP from other movement disorders, including PD. Even at the time of the final clinical evaluation, averaging more than 2 years after the initial evaluation and more than 5 years after symptom onset, the 4 combinations had sensitivities for the diagnosis of PSP of only 34% to 89%. Litvan et al proposed a new classification to optimize sensitivity and positive predictive value, incorporating 3 mandatory inclusion criteria and 8 mandatory exclusion criteria. With these criteria, sensitivity was only 57% at the first clinical evaluation and 66% at the final visit, and positive predictive value was 85% at the first visit and 76% at the last visit.

Goetz et al[60] evaluated 4 combinations of clinical features for their utility as criteria in differentiating patients with PD from patients with CBGD. All diagnoses were autopsy proven. For 3 of the 4 combinations, patients who met the criteria had a high probability of having PD, but a high proportion of patients with the neuropathologic diagnosis of PD failed to meet the clinical criteria.

In summary, diagnostic accuracy for PD and the diseases that resemble it can be improved by using appropriately selected combinations of clinical features rather than the individual features. Even using these combinations, however, a considerable number of diagnostic errors occur. Diagnostic specificity for a given disease can be improved by choosing criteria that are more restrictive, but this usually results in greatly reduced sensitivity.

DIAGNOSTIC NEUROIMAGING

Structural and functional neuroimaging techniques are evolving rapidly, and imaging characteristics that distinguish patients with PD from normal controls and from patients with other parkinsonian conditions have been described.[61,62] Relative to controls, patients with PD and other parkinsonian syndromes have narrowing of the substantia nigra pars compacta on heavily T_2-weighted magnetic resonance imaging scans. Putaminal hypointensity is seen in MSA and PSP but not in PD. Slitlike hyperintensity in the outer margin of the putamen may be specific for MSA, though this has not been established rigorously. Positron emission tomographic studies with fluorodopa F 18 and single photon emission computed tomographic studies with β-CIT iodine 123 or FP-CIT iodine 123 have shown significantly less striatal uptake in patients with PD than in controls, especially in the posterior putamen, and the striatal uptake is inversely correlated with severity of motor impairment. In contrast to the preferential involvement of the posterior putamen in PD, fluorodopa F 18 uptake is reduced more uniformly throughout the putamen and caudate nucleus in patients with PSP, MSA, and CBGD, but attempts to differentiate patients with PD from patients with other parkinsonian conditions on this basis have been only partially successful. Metabolic imaging with fluorodeoxyglucose F 18 positron emission tomography can discriminate patients with PD from normal subjects and from patients with atypical parkinsonism, and these findings also correlate with the severity of disease. Proton magnetic resonance spectroscopy has also been reported to differentiate between PD and other parkinsonian conditions.

All of these imaging modalities are costly, and some of them are not widely available. Before any can be recommended for routine diagnostic use, their relative advantages and disadvantages must be clarified. Studies based on autopsy-confirmed diagnoses will also be important. If future research confirms and extends the present results, neuroimaging studies have the potential to play a fundamental role in the diagnosis of PD.

PROPOSED CLINICAL DIAGNOSTIC CRITERIA

Several conclusions emerge from the preceding review. First, no individual clinical feature has sufficient sensitivity and specificity to serve as the sole basis for distinguishing PD from other diseases with parkinsonian features. Criteria based on combinations of clinical features improve diagnostic accuracy, but no criteria proposed to date have achieved a high enough positive predictive value to eliminate the need for autopsy confirmation.[63] Second, although no single clinical feature is completely reliable for differentiating PD from other conditions, some features are more useful than others.

Third, there is almost always a trade-off between sensitivity and specificity, so at least 2 different levels of diagnostic confidence should be included in the classification. These different levels are commonly designated Definite, Probable, and Possible. For some purposes, such as certain therapeutic trials, maximum diagnostic specificity is required and lower sensitivity is acceptable, so patients meeting the most restrictive criteria are preferred. For other purposes, such as epidemiologic studies or therapeutic trials in early stages of the disease, it is appropriate to sacrifice some specificity and use the more inclusive Possible criteria.

Fourth, the opportunity for diagnostic confusion is greatest early in the clinical course when some of the more distinctive clinical features may not yet have developed.[7,59] Thus, to increase specificity, the clinical diagnosis of PD should be regarded as preliminary until parkinsonian symptoms have been present for a substantial period of time to ensure that patients do not develop features suggestive of alternative diagnoses.

