Article abstract—To determine the prevalence of depression in Parkinson disease (PD) we evaluated 55 consecutive patients without dementia and 31 of their spouses. All subjects completed the Beck depression inventory and a quantitative mini-mental state examination. Using the Beck criteria, 47% of the patients and 12% of the spouses rated themselves as significantly depressed. Mental state scores were significantly lower in the patients. There was a correlation between the severity of depression and cognitive impairment, particularly for calculation, digit span, and visuomotor skills. The severity of parkinsonism, particularly bradykinesia, also paralleled cognition. There was a slight but significant relationship between parkinsonism and depression. These results confirm the high incidence of depression in PD, and suggest that depression in Parkinson patients may be accompanied by mild intellectual impairment and inattention which is independent of the severity of the illness.

Depression, intellectual impairment, and Parkinson disease

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Patients with Parkinson disease (PD) are often depressed,[1-7] but depression has not been consistently related to any specific aspect of the disorder. While attempting to determine the prevalence of depression and its relationship to PD, we found that depression was often accompanied by intellectual impairment. The pattern and degree of intellectual impairment did not warrant a clinical diagnosis of dementia, particularly if criteria for dementia were strict. Benson[8] considers dementia an acquired or persistent loss of intellectual function including some or all of the following mental activities: language, memory, perception, cognition, and emotionality. Dementia is, however, frequently encountered in PD[4,9,10] and seems to affect older individuals with more rapidly progressive PD that is likely to resist therapy.[10] In contrast, our patients with PD and depression were generally younger, and had a typical slow progression of PD that usually responded to anticholinergic or dopaminergic therapy.

These preliminary observations led us to investigate the prevalence of depression in PD and the frequency of intellectual impairment. We sought to determine whether depression was related to any aspect of PD or whether it was associated with other demographic characteristics of the patients.

Methods. *Subject selection.* Fifty-five consecutive adults with PD were assembled. Patients with overt clinical signs of dementia, i.e., a severe impairment of cognition, memory, and perception, were excluded. Drug therapy had been stable for at least 1 month before the study. Thirty-one of 34 available spouses of these patients served as controls. Three spouses refused to participate in the study. None of the spouses had a history or clinical signs of any neurologic disorder. A standard form completed on each subject included age, education, marital status, occupation, economic state, medical history, and psychiatric history (table 1). All subjects gave informed consent.

Procedures. Neuropsychologic and psychiatric evaluations for depression were carried out in a single 1½-hour session. On the same day, the subjects were assessed neurologically.

Neuropsychologic assessment. Tests were performed in a quiet, well-illuminated room. A modified version of the mini-mental state examination (MMS)[11] was used. The examination was lengthened to include digit-span (forwards and backwards), recall of the present and four previous presidents of the United States, confrontation-naming of 10 picture objects selected from the Boston Naming test,[12] an additional sentence for

Table 1. Subject demographics

	Adults with Parkinson disease	Spouses
Number	55	31
Sex: M	43	6
F	12	25
Mean age (± SD)	67.5 (8.7)	64.8 (8.8)
Years of education, mean (± SD)	12.5 (4.6)	12.08 (3.8)
Previous history of depression or other psychopathology	11	1

Table 2. Profile of Parkinson disease subjects

	Mean (± SD)	No.
Duration of illness	9.0 (9.7)	55
PDE score		
Total	29.0 (17.8)	55
Tremor	2.3 (3.2)	
Rigidity	5.2 (3.8)	
Bradykinesia	1.2 (1.0)	
% ADL	67.0 (23.3)	
Levodopa utilized (gm/day)	2.77 (1.9)	47
Anticholinergic utilized	*	24
Tricyclic antidepressant (mg/day)	42.0 (25.1)	10
Amitriptyline No. = 9		
Imipramine No. = 1		

* The extreme variability in type of anticholinergic utilized precluded grouping for statistical analysis.
PDE = Parkinson diseases evaluation.
ADL = Independence in activities of daily living.

repetition, and copying of two pictures (a circle with adjacent triangle and a cube). These modifications were chosen to broaden evaluation of language, memory, attention, and praxis skills in a brief interview. Results of the original mini-mental state examination relate well to more extensive intellectual assessments such as the Wechsler Adult Intelligence Scale.[11,13] Tasks were not timed, and 57 points was the maximum score. A total of 25 or greater was required to continue in the study. Four subjects did not meet this criterion, and are not included in the 55 subjects discussed.

