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DEMENTIA IN LONG-TERM PARKINSON'S DISEASE PATIENTS RECEIVING CHRONIC LEVODOPA THERAPY

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DECLARATION

I declare that this dissertation is my own work and has not been submitted to any other university.



DENICE BASNETT

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ABSTRACT

The present study investigated the hypothesis that two subgroups of Parkinson's Disease patients may exist: those susceptible to dementia and those resistant to dementia. The sample comprised 43 white patients (26 males and 17 females), all receiving levodopa therapy. Cognitive functioning was assessed using subtests from the WAIS and abbreviated scales from Luria's Neuropsychological Investigation. Three cognitive components, namely general intellectual functioning, memory span and linguistic skills, emerged from a principal component analysis of the test scores. Unidimensional and multidimensional cluster analytic investigations of the component scores failed to demonstrate the existence of patient subgroups. The cognitive functioning of the patient sample was characterised by a continuous distribution with the demented patients representing the severely impaired extreme. The influence of five patient variables on cognitive functioning in Parkinson's Disease was examined using stepwise multiple regression analyses. Present age, age at onset, duration of illness, depression and sex acted as predictor variables. The three time-related variables emerged as important determinants of dementia but, because of their high intercorrelation, their individual influences were difficult to establish. The influences of depression and sex proved to be negligible. The findings of the present study were reviewed against the background of recent histopathological evidence of the involvement of both subcortical and cortical brain structures in the Parkinson's Disease process.

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"Pavlov, when discussing the question of a 'respiratory centre', was compelled to recognise that, 'whereas at the beginning we thought that this was something the size of a pinhead in the medulla...now it has proved to be extremely elusive, climbing up into the brain and down into the spinal cord, and at present nobody can draw its boundaries at all accurately'."

From Luria's "Working Brain" (1973, p.30)

CHAPTER 1

INTRODUCTION

Over 170 years have past since James Parkinson first described the "shaking palsy" which was later to bear his name. Yet it is only over the last 15 years that significant strides have been made towards understanding the highly complex nature of Parkinson's Disease. The advent of levodopa in the late 1960's provided the spark for sustained and intensive research. Designed to monitor the therapeutic value of the drug, levodopa research inevitably uncovered new knowledge of the disease process itself.

Levodopa proved to be a "wonder drug" (Beardsley & Puletti, 1971) and today is widely accepted as the treatment of choice for Parkinson's Disease. As the immediate precursor of dopamine - the neurotransmitter deficient in Parkinson sufferers - levodopa provides an excellent clinical model of pharmacological replacement therapy (Whitehouse, Hedreen, White & Price, 1983). By providing dopamine replenishment, levodopa has proved to effectively alleviate the motor disorder associated with Parkinson's Disease and appreciably improve the quality of life of sufferers. But levodopa has failed to provide a cure.

Parkinson's Disease manifests primarily as a motor disorder with diagnosis established on the basis of characteristic motor symptomotology. But now attention has become focussed on cognitive impairment, a symptom that clinicians have long observed to be prevalent among Parkinson sufferers

and which is sufficiently severe in some cases to manifest as dementia. Whether or not a dementing process forms part of the clinical picture of Parkinson's Disease has continued to be an issue of some controversy.

It has been established that those extrapyramidal structures involved in the disease pathology - the nigrostriatal pathway - serve a motor function. Accepting a dementing process as part of Parkinson's Disease means either that these structures play a role in cognitive functioning or that the pathology is more diverse, extending beyond the extrapyramidal system. No longer could Parkinson's Disease be definitively described as a dopamine deficiency syndrome with pathology limited to the basal ganglia.

The concept of "subcortical dementia", as opposed to "cortical dementia", has been proposed as an explanation of dementia in Parkinson's Disease (Heilman & Valenstein, 1979). This supports the view of disrupted dopaminergic connections with subcortical structures as being the causative factors in the dementia. While this view has been adopted by various researchers (Marttila & Rinne, 1976; Mortimer, Pirozzolo, Hansch & Webster, 1982), others have disputed that subcortical dementia exists as a clinical entity (Mayeux, Stern, Rosen & Benson, 1983; Whitehouse et al., 1983).

Establishing the localization of higher mental functions continues to be a relatively elusive task for brain research, but historically "higher mental functions" have been synonymous with "higher cortical functions". With hindsight, it is difficult to understand why more serious attention was not afforded to the findings of Alvord and his associates who, as early as 1965, found that a common feature of Parkinsonian brains at post-mortem was diffuse cortical atrophy (Pollanen & Hubbrook, 1966). This atrophy takes the form of neurofibrillary tangles and

senile plaques, *strongly* suggestive of Alzheimer's Disease (Boller, Mizutani, Roessman & Gambetti, 1980). It has been suggested that Parkinson's Disease and Alzheimer's Disease coexist in demented Parkinson patients and this would provide the neuropathological basis for the Parkinson dementia. Clinically, an overlap between dementia and parkinsonism is well-known. Drachman and Stahl (1975) described dementia and parkinsonism as being two ends of a continuum rather than two distinct entities. However, a neuropathological explanation for the overlap was still to be found.

Perhaps the most exciting research finding in this regard is the recent implication of another neurotransmitter, acetylcholine, in the Parkinson's Disease process. The diminished cortical activity of acetylcholine, seemingly as a result of a degenerative process which begins at a subcortical level, effectively provides a link between the cognitive and motor disorders of Parkinson's Disease (Whitehouse et al., 1983). One disease process could be responsible for both the motor and cognitive aspects of the disease rather than two disease processes, namely Parkinson's Disease and Alzheimer's Disease, coexisting in certain patients.

But not all Parkinson sufferers become demented and not all Parkinsonian brains show evidence of cortical atrophy. Parkinson's Disease is known to be extremely variable. Lavy, Melamed, Cooper, Bentin & Rinot (1979) described Parkinson's Disease as a complex of several processes rather than a single disease entity. Riklan (1972, p.44) stated that Parkinson's Disease is "not a unitary or homogeneous disease but involves an extremely wide variety of both neurological and behavioural signs in different patients". Could subgroups of sufferers possibly exist?

The idea of patient subgroups is not new. Observations within the treatment situation often leaves the clinician

with the impression of a relatively non-deteriorating subgroup of sufferers. Pollack& Hornabrook (1966) refer to "stationary" forms of the disease evident in patients whose illness does not progress with the same severity as other sufferers. Rinne (1978) talks of "benign" and "malignant" forms of the same disease process.

Research has provided empirical support for these theoretical views. Garron, Klawans and Narin (1972) identified two groups of sufferers who differed in intellectual functioning attributable to different ages of symptom onset. These results were echoed in the findings of Lieberman, Dziatolowski, Kupersmith, Serby, Goodgold, Korein and Goldstein (1979). Sweet, McDowell, Feigenson, Loranger and Goodell (1976) gathered results which supported the possible existence of two Parkinson's Disease processes: Lewy bodies disease confined to subcortical areas and Alzheimer neurofibrillary tangles disease involving cortical areas as well. Boller et al. (1980) also suggest, on the basis of clinical and pathological evidence, the existence of two different disease processes: Parkinson's Disease with dementia and Parkinson's Disease without dementia. Mortimer, Pirozzolo, Hansch and Webster (1982) divided sufferers into two groups based on the presence or absence of dementia in relation to certain motor symptomotology.

In contrast to these findings, Pirozzolo, Hansch, Mortimer, Webster and Kuskowski (1982) carried out a particularly extensive neuropsychological study. They found that, with regard to intellectual functioning, Parkinson sufferers form a homogeneous group. Test scores showed no evidance of bimodality but rather showed patients' functioning to fall along a continuum, from the intact to the severely impaired.

The present study has been undertaken in an effort to clarify the discrepant data available on the cognitive

impairment in Parkinson's Disease sufferers. Encouraged by the clinical experience of the staff of the Parkinson's Disease Clinic at the Johannesburg General Hospital, our objective was to investigate the possible heterogeneous nature of the Parkinson group of sufferers.

It was hypothesised that two subgroups of sufferers exist: those susceptible to dementia and those resistant to dementia. Our task was to distinguish one group from the other on the basis of demographic data. Being able to "predict" dementia by identifying a vulnerable group, would not only increase our understanding of the Parkinson dementia but would also assist in the forward planning of patient management. Most importantly, it could presage alternative or additional treatment regimens.

CHAPTER 2

THE NEUROPATHOLOGY OF PARKINSON'S DISEASE

Parkinson's Disease (PD) is a progressive degenerative disease of the central nervous system. Onset of the disease generally occurs in late middle age (50-60 years) but may occur later. The disease is of unknown etiology but several theories have been postulated. Slow virus infections (Rinne, 1978), heavy metal intoxications (Heilman & Valenstein, 1979), an autoimmune response (Abramsky & Litvin, 1978), an aggravated aging process (Mann & Yates, 1982) and a genetic component (Martin, Young & Anderson, 1973) have all been proposed as being pathogenic factors.

Clinically, patients present with certain motor symptomotology which provides the basis for diagnosis. These symptoms are tremor, rigidity, bradykinesia and a gait disorder (Draper, 1980; Lieberman, 1974). Cognitive impairment and depressed affect are associated symptoms but are seldomly diagnostically relevant.

Neuropathologically, the disease is characterised by lesions of the basal ganglia. The degenerative process results in a loss of pigmented neurons in the pars compacta of the substantia nigra with similar changes occurring in the locus ceruleus and the dorsal motor nucleus of the vagus. To a lesser extent, there is a depletion of small nerve cells in the globus pallidus (Pearce, 1978). Lewy bodies are characteristically found spread throughout these areas but are particularly evident in the substantia nigra and locus ceruleus (Hakim & Mathieson, 1979).

Generalised cerebral atrophy has been found to occur in a disproportionate number of PD sufferers (Pearce, 1978). The atrophy takes the form of senile plaques, neurofibrillary tangles, granulovacuolar degeneration in the hippocampus and neocortical cell loss (Hakim & Mathieson, 1979). These histologic features are indistinguishable from Alzheimer's Disease (AD), the dominant disorder producing dementia in the elderly (Terry & Katzman, 1983).