These 4 conclusions provide the rationale for the proposed diagnostic classification scheme shown in **Table 1** and **Table 2**. Patient diagnoses are classified as Probable when the patients have clinical features that are absolutely typical of PD, at least 3 years of parkinsonian symptoms without the development of atypical features, and a clear clinical response to dopaminergic treatment. The criteria for Possible PD are less strict: patients are not required to have as many typical features of PD, symptom duration can be less than 3 years, and patients need not have received an adequate trial of dopaminergic therapy. A recent analysis of a large clinical

Table 1. Grouping of Clinical Features According to Diagnostic Utility

Group A features: characteristic of Parkinson disease
Resting tremor
Bradykinesia
Rigidity
Asymmetric onset
Group B features: suggestive of alternative diagnoses
Features unusual early in the clinical course
Prominent postural instability in the first 3 years after symptom onset
Freezing phenomena in the first 3 years
Hallucinations unrelated to medications in the first 3 years
Dementia preceding motor symptoms or in the first year
Supranuclear gaze palsy (other than restriction of upward gaze) or slowing of vertical saccades
Severe, symptomatic dysautonomia unrelated to medications
Documentation of a condition known to produce parkinsonism and plausibly connected to the patient's symptoms (such as suitably located focal brain lesions or neuroleptic use within the past 6 months)

Table 2. Proposed Diagnostic Criteria for Parkinson Disease

Criteria for POSSIBLE diagnosis of Parkinson disease:
At least 2 of the 4 features in Group A* are present; at least 1 of these is tremor or bradykinesia
and
Either None of the features in Group B* is present
Or Symptoms have been present for less than 3 years, and none of the features in Group B* is present to date
and
Either Substantial and sustained response to levodopa or a dopamine agonist has been documented
Or Patient has not had an adequate trial of levodopa or dopamine agonist
Criteria for PROBABLE diagnosis of Parkinson disease:
At least 3 of the 4 features in Group A* are present
and
None of the features in Group B* is present (note: symptom duration of at least 3 years is necessary to meet this requirement)
and
Substantial and sustained response to levodopa or a dopamine agonist has been documented
Criteria for DEFINITE diagnosis of Parkinson disease:
All criteria for POSSIBLE Parkinson disease are met
and
Histopathologic confirmation of the diagnosis is obtained at autopsy (see Table 3)

**Group A and Group B are detailed in Table 1.*

Table 3. Proposed Criteria for Histopathologic Confirmation of Parkinson Disease

Substantial nerve cell depletion with accompanying gliosis in the substantia nigra
At least 1 Lewy body in the substantia nigra or in the locus ceruleus (note: it may be necessary to examine up to 4 nonoverlapping sections in each of these areas before concluding that Lewy bodies are absent)
No pathologic evidence for other diseases that produce parkinsonism (eg, progressive supranuclear palsy, multiple system atrophy, cortical-basal ganglionic degeneration) (note: in excluding other diseases that produce parkinsonism, published consensus criteria should be used when available[65])

trial involving patients with early PD suggests that roughly 90% of patients who meet criteria for Possible PD will ultimately qualify for the diagnosis of Probable PD.[64]

No patient who has failed to respond to an adequate trial of dopaminergic therapy meets criteria for either Probable or Possible PD. All patients who meet the criteria for Probable PD also satisfy the requirements for Possible PD. Patients in either category who have autopsy findings consistent with PD (**Table 3**) are designated as Definite. Thus, neuropathologic examination remains an absolute requirement for the diagnosis of PD in patients with typical clinical features.

NEUROPATHOLOGIC DIAGNOSIS OF PD

The absence of a completely reliable clinical marker for PD makes neuropathologic confirmation essential in evaluating the diagnostic utility of clinical features or combinations of features. Classically, the neuropathologic features of PD are relatively straightforward: the substantia nigra reveals neuronal loss and Lewy bodies. Lewy bodies are also usually present in the locus ceruleus, nucleus basalis of Meynert, dorsal motor nucleus of the vagus, and hypothalamus, and often at other sites of predilection. In patients with typical clinical features and these pathologic findings, the diagnosis is clear.