Psychiatric assessment. After the MMS was completed, the subject was given the Beck Depression Inventory (BDI)[14] using the format suggested by the author. The reliability of this assessment has been established.[14,15] A BDI score of 10 or more was considered to reflect significant depression,[16] and severity of depression was determined in the following manner: mild (BDI = 10-17), moderate (BDI = 18-24), severe (BDI = 25-30).[15] Later subjects were interviewed and asked if they were currently depressed, had ever been depressed, or treated by a psychiatrist for depression. A "yes" response was acknowledged by us only when the subject reported a sustained depressive mood for at least 1 week.

Neurologic assessment. Each subject in the PD group was interviewed and examined by the same neurologist. A standard form included duration of illness, medications, and independence in activities of daily living (ADL).[17] Levodopa and carbidopa/levodopa combinations were recorded in grams of levodopa, with the carbidopa/levodopa combination calculated by multiplying the daily levodopa dosage by 4. A Parkinson disease evaluation (PDE) form rating signs and symptoms from 0 to 4 was completed, with 0 indicating the absence of a symptom and 4 indicating the highest severity. The PDE rated such factors as tremor, rigidity, bradykinesia, finger and foot agility, posture, postural stability, and gait disturbance. This assessment was similar to that of Lesser et al.[18]

Table 2 indicates the profile of the patients participating in the study.

Controls were also examined neurologically to ensure absence of neurologic disorder.

Results. *Depression survey.* The mean BDI score for the PD group was 11.1 (SD ± 6.4) compared to 6.2 (SD ± 4.2) for the spouses; the difference was significant (t = 4.22, p = 0.0001). Of the PD patients, 47.2% were deemed depressed, as were 12.9% of the spouses. The severity of depression in the patients was mild, although 35% did report moderate to severe depression as noted in table 3.

The BDI scores concurred with each patient's perception of his or her emotional state, as the mean BDI for the PD patients who acknowledged depression in the posttest interview was 14.6 (SD ± 6.7) compared to 9.1 (SD ± 5.3) for those who did not.

Parkinson disease evaluation. The severity of PD was determined by the sum of the scores of the signs and symptoms from the PDE. There was a small but significant negative correlation between the BDI and PDE scores, but other factors (such as duration of illness, percent of ADL, and medications utilized) did not correlate with depression. Nine of the 55 PD subjects were taking amitriptyline, and 1 imipramine, at the time of the investigation. These patients had significantly lower BDI scores (t = 3.52, p = 0.001). Since this could confound or weaken any relationship between PD-severity and depression, we calculated the results without these 10 subjects; the correlation between PDE and BDI was no longer significant.

Neuropsychologic tests. The mean MMS score for the patients was 46.9 (SD ± 7.4) and 52.3 (SD

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Table 3. Prevalence and severity of depression in Parkinson disease (PD) and spouse (SP) groups as measured by Beck Depression Inventory (BDI)

BDI	PD (No. 55)		SP (No. 31)	
	No.	%	No.	%
Mild	17	30.9	4	12.9
Moderate	7	12.7	0	0
Severe	2	3.6	0	0
Totals	26	47.2%	4	12.9%

± 4.3) for the spouses; this difference was significant (t = 4.17, p = 0.0001). A significant negative correlation between MMS score and BDI (r = −0.329, p = 0.02) existed in the patients (figure 1). That is, as severity of depression increased, performance on some tests of mental function diminished. Some items on the MMS varied as a function of the BDI, specifically calculations (r = −0.41, p = 0.002), constructions, reverse digit span, and recall of presidents (in each of the last three measures r = −0.3, p = 0.02). In addition, failure to repeat words for recall on the first attempt correlated with higher BDI scores (r = −0.26, p = 0.05) while recall of the words did not, indicating a possible defect of attention. These relationships did not exist in the spouses because of their generally lower and restricted BDI scores.