Biochemically, PD is characterised by a deficiency of the neurotransmitter, dopamine, and its metabolic end-product, homovanillic acid (Markham, Treciokas & Diamond, 1974). The nigrostriatal fibre system is the largest single dopamine-containing pathway in the human brain. The cell bodies are imbedded in the pars compacta of the substantia nigra with axons projecting at the caudate nucleus and putamen (Abramsky & Litvin, 1978). The well-documented clinical success of levodopa, the dopamine precursor substance, suggests pathology only at a presynaptic level but pharmacological investigations indicate post-synaptic impairment as well (Abramsky & Litvin, 1978; Rinne, 1978). It remains possible that the loss of dopamine could result from a primary defect in its metabolism rather than necessarily result from the degeneration of dopamine producing cells (Yahr, 1977). While a dopamine deficiency has now been undeniably established as the major biochemical correlate of the motor symptomotology of PD, so much of dopamine's complex activity still remains hypothetical.

Other neurotransmitters have been investigated in relation to the PD process. Gamma-aminobutyric acid, noradrenaline, serotonin, peptidergic neurons and monoamine oxidases are all reduced in Parkinson patients. Their role, if any, in the pathology of the disease remains uncertain but their activity is more likely to be secondary than primary to the disease process (Pearce, 1978; Rinne, 1978).

One neurotransmitter which new evidence is increasingly implicating is acetylcholine. The striatum contains an abundance of cholinergic neurons. The activity of acetylcholinesterase (in the presence of which acetylcholine is broken down) in the substantia nigra suggests the possibility of cholinergic striatal or pallidal projections in the substantia nigra (Iversen & Iversen, 1975). While the striatal dopaminergic system serves an inhibitory function, the striatal cholinergic system serves an excitatory function (Abramsky & Litvin, 1978). Research studies suggest that dopamine and acetylcholine operate in a delicately balanced system to control certain aspects of behaviour (Iversen & Iversen, 197· and this balance is achieved by the activity of these two neurotransmitters existing in a specific ratio with one another. Once the balance of activity is disturbed, dysfunction of the basal ganglia results in the Parkinson condition (Abramsky & Litvin, 1978). Dopaminergic activity is reduced and cholinergic dominance occurs. Pearce (1978) postulates that when dopaminergic neurons fail and abandon the receptors in the striatum, cholinergic neurons sprout to take their place resulting in a further increase in the striatal cholinergic system. This would explain why anticholinergic agents have had some therapeutic success in PD.

Besides the cortical atrophy mentioned earlier, other neuropathological and biochemical features are shared by PD and AD. All PD patients show a dopamine deficiency in the basal ganglia but some patients with PD also show cholinergic deficiencies in the cortex reminiscent of AD (Whitehouse et al., 1983). The loss of cholinergic neurons in the basal forebrain, and in particular the nucleus basalis of Meynert, has been demonstrated in AD. "The loss of neurons in the nucleus basalis of Meynert is the principal pathological substrate of the consistently demonstrated loss of presynaptic cholinergic markers in

the cortex of Alzheimer sufferers" (Whitehouse et al., 1983, p.245). Now, loss of cholinergic neurons in the nucleus basalis of Meynert has also been established in PD.

The nucleus basalis of Meynert has been implicated in PD for many years. Whitehouse et al. (1983) refer to Lewy's 1913 findings and write: "The original observations of Lewy bodies, the classic intracytoplasmic inclusions almost pathognomonic of idiopathic PD, were made not in the substantia nigra but in the substantia innominata, an area encompassing the nucleus basalis of Meynert" (p.245). Yahr, Wolf, Antunes, Miyoshi and Duffy (1972) also reported Lewy bodies in the innominate (basal) nucleus.

The involvement of the nucleus basalis of Meynert not only effectively provides a morphological basis for the dementia in PD but also provides a neurological link between the subcortical and cortical degeneration in PD. The first evidence of Alzheimer-like changes in demented patients with PD suggested that these patients may have PD with concomitant AD (Hakim & Mathieson, 1979) but it now appears that the same degenerative process may be responsible for nigrostriatal lesions and the cortical atrophy in PD (Mental changes, 1974). It also significantly asserts the diffuse neurological influence of the PD process.

A dementing process must be acknowledged as part of the clinical picture of the PD process but this does not detract from the possibility of a subgroup of sufferers who may be resistant to this dementing process. Also, while the above neurological premise may explain both the cognitive and motor symptoms of the disease it does not account for the associated affective symptomotology, namely depression.

Incidence figures for depression in PD vary from 37% (Celesia & Wanamaker, 1972) to 90% (Mindham, 1970). However, the latter study investigated depression in a hospitalised patient group suffering from "a mental illness" and can hardly be regarded as representative of the PD population. But Markham et al. (1974) also propose a high figure of 76% before treatment. Despite the discrepancies, the incidence of depression has been sufficiently high to arouse research interest.

The major issue with regard to the prevalence of depression in PD sufferers is whether the symptom is an understandable emotional reaction to a severely disabling disease or directly associated with the disease process. Two studies compared depression scores of a Parkinson group with sufferers of other equally disabling conditions. The first (Horn, 1974) included a paraplegic group while the second (Robins, 1976) included a severely physically disabled group, mostly hemiplegic due to cerebrovascular disorder. These control groups are acute patients who, like Parkinson sufferers, have enormous limitations placed on their mode of life by irreversible physical conditions and yet both studies clearly indicated that the Parkinson groups were significantly more depressed.

The Parkinson depression frequently seems to be out of proportion to the neurologic deficit (Mental changes, 1974). Also, reports of depression failing to lift despite improved motor functioning following treatment lend further support to depression in PD being other than reactive (Marsh & Markham, 1973). Depression suffered by PD patients appears unrelated to factors such as length of illness, severity of disability, age or sex (Celesia & Wanamaker, 1972; Horn, 1974; Markham et al., 1974; Robins, 1976) and is seemingly independent of the dementing process (Lieberman et al, 1979; Markham et al., 1974; Mayeux, Stern, Rosen & Leventhal, 1981). This suggests

that the neurological substrates of the affective disorder may be different to those underlying other aspects of the disease.

Mayeux et al. (1981) found a significant relationship (but not necessarily causal) between cognitive impairment (but not dementia) with depression. Again, the possibility of subgroups is proposed. They suggest two types of intellectual impairment accompanying PD: one group (approximately 30% of the patient population) consists of globally demented patients suffering from coexisting PD and AD while a second group (approximately 50%) is made up of patients with a mood disorder and some degree of cognitive impairment but no global dementia. This presumably leaves a third group (20%) who remain intellectually intact.

The pathophysiology of depression in PD remains uncertain. Biochemically, the genesis is unlikely to be attributable to a dopamine deficiency. Depressed patients, other than PD patients, are not generally dopamine deficient (Bunney, 1970) and there remains no clear correlation between dopamine metabolism and depression (Mayeux, 1982). Attention has been given to brain monoamines. Norepinephrine and serotonin are reduced in both patients with depressive disorders and PD patients (Celesia & Wanamaker, 1972; Mayeux et al., 1981; Robins, 1976) but these reduced levels have not been shown to be causal factors.

Mayeux et al. (1981) propose the involvement of the hypothalamus in the depressive condition. The hypothalamus appears to be another site of disease pathology. Neuronal loss and Lewy body formation have been shown to occur, particularly in the nondopaminergic pathways of the tuber-mamillary, posterior and lateral nuclei (Yahr, 1977). This evidence, in conjunction with PD endocrine studies, suggests hypothalamic abnormality. "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" (Mayeux et al., 1981, p.649). When one considers that integration of higher mental functions such as memory and cognition (Mayeux et al., 1981) as well as emotional expression and arousal (Jordaan, Jordaan & Nieuwoudt, 1975) have been attributed to the hypothalamus, the dysfunction of this brain structure in PD must be a possibility.

Additional signs of general brain changes in PD are the involvement of the mesolimbic and mesocortical dopamine systems in the disease pathology (Cicerone, 1982; Rinne, 1978). The disruption of these systems may be a contributing factor in the emotional and intellectual disturbances (Mayeux, 1982) but the lack of conclusive evidence of dopamine involvement in depression provides an argument against this disruption playing a causative role.

Reports of levodopa's effect on depression have been inconsistent. The drug has been known to induce (Mindham, 1970), alleviate (Yahr, Duvoisin, Schear, Barrett & Hoehn, 1969) and have no effect (Beardsley & Puletti, 1971; Marsh & Markham, 1973) on depression. It would appear that in the short-term, levodopa treatment improves depression. Celesia and Wanamaker (1972) showed a drop in the incidence of depression from 37% prior to treatment to 24% after treatment. Significant results were also obtained by Markham et al. (1974), documenting a fall from 76% to 43%. As both studies examined effects over the same period of time (18 months), differences are probably due to the use of different assessment techniques. The trend, however, is similar.

Longer-term studies show an increase in depression. Mayeux et al. (1981) found 47% of patients to be depressed. Forty-three percent of these patients (approximately 20% of the

the total group) were depressed prior to levodopa treatment. More moderate increases, from 22% prior to levodopa to 25% after 6 years of treatment, have been noted (Levodopa: long-term, 1981). In a particularly long-term study, Portin and Rinne (1980) found that depression rose significantly after 8 to 10 years of treatment following little change after 2 to 3 years of treatment. The reason for the increase remains unclear. Riklan, Halgin, Maskin and Weissman (1973) claim that the depression is mainly psychogenic in nature as a result of levodopa failing to cure the disease along with ongoing symptom deterioration. However, it should be remembered that PD patients are significantly more depressed than other equally disabled patients. Levodopa has been shown to displace serotonin from serotonergic neurons and this could provide one biochemical explanation for depression following chronic treatment (Sweet et al., 1976) but leaves unexplained the number of PD patients depressed even before levodopa treatment.