The neuropathologic findings are sometimes ambiguous or conflicting, however, and the specificity and sensitivity of individual pathologic features are not known. For example, some patients have typical clinical features and neuronal loss in the substantia nigra but no Lewy bodies. Conversely, some patients have Lewy bodies without neuronal degeneration or even clinical abnormalities. Indeed, the incidence of Lewy bodies in the brains of asymptomatic individuals increases with advancing age, raising the question of whether Lewy bodies are markers for presymptomatic PD or a feature of normal aging.[1,66,67] Lewy bodies also occur in 10% to 40% of individuals with Alzheimer disease, motor neuron disease, subacute sclerosing panencephalitis, ataxia telangiectasia, CBGD, and Hallervorden-Spatz disease,[66-68] suggesting that Lewy bodies may not represent specific underlying pathophysiological mechanisms. Similarly, many parkinsonian patients with Lewy bodies also have pathologic findings of Alzheimer disease (neuritic plaques and neurofibrillary tangles).[10,30,67,68]

The importance of the distribution of Lewy bodies is also unclear. Some reports have described Lewy bodies in the neocortex of all or nearly all patients with PD,[8,69] suggesting that there may be a continuum ranging from patients with relatively pure neocortical involvement to patients with primarily brainstem Lewy bodies, rather than a strict distinction between PD and DLB. Samuel et al[70] found a correlation between the degree of dementia and the extent of neocortical Lewy bodies, although other authors[9,46,71] have described patients with PD and demen-

tia who had little or no cortical abnormality (ie, few if any cortical Lewy bodies, plaques, or tangles).

In light of these unresolved issues, there are no universally accepted histopathologic criteria for the diagnosis of PD. The criteria presented in Table 3 are consistent with the criteria typically used in published clinicopathologic series. In particular, the presence of even a single Lewy body in the substantia nigra or locus ceruleus is regarded as important in patients with typical clinical features of PD. Indeed, Lewy bodies are uncommon enough in asymptomatic people to justify the suspicion that these individuals may have had early PD and died before they became symptomatic. In contrast, the implications of cortical Lewy bodies are poorly understood, so although their density and distribution should be recorded, they do not influence the diagnosis of PD in patients with typical clinical features and brainstem histopathologic abnormality.

TOPICS FOR FURTHER STUDY

The clinical diagnostic criteria proposed here will need to be validated in future clinicopathologic studies. These studies can also be used to refine the criteria empirically. For example, it might be appropriate to weigh some clinical features more heavily than others, or it could be helpful to consider the severity of some clinical features rather than just their presence or absence. Inclusion of radiologic findings could add considerable diagnostic power. Some of the features that preclude the diagnosis of Definite PD, such as the failure to respond to an adequate trial of dopaminergic treatment or the presence of hallucinations early in the course, may require modification if enough patients are found to have these features together with otherwise typical clinical and pathologic findings of PD. These issues should be addressed systematically by prospectively identifying a broad range of clinical findings and assessing them consistently in patients recruited from diverse clinical settings. Neuropathologic examinations also should be conducted in a standardized fashion with as few preconceived notions as possible. To determine the importance of cortical Lewy bodies, for example, they should be analyzed routinely in a large group of patients presenting with either parkinsonism or cognitive impairment or both, and the results should be correlated with information on cognitive and motor function collected systematically throughout the clinical course.

An inherent limitation of clinicopathologic studies is that the pathologic information is typically obtained after the disease has reached advanced stages. Clinical examinations are often technically difficult in patients with advanced disease, limiting the reliability of clinicopathologic correlation. Moreover, a variety of different disease processes may converge in advanced stages to produce similar clinical phenotypes. This limitation is surmounted by some of the new neuroimaging techniques that permit clinical-anatomical correlation at earlier stages of the disease. Even so, the interpretation of these studies will be difficult until the neuroimaging results have been evaluated in patients who have come to postmortem examination.

There is no doubt that the diagnostic criteria proposed here ultimately will be revised. In the meantime, there is an immediate need for plausible, straightforward, standard criteria for use in clinical research. The criteria proposed here, based on a thorough review of currently available information, are intended to serve this purpose.

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Reprints: Sid Gilman, MD, Professor and Chair, Department of Neurology, University of Michigan Medical Center, 1500 E Medical Center Dr, Ann Arbor, MI 48109-0316.

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