The severity of PD, as judged by the PDE score, also correlated significantly with MMS (r = −0.426, p = 0.002), suggesting that intellectual function was impaired as the severity of PD increased (figure 2). PDE was subdivided into specific components, but only rigidity and bradykinesia correlated significantly with MMS (r = −0.403, p = 0.002 and r = −0.436, p = 0.002, respectively) as noted in table 4. In addition to severity of PD and depression, age and education influenced MMS scores of the patients (r = −0.327, p = 0.02 and r = 0.360, p = 0.02, respectively). Similarly, age and education influenced performance in the spouses (r = −0.49, p = 0.005 and r = 0.46, p = 0.02 respectively). To determine the extent of the unique relationship between depression and intellectual impairment in the PD group, a stepwise multiple regression[19] was performed to partial out variability attributed to age, education, and PD severity. The relationship between depression and intellectual impairment remained significant (F = 4.71, p = 0.04).

Discussion. James Parkinson[20] recognized depression, referring to the patient as an "unhappy sufferer" and noting the "wished-for release" or death. He cited a dramatic example: "Dr. Maty first saw the patient, and gives the following description of his situation. 'A more melancholy object I never beheld. The patient, naturally a handsome, middle-sized, sanguine man, of cheerful disposition, and an active mind, appeared much emaciated, stooping, and dejected.'"

Subsequent investigators observed depression in 37%[4] to 90%.[2] The higher figure has been criticized because these parkinsonian patients were being treated specifically for psychiatric problems.[3] Some investigators used standardized depression rating scales,[2,3,5,7] while others recorded only subjective feelings.[1,4] Nevertheless, depression is important in PD, as noted in the present investigation. The severity of depression varies, but is usually considered "mild."[1,4] Of our depressed PD patients 65% had only mild symptoms, but 35% reported moderate to severe depression.

Depression has been inconsistently related to sex of the patient,[1,4] degree of disability,[2,6] or levodopa therapy.[21-23] Other investigations have found no relationship between these factors and depression.[3,5,7] Paradoxically, levodopa has been implicated as the cause of depression, as causing an exacerbation of depression in patients who were depressed before the onset of PD,[6,24] and as having antidepressant effects.[4,25] The latter point is controversial,[6,26] and we found no relationship between levodopa and depression. Depression in PD has often been considered a realistic reaction to a progressive crippling illness,[27] but when equally disabled patients with other medical diseases were used for comparison, the prevalence of depression in PD was always significantly higher.[1,3,5,7] Endogenous depression might be considered because there is no relationship to the severity of PD and because we found that 43% of our depressed parkinsonian patients were depressed before the clinical onset of PD. Reduction of brain monoamines has also been considered a factor in the depression of PD.[3,4,7] The content of metabolites of norepinephrine (NE) and serotonin (5-HT) are decreased in primary depressive disorders,[28] and NE and 5-HT are also reduced in PD;[29] the significance of these changes in PD is uncertain.

We found a significant relationship between depression in PD and impaired intellectual function, especially for calculation, digit span, constructions, and repetition of words for recall. Age, education, and severity of PD were all factors associated with impaired cognitive skills, but depression was independently and significantly linked to cognitive disturbance in PD. Mindham and co-workers[6] did not find such a relationship between depression and intellect in PD, but they concluded that their assessment of this relationship was incomplete.