Levodopa provides enormous benefit by significantly alleviating the clinical symptoms of PD sufferers and in so doing appreciably improving their quality of life (Cotzias, Papavasiliou & Gellene, 1969; Rinne, 1978; Yahr et al., 1969). "Levodopa...not only improves the symptoms, but prolongs the period during which patients are physically and socially independent" (Pearce, 1978, p.1666). However, despite levodopa's efficacy, it has failed to provide a cure. The natural course of the disease remains unaltered with the neurological degenerative process continuing unabated (Botez & Barbeau, 1973; Halgin, Riklan & Misiak, 1977; Markham et al., 1974; Yahr, 1977). At autopsy, nigral neurons in various stages of degeneration suggest that the pathological disease process continues during levodopa treatment (Yahr et al., 1972). While PD shortens life expectancy, chronic levodopa treatment lengthens the life span of sufferers by, on average, some 14 years (Levodopa: long-term, 1981).

But while levodopa stabilises the Parkinson clinical state, these desired results are temporally limited. According to Rinne (1978), who presents a particularly thorough review of Parkinson research, levodopa's long-term therapeutic benefits may be summarised as follows:

- during the first 6 months a significant improvement of the Parkinson condition is achieved
- after 2 to 3 years a progressive decrease in overall performance capacity becomes evident
- after 6 years the mean overall disability remains better than before treatment
- after 7 years levodopa's therapeutic assistance is no longer evident.

Response to treatment varies from patient to patient but generally the above "timetable" applies. Because there appears to be a fixed period during which levodopa is effective, Rinne (1974) has suggested that levodopa administration be withheld while symptoms are mild and only begun when the patient's condition necessarily warrants its use.

The reason for levodopa's waning influence is still to be satisfactorily explained. Pederzoli, Girotti, Scigliano, Aiello, Carolla and Caraceni (1983) simply propose that response to dopaminergics may decline with age. Pearce and Pearce (1975) suggest that diminishing response to levodopa may be due to dopamine receptor exhaustion. The nigrostriatal pathway may be rendered inaccessible to exogenous dopamine possibly because so many nerve cells will have been lost that the extrapyramidal system no longer has the capacity to maintain functional status (Rinne, 1978). Fading benefits may be due to a combination of factors such as aging in conjunction with progressive disease deterioration.

Levodop reatment has not been without troublesome side-effe To optimise therapeutic effects, levodopa has been c bined wi a decarboxylase inhibitor and is often administered along with anticholinergic agents and antidepressants. However, mental disturbances following levodopa administration have often been reported (Celesia & Barr, 1970; Jenkins & Groh, 1970), ranging from confusion and disorientation to psychosis, anxiety and euphoria. The more extreme side-effects are invariably experienced by older patients with associated organic brain syndrome (Celesia & Barr, 1970). Levodopa has been found to aggravate already existing dementia (O'Brien, Digiacomo, Fahn & Schwartz, 1971; Sacks, Kohl, Messeloff & Schwartz, 1972 and it would seem that the patient's age and pre-existing dementia would predispose patients to levodopa-induced psychiatric disturbances. Pederzoli et al. (1983) found that age of symptom onset is a relevant consideration in predicting side-effects. Patients with disease onset before age 60 are more likely to experience abnormal movements and on-off phenomena while patients with onset after age 60 are more likely to experience major mental disturbances. It would then seem that the ideal candidate for levodopa therapy is the younger patient with good premorbid emotional and intellectual status (Loiber, 1977).

The biochemical basis for unfavourable responses to levodopa remains unclear. It would appear that an excess of dopamine as a result of levodopa administration may displace other amines from their normal storage sites and interfere with their metabolism (Celesia & Barr, 1970; Yahr et al., 1969). "Regions of the brain, such as the thalamus and cerebral cortex, which normally contain little or no dopamine show significant concentrations of this monoamine and its acid metabolite...after levodopa therapy" (Yahr et al., 1972, p.64). These findings may be of prime importance in understanding the mode and sites of action of levodopa in producing unwanted effects (Yahr et al., 1972).

The value of levodopa as a therapeutic agent in the treatment of PD is succinctly stated by Celesia and Barr (1970): "Side-effects from levodopa are frequent, but its benefits far outweigh its shortcomings" (p.197).

Riklan (1972) wrote: "The fact that the same drug in similar doses, can lead to lethargy in some instances and sleeplessness in others, to increased alertness in some and confusion in others, reflects some of the complexity of...biochemical-behavioural events" (p.44). These biochemical-behavioural events involve the interaction of individual patient variables, the activity of a highly complex drug and a highly complex disease process.

Although PD seems to have a particular affinity for the dopaminergic neurons of the substantia nigra (Rinne, 1978), neuropathology indicates that it does not observe the boundaries of the extrapyramidal system. The degenerative process is pervasive, interfering with the functioning of several brain structures and biochemical systems. The limits of disease influence are yet to be established. The important implication of the nucleus basalis of Meynert uncovered a neurological pathway along which degeneration transgresses from the subcortical areas to the cortex. Other pathways may exist. It remains the task of medical and allied research to find them.

CHAPTER 3

PARKINSON'S DISEASE AS A DEMENTING CONDITION

Dementia may be loosely defined as the acquired loss of intellectual functioning. It is a clinical symptom and is not in itself a diagnostic entity (Heilman & Valenstein, 1979).

Clinically, the demented patient presents with impaired judgement, a lack of insight and will demonstrate abstract reasoning difficulties. His memory will be markedly affected, particularly short-term memory, to the extent that learning new skills will be almost impossible. Agnosia, aphasia and apraxia may occur. The patient is likely to be confused for time, place and person. He may present as highly distractable. He will probably be careless of his personal condition. He will manifest personality disturbances such as becoming increasingly eccentric, developing a rigid outlook and displaying diminished initiative. His interests will become restricted. There may be abrupt mood swings but affect will become progressively blunted or he may become depressed. His functional status will be markedly affected, restricting his independence and the normal activities of daily living.

Of the Parkinson patient population, approximately 30% develop dementia (Levodopa: long-term, 1981; Marttila & Rinne, 1976; Mayeux et al., 1981; Mindham, 1970; Sweet et al., 1976), but because of the progressive nature of the disease, the figure may rise to as high as 50% before death (Boller et al., 1980; Whitehouse et al., 1983).

Levodopa has no ameliorative effect on the dementia (Whitehouse et al., 1983) and the dementia will progress despite levodopa administration. Markham et al. (1974) showed the incidence of dementia to increase from 26% prior to levodopa to 38% after 5 years of treatment. However, dementia cannot be regarded as an effect of levodopa administration. Withdrawal of levodopa has been shown to decrease side-effects, such as confusion and agitation, and lead to the worsening of motor symptoms but leave dementia unchanged (Sweet et al., 1976). Also, because histopathological evidence indicates no difference between treated and non-treated patients (Yahr et al., 1972), no structural changes appear to occur as a result of levodopa administration. The organic syndrome producing the Parkinson dementia is most unlikely to be levodopa-related.

The dementia associated with PD appears to be an age-related phenomenon. The demented Parkinson patient is older (Celesia & Wanamaker, 1972; Lieberman et al., 1979), with onset of the disease occurring later in life (Garron et al., 1972; Marttila & Rinne, 1976). Lieberman et al. (1979) found few demented patients to have experienced symptom onset before age 60. Information regarding the duration of illness of the demented patient has been variable. Demented patients have had the disease for a longer period of time (Celesia & Wanamaker, 1972), a shorter period of time (Lieberman et al., 1979) and also show no significant difference in disease duration (Marttila & Rinne, 1976) when compared with non-demented patients. However, in studies which show the demented patient not to have been ill for longer (Garron et al., 1972), he has been more physically disabled (Lieberman, 1974) which suggests that his symptoms, and therefore the disease process, had progressed more rapidly (Pederzoli et al., 1983). The dementia will progressively worsen and prove

irreversible. In fact, the dementia may well be more disabling than the motor disorder (Pollack & Hornabrook, 1966).

The Parkinson dementia cannot be accounted for on the basis of *aging alone*. Patients with PD are at a greater risk of dementia than the general population (Hakim & Mathieson, 1978). Boller et al. (1980) found the prevalence of neuropathological changes characteristic of AD (the most prevalent dementing disorder) to be more than six times that of age-matched controls. Lieberman et al. (1979) found the incidence of dementia in PD to be as high as ten times that of age-matched controls. It is therefore *possible* that the aging process in conjunction with the degenerative disease process produces the dementia.

It appears that age of symptom onset is a major predisposing factor in the development of the Parkinson dementia and therefore could also be considered a determining factor in the course the disease will take. This would essentially be in accord with Doshay's *view, cited by* Pollack and Hornabrook (1966), that patients with disease onset early in life showed a slower progression of the disease.

Some may argue that two disease subtypes exist, namely early-onset PD (without dementia) and late-onset PD (with dementia). Garron et al. (1972) and Lieberman et al. (1979) would concede to this view. However, the same disease process may be *altered by patient variables* such as age at onset (although, of course, other variables may be influential). If we accept that there is one *disease process, then* the younger brain, for reasons unknown at present, may respond differently to the neurological disorder. It is possible that the younger, healthier brain produces some form of resistance to the disease, not to the extent that the disease process is halted, but at least "slowing" *its spread*.

Because the Parkinson dementia has so many correlates with AD, it is noteworthy that age at onset seems to result in different manifestations of AD with respect to biochemical activity in different parts of the brain (Bird, Stranahan, Sumi & Raskind, 1983). However, an age-related anomaly exists in that early-onset AD culminates in a more severe disorder while in PD early onset seems to predict a less severe disorder.

PD is not unique in manifesting as a motor disorder accompanied by a dementing process. Huntington's Disease (HD) and late AD are two cases in point and provide suitable comparisons to illustrate similar pathological spreads of degeneration that fail to observe neat neurological boundaries.

The primary site of lesions in HD and PD is the basal ganglia, a subcortical structure. The degenerative process begins in the substantia nigra in PD. In HD, it begins in the caudate nucleus and putamen. The basal ganglia are subcortical nuclei with extensive cortical and subcortical connections (Heilman & Valenstein, 1979) and the influence of these primary lesions may be far more extensive than we have so far determined. Besides the subcortical involvement, both HD and PD have consistently been noted to include frontal lobe involvement (Barbeau, 1972; Botez & Barbeau, 1973; Heilman & Valenstein, 1979; Portin & Rinne, 1980). The motor deficits, lack of spontaneity and motivation attributed to frontal lobe lesions are evident in PD, HD and AD. These behaviours must involve a cognitive aspect, but the cognitive functioning associated with the frontal lobes may not only be related to motor and emotional regulatory behaviour. "Although superficially, the frontal lobes do not seem to be involved in maintaining intellectual abilities, we cannot accept this without further proof. There are indications that the frontal lobes play a part in complicated

intellectual processes, e.g. in the application of abstract logic" (Jordaan et al., 1975, p.144).

Although the genesis of degeneration in HD and PD occurs in a subcortical structure, both diseases seemingly involve cortical structures as well. The literature has noted generalised cortical atrophy occurring in PD but even if cortical involvement is limited to the frontal lobes this may be sufficient, along with subcortical involvement, to produce the related dementia.

In late AD a similar condition prevails. Cognitive and motor symptoms conjoin, with extrapyramidal (or parkinsonian) features being demonstrated in demented patients. Drachman and Stahl (1975) commented on the close relationship between dementia and extrapyramidal features, and observe that "often the decision as to whether a patient has dementia (with extrapyramidal signs) or parkinsonism (with dementia) is largely a matter of different emphasis" (p.809). Pearce and Pearce (1975) dispute that the relationship is that close as clinically one is invariably able to distinguish the two disorders on the basis of the presenting symptom but they concede that as AD and PD become more severe and progressive the two conditions appear very similar.

If we accept Heilman and Valenstein's 1979 classification of dementias on the basis of localization, AD is an example of a cortical dementia while PD and HD are both examples of subcortical dementias. These divisions suggest that two forms of dementia exist, essentially different in locus of pathology as well as clinical manifestation. With regard to subcortical dementias, Heilman and Valenstein (1979) state: "The hallmark of these dementias is the prominent appearance of signs relating to deficits in frontal lobe function without signs of language involvement" (p.485). Mayeux et al.

(1983) cite previous descriptions of subcortical dementias and also note "no impairment of language" (p.278). From this it could be deduced that cortical and subcortical dementias would produce differing patterns of intellectual impairment. Mayeux and his co-workers (1983) set out to establish if subcortical dementia, as opposed to cortical dementia, is a recognizable clinical entity. They compared the intellectual functioning of patients with AD, HD and PD but discovered no differences in neuropsychological functioning to exist between the three groups. This lead the researchers to believe that the divisional nomenclature is misleading. Rather, a combination of cortical and subcortical degeneration may be responsible for the intellectual impairment in all three diseases.

It would be foolish to conclude that the dementia in these three diseases arises from the same morphological and biochemical changes. As Mayeux and his colleagues point out, AD and PD have some neuropathological similarities but AD and HD do not. Also, while we know that in AD and PD the dementing process occurs as a result of neuronal loss in the nucleus basalis of Meynert, and it is along this route that cortical cholinergic markers are eradicated, in HD the nucleus basalis of Meynert is left intact with levels of cortical cholinergic markers remaining relatively normal (Parhad, Clark, Polstein, Whitehouse, Hedreen, Price & Chase, 1982). AD and HD are used here as analogous examples to illustrate the pervasive effect, perhaps common to neurological degenerative diseases, which ultimately culminates in intellectual as well as motor disorders. It therefore seems that neurological diseases of this sort inevitably involve a spreading process, from cortical to subcortical areas as in AD, or from subcortical to cortical areas as in PD and HD. Any claim that the process is limited to any specific level would appear to be false.

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PD has a varied and extensive influence on the behaviour of sufferers. Perhaps an earlier return to a holistic view would have provided a more satisfactory framework in which to conceptualise brain dysfunction in PD. Divisions based on localization have produced a somewhat blinkered view with investment in PD being simply regarded as a motor disorder. There can no longer be informed resistance to PD being a dementing condition.

CHAPTER 4

COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE

From what has been said, the impression may have been created that PD sufferers either remain intellectually intact or become demented. In reality a range of impairment exists between these two extremes. Early thinking was that these cognitive changes were accessory or fortuitous occurrences and not part of the disease process (Pollack & Hornabrook, 1966). Even James Parkinson in his first description of the disease claimed that the intellect of sufferers remained intact (Mental changes, 1974). Over the years, the accuracy of this statement has been repeatedly questioned but the reaching of consensus has been slow for a number of reasons.

No clear relationship had been established between cognitive impairment and the accepted pathophysiology of PD, namely a dopamine depletion and basal ganglia dysfunction. As previously mentioned, perhaps a more holistic view would have offered the flexibility to include cognitive impairment as a direct result of the disease. PD is a syndrome of marked variability (Hoehn & Yahr, 1967) and it is in the area of cognitive impairment that this variability is most clearly demonstrated. While some patients become severely impaired to the point of dementia, others remain seemingly unaffected. However, cognitive changes can be so subtle that without the aid of sensitive assessment techniques they may escape the attention of even the most astute clinician. Also, it has been difficult to separate the effects of aging and

antiparkinsonian drugs from the disease process (Barbeau, 1972; Celesia & Wanamaker, 1972; Portin & Rinne, 1980).

Extensive research studies have been undertaken to investigate the nature and extent of the cognitive impairment in PD sufferers. Unfortunately, these studies have included a wide variety of assessment techniques in both clinical and psychometric situations so particular care has to be taken in comparing results and only tentative conclusions can be drawn. Various components of cognitive functioning have been explored and while some researchers argue that impairment is limited to certain cognitive deficits which operate selectively (Horne, 1973), alternative research evidence indicates a general intellectual decline (Garron et al., 1972; Pirozzolo et al., 1982; Portin & Rinne, 1980; Reitan & Boll, 1971; Riklan, Whelihan & Cullinan, 1976).

In a relatively early psychometric study, Hardyck and Petrinovich (1963) found that the IQ test performance (Wechsler-Bellevue test) of Parkinson patients was similar to both a chronologically much older group and a much younger sample with a diagnosis of organic brain damage. They concluded that the changes in intellectual functioning accompanying PD were therefore of a fairly drastic nature. This was substantiated by Reitan and Boll (1971) who found that, even on abilities usually resistant to deterioration as a result of age or mild diffuse cerebral damage, PD patients showed clear signs of deterioration in comparison to age-matched controls. Both these studies were carried out on patients prior to levodopa administration so the drug cannot be considered a confounding variable. The nature of the cognitive changes discussed here should be regarded as fundamental to PD and not treatment-related.

Cognitive functioning involves a number of processes (Jordaan et al., 1975): perception, thinking, memory and learning. This classification is arbitrary as cognitive functioning has an inherently unitary character but the above divisions provide a convenient framework for evaluating cognitive change in PD. I shall examine each process in turn

Perception

While other areas of sensory perception may well be affected in PD, most research attention has been focussed on visual-spatial perception. Deficits in visual-spatial perception and behaviour of PD sufferers have been well-documented (Botez & Barbeau, 1973; Bowen, Kamienny, Burns & Yahr, 1975; Horne, 1973; Loranger, Goodell, McDowell, Lee & Sweet, 1972; Mortimer et al., 1982; Villardita, Smirni, Le Pira, Zappala & Nicoletti, 1982). As lesions of the basal ganglia and disruption of the dopaminergic system are known to interfere with visual-spatial behaviour, and particularly visual-spatial perception (Boller, 1982), a direct link between the known subcortical disease pathophysiology and this particular dysfunction is evident. However, no other impaired aspect of cognition can be so neatly accounted for on a structurofunctional basis.

Thinking

It appears that the abstract thinking ability of PD sufferers becomes disturbed. Patients have difficulty with mental organisation (Roitan & Boll, 1971) and they experience problems with manipulating internal symbols such as numerical quantities required when performing calculations (Portin & Rinne, 1980). Patients have difficulty shifting sets (Bowen et al., 1975; Matthews & Haaland, 1979; Portin & Rinne, 1980) and the concept-forming performance of sufferers has been shown to become disrupted to a greater degree with increasing task complexity (Bowen et al., 1975). But their greatest

difficulty appears to be comprehending and analysing novel or unfamiliar stimuli (Loranger et al., 1972).

Memory

The aspect of intellectual impairment most readily noticeable to both patient and observer is a memory deficit. All forms of memory - immediate, short-term and long-term - are affected, with long-term memory proving to be the least impaired (Boller et al., 1980; Loranger et al., 1972). While the ability to recall and utilize recently stored information is impaired (Brilan & Boll, 1971), there appears to be an "island" of relatively well-preserved intellectual functioning consisting of over-learned, more impermeable, long-standing cognitive operations (Pirozzolo et al., 1982).

Learning

This would relate directly to the memory process. While little attention has been paid to the learning process of PD sufferers as such, it may be deduced from what has been said that cognitive tasks involving long-term, over-learned material would remain relatively well-preserved and the learning of new tasks, particularly complex tasks, would prove troublesome. Social judgement, for example, may be considered as intellectual over-learned behaviour patterns, but while some researchers have found this to remain functionally intact (Boller et al, 1980; Loranger et al., 1972), others have found this aspect of cognition also to be subject to some impairment (Portin & Sinne, 1980).

On considering the above, it is evident that the cognitive impairment in PD is extensive. As PD is a disease of old age, these changes would be regarded as reflecting the natural effects of aging. The slowing of sensory, motor and cognitive functions are cardinal functional features of the aging nervous system but the slowing of thought

processes in PD seems to be in addition to age-related neural slowing (Hansch, Syndulko, Cohen, Goldberg, Potts & Tourtellotte, 1982). A large number of *research studies* have used age-matched controls and have shown PD sufferers to consistently perform worse on measures of cognitive functioning (Bowen et al., 1975; *Horn*, 1974; Reitan & Boll, 1971). We are therefore forced to assume that factors in addition to aging are operative (Loranger et al., 1972) and these factors are other than the restrictions placed on sufferers' performance as a result of motor deficits. It has been suggested that the action of disease phenomena is facilitated by the aging process (Pederzoli et al., 1983) so that the natural aging process combines with the disease process *to form what may* be termed an "accelerated aging process" (Pirozzolo et al., 1982). This would be in accordance with Hardyck and *Petrinovich's* 1963 *findings* of the IQ performance of PD patients being similar to a chronologically much older group of subjects.