Ten subjects in this study were being treated for depression. These patients were less depressed and less disabled from PD, but because of the small number of patients involved we could not deter-
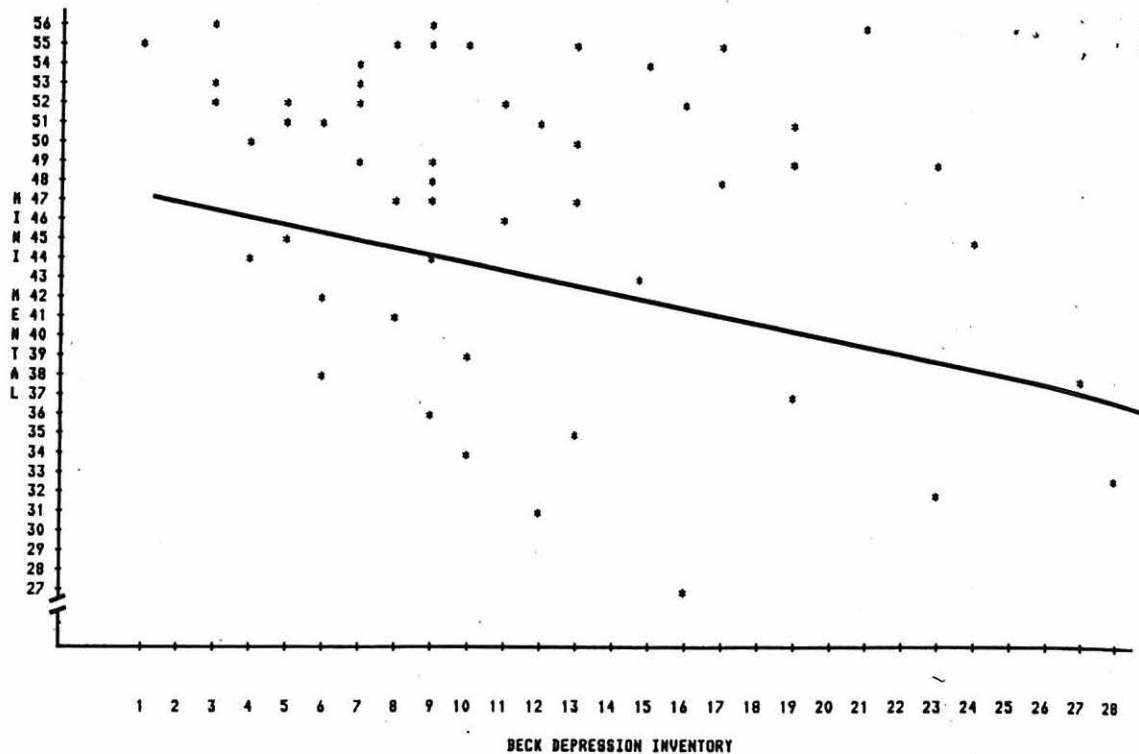
Figure 1. Correlation between mini-mental status and Beck Depression Inventory (r = −0.329, p = 0.02).

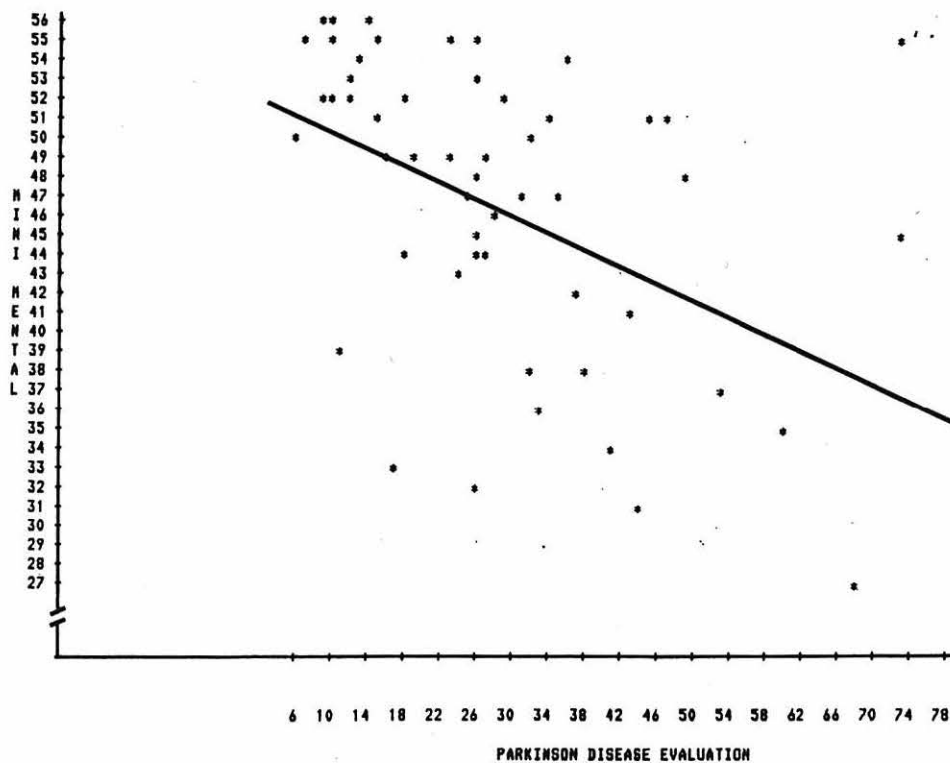*Figure 2. Correlation between mini-mental status and severity of Parkinson disease (r = −0.426, p = 0.002).*