This rapid aging process, manifesting on a functional level as impaired cognition, is also *evident on a* structural or pathophysiological level. Degeneration of substantia nigra cells occurs as a consequence of normal aging but *cellular atrophy* and loss is more severe in PD sufferers, particularly with regard to pigmented cells (Mann & Yates, 1982). Evidence of accelerated neural aging is not confined to subcortical structures. A disproportionate number of PD sufferers show signs of cortical atrophy earlier than age-matched controls (*Hakim* & Mathieson, 1979). Aging possibly increases the brain's vulnerability to the severe degenerative assault of the PD process.

Numerous attempts have been made to establish the prevalence of cognitive impairment in PD. Incidence figures have varied enormously with figures as low as 10% (Riklan, 1972) and as high as 93% (Pirozzolo et al., 1982) being

cited in the literature. Besides *differences in assessment techniques and sample selection procedures*, one reason for the discrepancies may be differences in terminology. "Cognitive impairment", "intellectual deterioration" and "dementia" are used interchangeably. Researchers carrying out psychological/psychometric studies prefer the term "cognitive impairment" while "dementia" is used more often in clinical studies. This argument may be considered mere semantics but it becomes an issue of some importance for the purpose of clarification. Matthews and Haaland (1979) wrote: "Use of the label "dementia" in patients with Parkinson disease is often inaccurate and misleading" (p.955). Horne (1973) also questioned the accuracy of the label being used generally in relation to PD sufferers. For our purposes cognitive impairment should be regarded as covering the full spectrum of intellectual deficits, from the subtle to the severe, encompassing dementia which denotes severe cognitive impairment.

The literature indicates that cognitive impairment in PD is highly prevalent, almost the rule rather than the exception. Martin, Loewenson, Resch and Baker (1973), using a clinical interview technique, found that 81% of patients were impaired intellectually while Piozzolo et al. (1982), in a particularly extensive psychometric study, obtained results which showed cognitive impairment to be as high as 93%. The latter study included motor tasks which could account for the high figure but if the above findings are an accurate reflection of the situation only a minority of patients are left intellectually intact. Even these patients may eventually show disease-related (rather than age-related) cognitive changes with time because of the progressive nature of the impairment. This does not detract from the possible existence of subgroups of sufferers who respond differently to this aspect of the disease.

The research studies suggesting the existence of sub-groups of sufferers share little uniformity in their methods. Garron et al. (1972) used a self-testing computerised teletyper to test the intellectual ability of a group of PD patients. The group excluded the significantly demented. Speed of intellectual functioning was measured and two groups emerged: a faster group and a slower group. The slower group were significantly older and significantly more disabled but had not been ill for a longer period of time than the faster group. Later onset of the disease appeared to be a determining factor in the performance differences.

Lieberman et al. (1979) also identified two groups of sufferers from which they concluded the existence of two different disorders rather than different patient responses to the same disorder. Patients were monitored over an eight-year period during which time they received levodopa treatment and repeated assessments of intellectual functioning using "a simple bedside evaluation". From the results the researchers described two disorders. The first disorder is a motor disorder with a longer and benign course and good response to levodopa affecting a younger population. The second disorder is a motor and cognitive disorder with a more fulminate course and poorer response to levodopa affecting an older population. Again, age of onset is a determining factor.

Boller et al. (1980) reviewed the pathological specimens obtained at autopsy, together with clinical information including mental status data, of twenty-nine PD patients. Unfortunately, they use the term "dementia" very broadly so nuances of cognitive impairment are difficult to extract from the data. However, 55% showed evidence of "dementia" and most of these patients (75%) had pathological changes consistent with AD. Two forms of PD were suggested: the first is PL with dementia characterised

pathologically with subcortical PD changes and cortical AD changes. The second is PD without dementia with pathology limited to the basal ganglia. Unfortunately, age of symptom onset is not given.

Mortimer et al. (1982) examined presenting motor symptomotology in relation to psychometric measures of neuropsychological functioning. Two forms of PD were implied: one with predominant tremor and relatively intact intellectual functioning and another with more marked bradykinesia and neuropsychological impairment. Age of onset was not an influential factor. Mortimer and his co-workers comment that treatment (levodopa) may have masked an even stronger relationship between motor and cognitive functioning than was shown.

The effects of levodopa on cognitive impairment were initially extremely encouraging. Levodopa seemed to have an "awakening" effect (Cotzias et al., 1969) immediately improving cognitive functioning. Researchers marvelled at its effectiveness. "Levodopa increases overall brain efficiency such that one of its most specific effects at the cognitive level may be improved functioning at the most abstract and verbal level" (Beardsley & Puletti, 1971, p.150). Others viewed levodopa's effects with more caution arguing that levodopa merely improved "attention span" or "vigilance" without increasing the patient's overall cognitive ability (Bowen et al., 1975). As the subcortical arousal network is dopaminergic, increased activation or arousal would be an expected effect of levodopa administration (Riklan et al., 1976).

Research studies have been carried out at varying stages of levodopa treatment. Beardsley and Puletti (1971) showed levodopa to increase full scale IQ test scores of PD patients by as much as 10 points over the first

6 months of treatment. Halgin et al. (1977) compared the recent memory performance of a short-term levodopa group (22 months or less) with a longer-term group (40 months or more) and their results indicated that initial improvement was temporally limited. They concluded that while cognitive functioning significantly improved following levodopa treatment it failed to reach the level of normal age-matched controls and after 2 years of treatment showed a subtle regression to pre-levodopa levels.

Riklan et al. (1976), in a long-term study, showed no significant difference or progressive deterioration when he compared the cognitive functioning of sufferers after 5 years' treatment to sufferers receiving no levodopa and short-term users (1 month to 3 years) but their performance remained significantly worse than non-diseased controls. After 8 to 10 years of levodopa treatment, Portin and Rinne (1980) noted highly significant deterioration in motor, visual-spatial, verbal and memory processes following marked improvement in the same patients after 2 to 3 months of treatment. The reasons for this waning influence remain hypothetical, as discussed in Chapter 2.

There is no type of cognitive impairment specific to PD (Horn, 1974; Mayeux et al., 1983). Deterioration is of a general and progressive nature and few escape its effects. The literature includes several references to the variable response of sufferers to the Parkinson dementing process which appears to be of combined cortical and subcortical pathological activity. The factors contributing to the variable response remain to be established.

CHAPTER 5

THE ASSESSMENT OF DEMENTIA

Dementia presupposes a significant deterioration from a higher level of intellectual functioning. The assessment of dementia must however take into account "normal" decline or deterioration, which is part of the general organic process of aging, and "abnormal" decline due to other factors. An individual can only be said to show signs of mental deterioration when, in comparison with his own previous functioning, there is a significant loss of ability and the decline is greater than the changes expected for a person of that age (Wechsler, 1958). When distinguishing between a normal decline in human abilities and abnormal loss or impairment, the distinction can be arbitrary as it is not always easy to indicate where one ends and the other begins. However, a marked and disabling loss at any age must be regarded as a definite sign of impairment (Wechsler, 1958).

A precise measure of the degree of mental deterioration demands that the previous level of functioning is accurately established. This is rarely possible as it is only once the deteriorating process is in progress that a reason for assessment arises. Estimates of previous functioning levels may be gleaned from interviews with family and friends together with information regarding educational and career background. At best these must remain estimates as they are subjectively formulated.

The ideal procedure for monitoring the Parkinson dementing process would involve predicting PD. This would allow us

to earmark those patients likely to contract the disease and then, by systematic and repeated assessment, to monitor changes in intellectual functioning over a period of time prior to symptom onset and during disease progression. Current longitudinal research, such as Portin and Rinne's 1980 study which evaluated patient functioning over a 10-year period, is only able to measure disease effects once the disease is in progress and therefore can only partially reflect deterioration because no accurate functional measure prior to disease onset exists.

When planning to assess PD patients for dementia, we were faced with a number of alternatives in assessment techniques. The first is the clinical interview which is designed to yield an indication of cognitive functioning including responsiveness, attention, language, memory, perception and reasoning (Heilman & Valenstein, 1979). Horne (1973) writes: "The assessment of dementia can be simply a subjective, clinical evaluation, which is, unfortunately, most often how it is made in studies on Parkinsonism" (p.548).

There are inherent disadvantages in assessing dementia by clinical interview even when the interview data are obtained in a controlled format as in the Mental Status Examination. Meyer (1983) writes: "The examination contains the weakness of all data obtained from interviews: there are few or no statistical or normative standards for the obtained responses on which to base a communicable inference and an eventual diagnosis. Examiners are too often left to develop their own idiosyncratic notions of what a certain response means" (p.1). Those disadvantages must be acknowledged particularly when more subtle differences in cognitive functioning between patients are at issue and quantitative measures of these differences are required.

The second group of techniques available for assessing dementia are laboratory examinations, such as the CT scan and the EEG, and the physical examination which investigates the cranial nerves, sensory and motor systems (Heilman & Valenstein, 1979). These techniques provide information regarding neurological functioning and status. They can identify neurological correlates of dementia, but our concern is the patient's actual functional status. For example, not all demented patients show signs of cortical atrophy (Pearce & Pearce, 1975) and not all patients with cortical atrophy are functionally demented (Miller et al., 1960). These instruments have high diagnostic value but, while they can provide valuable supplementary neurological information, their value as indicators of cognitive functioning is limited.

Because the assessment of dementia involves a sampling of behaviour within the assessment situation from which certain deductions are made regarding the patient's general functional status, the merit of an assessment technique rests on how accurately general functional status can be deduced from the results. This can be done most usefully by carrying out appropriate psychometric tests, the third assessment alternative available to us. The value of psychometric techniques lies in their objectivity of standardised rating methods and administrative procedures. They can detect subtle changes in mental functioning long before these changes have so disorganised behaviour that deterioration is obvious to all (Wechsler, 1958). Also, psychometric instruments provide quantitative measures of cognitive functioning which are conducive to the analysis of differences between patients.

Assessing subjects who have a motor disability, with a psychometric instrument like the WAIS (which was used in

the present study), presents a problem in that the procedure includes a performance scale involving timed items which measure the speed of motor-related intellectual functioning. Visual-spatial perception and behaviour play a strong role in these performance tasks and PD patients are particularly disabled in this area as a direct consequence of disease pathology. Villardita et al. (1982) write: "The visuoperceptive deficits ... of parkinsonians cannot be considered as a mental deterioration index" (p.119). Because of their motor and visual-spatial deficits, PD patients are at a double disadvantage when faced with performance tasks so the use of these measures in the assessment of cognitive functioning in PD must be invalid. This view is in accordance with Villardita and his co-workers who suggest the exclusion of visuoperceptive and spatial tests and the inclusion of appropriate verbal tests. Performance tasks do not measure a different kind of intelligence. Rather, they provide a different measure of the same intelligence underlying verbal tests (Wechsler, 1958). Also, scores obtained on the Information and Vocabulary subtests from the WAIS correlate most highly with total IQ test scores so they offer suitable tools for assessing intellectual functioning in PD.

In addition to verbal subtests from the WAIS, the present study included abbreviated scales from Luria's Neuropsychological Investigation (Christensen, 1975). These scales were included as they are particularly sensitive to intellectual impairment.

CHAPTER 6

METHOD

Subjects

Forty-three white subjects (26 males and 17 females) were selected from the outpatients attending the PD Clinic at the Johannesburg General Hospital. Participation in the study was limited to long-term sufferers of idiopathic PD who had not undergone surgical intervention for symptom relief and who were currently receiving levodopa therapy. Treatment dosage had been individually determined for each patient over time in order to afford maximum therapeutic effect with a minimum of side-effects. Final subject selection was then determined simply by the simultaneous availability of both tester and patient.

The ages of the patients at testing ranged from 47 to 86 years ($\underline{M}$ = 68,21; $\underline{SD}$ = 8,93). The duration of illness ranged from 3 to 36 years ($\underline{M}$ = 11,46; $\underline{SD}$ = 5,86) calculated from symptom onset. Age at disease onset ranged from 21 to 77 years ($\underline{M}$ = 56,72; $\underline{SD}$ = 12,13).

Of our forty-three patients, four (9%) had no formal education, five (21%) had some primary school education and thirty-four (79%) had some high school education, thirteen (30%) having passed matric. Twenty-two patients (52%) had some form of post-school education or training. Only one patient had a university degree.

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The premorbid careers of the patient sample were diverse. Seven patients had held executive/managerial positions, eleven were involved in sales, six were tradesmen, three were employed in the accounting field, seven were secretaries, two were involved in publishing and three were housewives. The remaining five patients included a music teacher, a nurse, a customs officer, a storeman and a truck driver. Only two patients were still working at the time this study was undertaken.

Thirty-nine patients (91%) were married. Thirty-five of these patients had children.

Materials

A battery of neuropsychological tests was compiled to assess the cognitive functioning of the patient sample. The following tests were included in the battery:

A. Subtests from the South African version of Wechsler's Adult Intelligence Scale

The WAIS subtests are extremely well-documented and well-known. Therefore, the four verbal subtests selected for use are only briefly described here.

Information

This is a measure of the general information absorbed from the environment by the subject (Zimmerman & Woo-Sam, 1973). It reflects educational background, intellectual curiosity and reading habits. Motivation, verbal comprehension and rote memory all play a role in the subject's performance. Information is a "hold" test, involving cognitive abilities relatively invulnerable to mental deterioration (Wechsler, 1958). Deterioration must be very severe to have any profound effect on the storage of information (Zimmerman & Woo-Sam, 1973).

Similarities

Similarities is a test of concept formation. It measures the ability to generalize, abstract and identify relationships. "Concept formation is one of the aspects of every thought process, and...it is one of the main channels through which maladjustment encroaches on intellection" (Rappaport, Gill & Schafer, 1945, p.100). It is a "don't hold" test, involving cognitive abilities vulnerable to mental deterioration (Wechsler, 1958).

Digit Span

This is a test of the immediate recall of auditory symbols. In addition to immediate memory, it measures attention and freedom from distractability. A marked falling off of memory span is often one of the earliest indications of mental impairment (Wechsler, 1958). It is a "don't hold" test.

Vocabulary

Vocabulary is a particularly good measure of general intelligence. It involves rote memory to some extent but is a strong reflector of educational background and life experience. "This subtest is one of the least vulnerable to pathology of any kind and is generally felt to provide a reliable estimate of premorbid functioning in a person suspected of suffering intellectual deterioration" (Zimmerman & Woo-Sam, 1973, p.117). Vocabulary may tend to fall with deterioration but will remain the least impaired of the cognitive functions (Rappaport et al., 1945). It is a "hold" test.

B. Abbreviated forms of Luria's Neuropsychological Investigation (Christensen, 1975)

The Luria scales are generally used as a diagnostic tool in the assessment of neuropsychological status.

Although no normative standards are available on these scales, they have been included here because their sensitivity to cognitive impairment has been demonstrated within the clinical situation. The following subscales were used in abbreviated form (see Appendix I):

Memory Scale

A number of assessment techniques are used to measure the different complex facets of immediate auditory recall.

Investigation of the Learning Process (item 1): The subject is presented with a series of seven words and the number of words remembered is noted after each of five trials. This reflects the way in which the volume of retained material increases during the learning process (Luria, 1966).

Investigation of the direct impression of traces (items 2, 3 4 and 5): The object of this investigation is to determine to what extent the patient is able to preserve direct traces or after-effects left behind by verbal stimuli. The subject is presented with words which he is told to remember. He is then presented with verbal or visual distractions in the form of additional words, sentences or picture cards which he is also asked to remember. The subject is then asked to recall the words presented initially. Recall is then a measure of the inhibitory effect produced by the distracting material (Luria, 1966).

Investigation of logical memorizing (item 6): The subject is asked to remember seven words with picture cards presented as memory aids. These cards do not depict the direct meaning of the word but rather demand that the subject establish a chain of meaning between word and picture.

Receptive Speech Scale

Receptive speech is the perception of speech received from an external source and the decoding of the speech symbols (Luria, 1973). It refers to the perception of speech sounds, the understanding of the meaning of words and phrases, and finally the understanding of consecutive speech (Luria, 1966).

The investigation of the understanding of logical-grammatical structures assesses the following aspects of receptive speech:

i) the understanding of object names and the grammatical constructions expressing relationships between objects (items 1, 2 and 3)
ii) the understanding of constructions using the attributive genitive case (items 4 and 5)
iii) the understanding of prepositional constructions involving spatial and similar relationships (items 6, 7 and 8)
iv) the understanding of comparative constructions involving mental inversions (item 9)
v) the ability to analyse phrases of complex grammatical structures (item 10).

Expressive Speech Scale

Expressive speech begins with an idea which is coded into a speech scheme with the aid of internal speech and is converted into narrative speech based on a 'generative' grammar (Luria, 1973). The items included investigate facets of narrative speech which constitutes a vital part of the study of the most complex functions of expressive speech activity (Luria, 1966). The items measure the extent to which the patient is able to operate complex systems of grammatical expressions. Subjects are asked to complete sentences presented with words missing (item 1), to construct sentences including words presented to them (item 2) and to

construct sentences by rearranging words presented in a disarranged order (item 3).

Reading Scale

Reading is a form of receptive speech. It involves the visual perception and analysis of written linguistic symbols and the comprehension of what has been written (Luria, 1966). The reading investigation includes the reading of a simple sentence (item 1), the reading of sentences not conforming to their anticipated meaning (item 2) and the reading of a complete text (item 3) which demands the comprehension of the relationship of one sentence to another rather than the discrete understanding of individual words.

Writing Scale

Both reading and writing are acquired skills demanding special training which is in contrast to spoken speech which proceeds automatically (Luria, 1966). Writing is a form of expressive speech. It begins with a thought which is coded into phonetic structures of internal speech which in turn leads to the construction of the written symbols. The writing investigation is designed to analyse the state of the various levels of writing with the items selected measuring the following aspects:

i) the patient's ability to perform the fine movements of writing (item 1)
ii) the quality of the patient's ability to write from dictation (items 2 and 3)
iii) the patient's capacity to devise a deliberate plan of writing activity by decoding internal speech into a system of written signs (item 5)
iv) the patient's functional writing ability to execute a task from everyday life (item 4).

C. The Harris Subscale (Subjective Depression) of the MMPI Depression Scale (Graham, 1977)

This subscale was devised by undertaking a content analysis of the items constituting the MMPI depression scale and extracting those items measuring subjective depression. The Harris subscale contains 32 items. It is shorter and less cumbersome to administer than the original MMPI depression scale (Graham, 1977).

Procedure

Subjects were informed that a study of the effects of PD was being conducted and they were requested to participate. The nature and method of testing were explained to them and all subjects willingly co-operated.

A team of post-graduate psychology students, well-trained in the administration of the test material, carried out the testing. The testers were instructed to fully record their subjects' responses. All scoring was then undertaken by the writer to ensure scoring uniformity.

Each subject was individually tested in a quiet, well-lit room at the Johannesburg General Hospital. Testing took place in the mid-morning during a routine visit to the PD Clinic. Each testing session lasted approximately two hours with frequent rest periods being offered to the subjects in an effort to avoid tiring them.

The session commenced with the gathering of biographical details. The following were noted:

1. name, present age, sex
2. marital status, number of children
3. educational background including post-school training

4. premorbid career and present employment status
5. history of PD including age at which onset occurred, duration of illness and present treatment.

The tests were then administered in the following order:

A. WAIS Subtests
   1. Information
   2. Similarities
   3. Digit Span
   4. Vocabulary

B. Luria Subscales
   1. Memory
   2. Receptive Speech
   3. Expressive Speech
   4. Reading
   5. Writing

C. Harris Depression Subscale

CHAPTER 7

RESULTS

Descriptive statistics for the demographic data and test scores are presented in Table 1 below.