Table 4. Variables correlating with mini-mental status (MMS)

	r	p
BDI	−0.329	0.02
PDE	−0.426	0.002
Rigidity	−0.403	0.002
Bradykinesia	−0.436	0.002
Eduation	0.360	0.02
Age	−0.327	0.02

BDI = Beck Depression Inventory.
PDE = Parkinson disease evaluation.

mine whether this had a significant effect on mental function.

The combination of depression and cognitive impairment in PD might represent "dementia syndrome with depression."[30] Memory, perception, and attention may be impaired in primary depressive disorders.[13,30-32] The severity of this impairment in primary depression may be minimal or severe, and it is usually reversed by appropriate antidepressant therapy.[13,30] Many patients have a history of recurrent depression or mania and may have a family history of bipolar affect disorders before the onset of dementia. Eleven of our depressed subjects with PD had a history of depression before the onset of parkinsonian symptoms, but none had a history of mania or a family history of psychopathology. McHugh and Folstein[13] found the dementia syndrome of primary depression was abrupt in onset and became more severe within a few weeks. In our patients with PD, the onset of depression was usually gradual and subtle, and our screening procedure, inquiring about possible signs or symptoms of dementia, should have excluded any subject with abrupt onset of intellectual disorder. The intellectual impairment we observed correlated with depression but a causal relationship could not be established because several other factors (such as age, education, and severity of PD) contributed independently.

In progressive supranuclear palsy (PSP), Albert and associates[33] described "subcortical dementia," characterized by memory impairment, slowness of thought, apathy or depression, and difficulty in manipulating knowledge. The lack of aphasia, apraxia, and agnosia distinguished subcortical dementia from cortical dementias such as Alzheimer disease. Later, Albert[34] and Marsden[35] suggested that subcortical dementia might also exist in Huntington disease, Korsakoff syndrome, and PD. In none of our depressed PD patients did we find altered language, praxis, or recognition to suggest focal cortical dysfunction. The concept of subcortical dementia has been debated because neuronal degeneration is found in some patients

with PD and intellectual impairment, affecting both cortical and subcortical structures.[36] Morphologic signs of Alzheimer disease may also be found in demented patients with PD,[37-39] but it is not known whether depression was present in these patients and the pattern of dementia has not been described in these retrospective studies. Lieberman et al[10] found depression in both their demented and nondemented patients with PD but concluded that depression was not a prelude to dementia, as did Boller et al;[39] neither group defined criteria for depression.

It appears that there may be two types of intellectual impairment associated with PD. About 30% of patients develop a global dementia probably due to coexistence of Alzheimer disease and PD with cortical and subcortical pathology. The current study suggests that another 50% of patients may develop a mood disorder accompanied by impaired cognitive skills and inattention, but not a global dementia.

Loss of dopamine and the degenerative changes within substantia nigra and locus ceruleus cannot fully account for the depression and mild cognitive changes we found, because not all of the parkinsonian patients were affected.

An alternative hypothesis might consider the neuronal loss and Lewy body formation found in the hypothalamus, particularly in the nondopaminergic pathways of the tuberomamillary, posterior, and lateral nuclei.[40] Several functions are attributed to the tuberal and posterolateral hypothalamus (including maintenance of consciousness, integration of higher mental functions such as memory, cognition, emotional expression, and sexual behavior).[41] Plum and Van Uitert[41] noted that chronic diseases of the hypothalamus characteristically advance slowly, sparing some anatomic regions, and not causing clinically overt autonomic or endocrine disorders. Endocrine studies in PD have revealed abnormal glucose metabolism,[42] impaired sexual function,[43] and impaired release of growth hormone,[44] implicating a hypothalamic abnormality. Thermoregulation is also impaired in PD.[45,46] Whether degenerative changes in the brainstem and hypothalamus with resultant loss of central monoamines produces or predisposes the individual to depression in PD remains to be determined.

Acknowledgments

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