Table 1

Means and Standard Deviations for Patient Variables and Test Scores

	Mean	SD
Demographic Data		
Present Age	68,21	8,93
Duration of Illness	11,49	5,86
Age at Disease Onset	56,72	12,13
WAIS Subtests		
Information	13,49	4,20
Digit Span	11,12	2,42
Similarities	14,51	4,59
Vocabulary	19,26	7,98
Luria Subscales		
Memory	7,58	3,63
Receptive Speech	2,23	1,78
Expressive Speech	1,14	1,10
Reading	0,63	0,95
Writing	2,56	3,48
Depression	13,77	5,52

Pearson product-moment correlation coefficients were computed to investigate the nature of the relationship between the four patient variables and the test scores. The complete correlation matrix is presented in Appendix II. Sections have been reproduced here for discussion purposes. Table 2 shows the intercorrelations between present age, duration of illness, age at onset and sex.

Table 2

Pearson Product-Moment Correlation Coefficients between Patient Variables

	Present Age	Duration of Illness	Age at Onset	Sex
Present Age	1,0000			
Duration of Illness	-0,3160*	1,0000		
Age at Onset	0,8887***	-0,7158***	1,0000	
Sex	0,0994	-0,1831	0,1617	1,0000

* p<0,05
*** p<0,001

An examination of the relationships between patient variables showed a significant correlation between present age and age at onset (r=0,8887; p<0,001). Present age showed a significant negative correlation with duration of illness (r=-0,3160; p<0,05). A significant negative correlation also emerged between age at onset and duration of illness (r=-0,7158; p<0,001). These results indicate that the older patients had experienced disease onset at a later age and had been ill for a shorter period of time. The converse would apply to the younger patients.

The relationship of sex to the other patient variables was not significant.

Intercorrelations between patients variables and test scores are presented in Table 3. It should be noted that the Luria Subscales are negatively scored.

Table 3

Intercorrelations between Patient Variables and Test Scores

Tests	Present Age	Duration of Illness	Age at Onset	Sex
Depression	-0,0430	-0,0707	0,0026	-0,0353
Information	-0,5921***	0,0085	-0,4399**	-0,1181
Digit Span	-0,1983	-0,1433	-0,0767	-0,0194
Similarities	-0,3843**	0,1074	-0,3348*	0,0242
Vocabulary	-0,4568***	-0,0202	-0,3226*	0,1547
Memory	0,2237	0,0367	0,1469	-0,1307
Rec. Speech	0,1628	0,0617	0,0900	-0,1067
Exp. Speech	0,6548***	-0,0991	0,5294***	-0,1034
Reading	-0,1812	0,0675	-0,1660	0,0165
Writing	0,1418	0,0762	0,0675	-0,2004

* p<0,05
** p<0,01
*** p<0,001

Present age showed a significant negative correlation with scores on Information (r=-0,5921; p<0,001), Similarities (r=-0,3843; p<0,01), Vocabulary (r=-0,4568; p<0,001) and Expressive Speech (r=0,6548; p<0,001). This indicates that the older the patient, the worse his performance on these subtests proved to be. Age at onset showed significant negative correlations with these subtests: Information (r=-0,4399; p<0,01), Similarities (r=-0,3348; p<0,05), Vocabulary (r=-0,3226; p<0,05) and Expressive Speech (r=0,5294; p<0,001). The older the patient was at disease onset, the lower he scored on these subtests.

Test performance showed no significant relationship to duration of illness or sex. The relationship between

depression and the four patient variables was not significant.

An iterative principal components analysis with varimax rotation was conducted on all test scores in order to determine the nature of the underlying dimensional structure of these measures. The component matrix is presented in Table 4.

Table 4

Varimax Rotated Component Matrix:
Loadings of Test Scores on Components 1, 2 and 3

	Component		
Tests	1	2	3
Information	0,83080	0,23962	-0,14493
Digit Span	0,24588	0,93893	-0,20222
Similarities	0,62563	0,25746	-0,45506
Vocabulary	0,86649	0,12516	-0,22225
Memory	-0,35168	-0,43934	0,41025
Rec. Speech	-0,46394	-0,23476	0,52712
Exp. Speech	-0,70187	-0,31150	0,06749
Reading	-0,04356	-0,10340	0,66792
Writing	-0,41495	-0,28762	0,51012

Note. A salient loading was taken as 0,4 or more.

The first two components were associated with an eigenvalue of 5,4922 and 1,2577 respectively. The third component produced an eigenvalue of 0,6595. Although Component 3 was not significant in terms of Kaiser's criterion, it was included in all subsequent analyses as it was considered to be of statistical interest. Component 1 accounted for 74,1% of the variance, Component 2 for 17,0% of the variance and Component 3 for 8,9% of the variance.

Table 5

Summary of Tests Loading on Components 1, 2 and 3

Component 1 "Intellect"	Component 2 "Memory"	Component 3 "Linguistic Skills"
Information (W)	Digit Span (W)	Receptive Speech (L)
Similarities (W)	Memory (L)	Reading (L)
Vocabulary (W)		Writing (L)
Expressive Speech (L)		

Note. W = WAIS Subtest, L = Luria Subscale.

Component 1 reflects general intellectual functioning and was therefore labelled "Intellect". Information, Vocabulary and Similarities are all good measures of general intelligence or G. Correlation figures with G for the older age group (over 60) are given as 0,73 for Information, 0,65 for Similarities and 0,66 for Vocabularly (Zimmerman & Woo-Sam, 1973).

Initially, it was surprising that Expressive Speech loaded so strongly on Component 1. However, an appraisal of the Expressive Speech test items indicated that processes of narrative speech were measured. As noted earlier, narrative speech constitutes the most complex functions of expressive speech activity (Luria, 1966) and must be considered a highly "intellectual" form of speech demanding analysis, synthesis and conceptual ability. Performance on these items would, therefore, also reflect general intellectual functioning.

All four of the subtests loading on Component 1 showed significant correlations with present age and age at onset as noted previously (Table 2).

Component 2 was labelled "Memory". As both subtests contributing to this component measure immediate auditory recall (albeit different facets of this function), the basis for their common loading on Component 2 is clear.

In attempting to interpret the common construct underlying the subtests loading on Component 3, an analysis of the tests' items revealed that they were all reflecting "low" or habitual forms of speech activity as opposed to items selected from the Expressive Speech scale, for example, which measured "high" or intellectual speech forms (Luria, 1966). The items constituting the subtests loading on Component 3 may all be regarded as the least complex, and generally the least intellectually demanding, of all the items included in the study. Also, there is a strong element of trained speech activity underlying the three subtests although certain Receptive Speech items do demand abstract reasoning ability. It was decided that Component 3 was best defined by "Linguistic Skills" and was given this label.

The three components were each subjected to unidimensional hierarchical cluster analyses. The purpose of this investigation was to determine whether or not the patient sample was heterogeneous in composition as reflected in differential test performance. Any clustering activity would therefore be based on test score differences. The amalgamation histories of each analysis are presented in figures 1, 2 and 3.

Examination of the amalgamation histories for Intellect (figure 1) and Linguistic Skills (figure 3) indicates that discontinuity in the amalgamation distance was produced by small mergers but no reliable evidence of major underlying clusters was demonstrated. The amalgamation history of Memory (figure 2) shows more promise of cluster formation. On visual examination, three clusters appear to exist and they were labelled Group 1, 2 and 3 respectively.

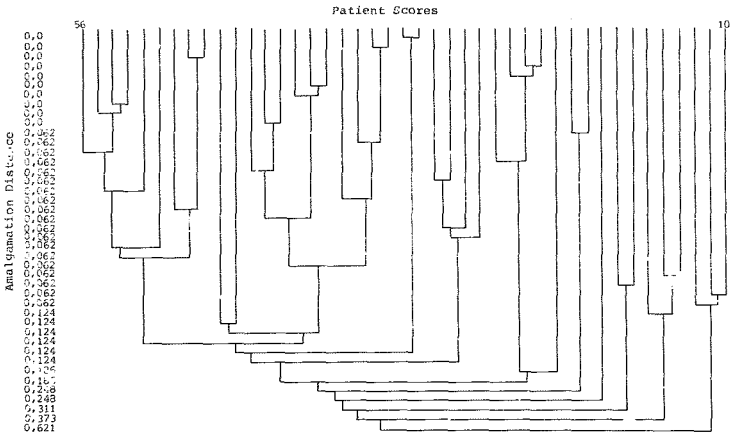
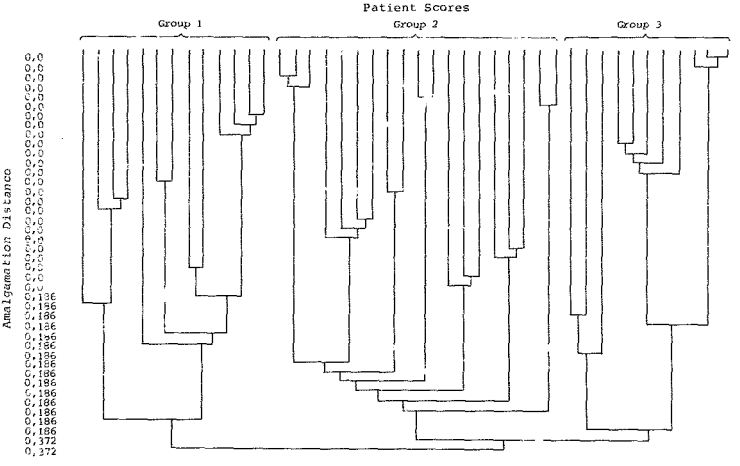
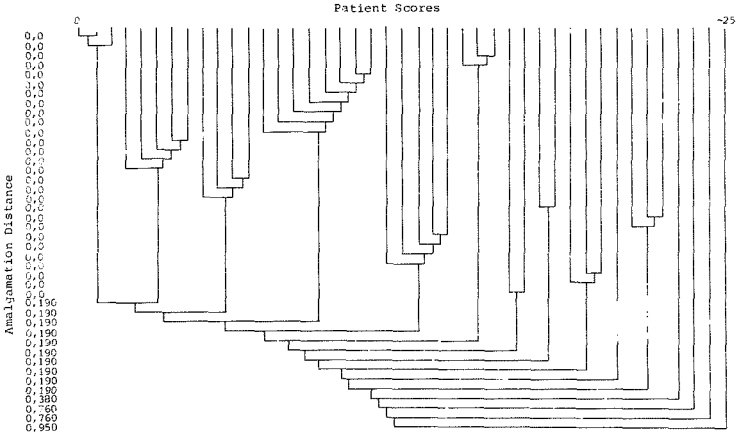


Figure 1. Amalgamation History of the Cluster Analysis Performed on the Intellect Component


Patient Scores
Group 1
Group 2
Group 3
Amalgamation Distance
0,0
0,0
0,0


Patient Scores
0
25
Amalgamation Distance
0,0
0,0
0,0

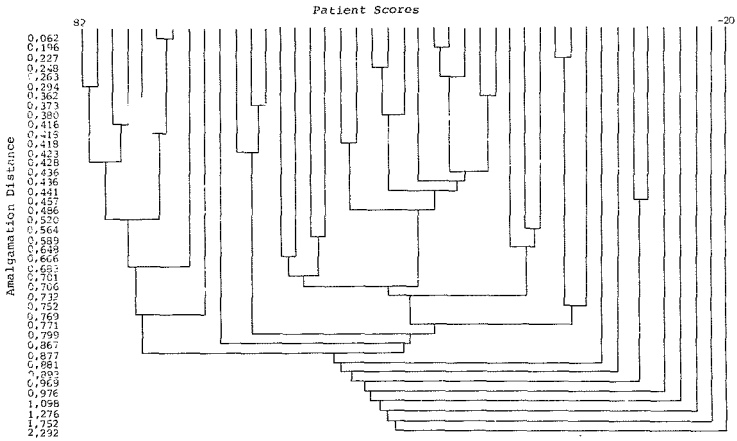


Figure 4. Amalgamation History of the Cluster Analysis Performed on the Three Components Combined

Table 6

Means and Standard Deviations of Patient Variables and Scores of the Three Groups Emerging from the Cluster Analysis Performed on the Memory Component

Variable	Group 1 (n=13)		2 (n=19)		3 (n=11)	
	M	SD	M	SD	M	SD
Present Age	66,69	7,27	66,52	7,41	72,91	10,83
Duration of Illness	9,92	4,30	12,63	7,26	11,36	3,63
Age at Onset	56,77	9,36	53,89	12,30	60,64	14,90
Scores	10,15	1,96	2,95	1,82	-3,27	1,21

The differences between the patient groups constituting these three clusters were explored. The means and standard deviations of present age, duration of illness, age at onset and patient scores were calculated for each group and are presented in Table 6. Table 7 shows the t scores generated by the differences between group means for each of the patient variables. A significant difference between the three groups was demonstrated with regard to test scores. The groups were identified as "high" (Group 1), "moderate" (Group 2) and "low" (Group 3) scorers. No other patient variable produced significant between-group differences to further differentiate the three groups. On inspection of Table 6, the "low" scorers appeared to be older at testing and older at onset but no significant results emerged.

The three clusters maintained separate identities until the last two steps of the analysis. At this point, Group 2 and Group 3 were amalgamated to form one group and at the final step, Group 1 was amalgamated with the

Table 7

Differences between Group Means of Patient Variables and Scores of the Three Groups Emerging from the Cluster Analysis Performed on the Memory Component

Variable	Groups	t
Present Age	$\bar{1}$ vs $\bar{2}$	0,0622
	$\bar{2}$ vs $\bar{3}$	1,6014
	~ vs $\bar{1}$	1,8475
Duration of Illness	$\bar{1}$ vs $\bar{2}$	1,1703
	$\bar{2}$ vs $\bar{3}$	0,8397
	$\bar{3}$ vs $\bar{1}$	0,5242
Age at Onset	$\bar{1}$ vs $\bar{2}$	0,6919
	$\bar{2}$ vs $\bar{3}$	0,;407
	$\bar{3}$ vs $\bar{1}$	1,2934
Scores	$\bar{1}$ vs $\bar{2}$	10,3226*
	$\bar{2}$ vs $\bar{3}$	18,9307*
	$\bar{3}$ vs $\bar{1}$	9,7676*

*p<0,001

newly formed group without any increase in amalgamation distance. Homogeneity of the patient group was therefore established.

The three components were then combined and subjected to a multidimensional hierarchical cluster analysis. The amalgamation history is presented in Figure 4. The smooth, continuous increase in amalgamation distance shows no reliable evidence of underlying clusters.

In order to investigate the predictive power of the patient variables, stepwise multiple regression analyses were carried out on each of the three components. Present age, duration of illness, age at onset, sex and depression acted as predictor variables. Only main effects were examined. The inclusion procedure which operated for these analyses is presented in Table 8.

Table 8

Inclusion Procedure for Stepwise Multiple Regression Analyses

Predictor Variable	Hierarchical Inclusion Order	Stepwise Inclusion
Age at Onset		
Duration of Illness	1	Yes
Present Age		
Depression	2	Yes
Sex		

Multiple Regression of Intellect on present age, duration of illness, age at onset, depression and sex

A summary of the independent variables entered at each step of the analysis, together with R^2, the coefficient of determination, change in R^2 and related F values is presented in Table 9.

Table 9

Multiple Regression of Intellect on Present Age, Duration of Illness, Age at Onset, Depression and Sex

Predictor Variable	R^2	F^a	Change in R^2	F^b
Age at Onset	0,15	7,32**		
Duration of Illness	0,27	7,30**	0,12	6,34*
Present Age	0,35	7,09*	0,09	5,15*
Depression	0,41	6,58*	0,06	3,62
Sex	0,41	5,20*	0,00	0,23

[a] - test of the null hypothesis that $R^2=0$ (df=k,N - k - 1)

[b] - test of the null hypothesis that change in $R^2=0$ (df=1,N - k - 1)

* p<0,05 ** p<0,01

Inspection of the F^a values in Table 10 indicates that each independent variable was a significant contributor to Intellect. However, the significance of the individual contributions altered once the influence of the other predictor variables was taken into account, as shown by the F^b values.

Age at onset was entered into the regression equation first and explains 15% of variation in Intellect ($F(1,41)=7,32$) which is significant beyond the 0,01 level. Duration of illness was entered at step 2 and contributed a further 12% to variation in Intellect ($F(1,40)=6,34$; $p<0,05$). However, once present age was entered at step 3, age at onset and duration of illness were no longer significant. Present age's contribution to change in R^2 was significant beyond the 0,01 level ($F(1,39)=5,15$). Once all the predictor variables had been partialled out, present age remained the only significant predictor of Intellect ($F(1,37)=4,82$; $p<0,05$).

Because of the multicolinearity between these three time-related variables, the interpretation of these results is complex. Present age, duration of illness and age at onset are all heavily confounded variables because of their close relationship. It should be noted that it is difficult to examine the effects of one of these variables without indirectly examining the effects of the others. Therefore, these results cannot simply be interpreted as present age alone being the decisive variable in determining the performance on Intellect. The influence of the other time-related variables cannot be ignored even though their unique contributions were not significant.

The relationship between Intellect and present age was negative ($r=-0,5353$). Therefore, the older the patient, the poorer his score on Intellect proved to be.

Table 10

Multiple Regression of Memory on Present Age, Duration of Illness, Age at Onset, Depression and Sex

Predictor Variable	R^2	F^a	Change in R^2	F^b
Age at Onset	0,01	0,43		
Duration of Illness	0,06	1,27	0,05	2,10
Present Age	0,20	3,28	0,14	6,91*
Depression	0,27	3,50	0,07	3,52
Sex	0,27	2,74	0,00	0,05

[a]- test of the null hypothesis that $R^2=0$ (df=k,N - k - 1)

[b]- test of the null hypothesis that change in $R^2=0$ (df=1,N - k - 1)

* p<0,05

The predictor variables in concert explained 41% of the variation in Intellect.

Multiple regression of Memory on present age, duration of illness, age at onset, depression and sex

As Table 10 shows, the independent variables explained 27% of variation in Memory. The only contributor to produce a significant change in R^2 was present age, accounting for 14% of the explained variance ($F(1,39=6,91$; $p<0,05$).

The contribution of age at onset to variation in Memory did not emerge as significant until present age entered the equation at step 3. Once present age was held constant, age at onset became significant ($F(1,37=5,53$; $p<0,05$). Age at onset's unique contribution to variation in Memory remained significant ($F(1,37)=5,14$) beyond the 0,05 level when all the other predictor variables had

been partialled out. However, present age emerged as the strongest predictor of performance on Memory ($F(1,37)= 6,63$; $p<0,05$). Memory was unaffected by duration of illness, depression and sex.

An examination of the relationship between Memory and the two significant predictors indicates that as age at onset increased, Memory scores decreased ($r=-0,1016$) and, likewise, as present age increased, Memory scores decreased ($r=-0,2404$). Therefore, the older the patient and the later disease onset occurred, the poorer the patient performed on Memory.

Multiple regression of Linguistic Skills on present age, duration of illness, age at onset, depression and sex

An examination of Table 11 reveals that present age and depression both produced significant changes in R^2. Present age contributed 28% ($F(1,39)=15,67$; $p<0,01$) and depression contributed 12% ($F(1,38)=7,41$; $p<0,01$) of the 42% of explained variation in Linguistic Skills.

Duration of illness took precedence over age at onset and was entered first at step 1, but neither duration of illness nor age at onset showed a significant contribution to variation in Linguistic Skills until the influence of present age had been partialled out. In the final regression analysis, the unique contributions of duration of illness ($F(1,37)=12,19$; $p<0,01$), age at onset ($F(1,37=15,08$; $p<0,01$), present age ($F(1,37)=16,45$; $p<0,01$) and depression ($F(1,37)=7,15$; $p<0,05$) were all significant. Linguistic Skills was unaffected by sex.

The simple correlation coefficients computed between Linguistic Skills and duration of illness ($r=-0,0847$), age at onset ($r=-0,0115$) and present age ($r=-0,1133$) and depression ($r=-0,3460$) indicate that the patient who

Table 11

Multiple Regression of Linguistic Skills on Present Age, Duration of Illness, Age at Onset, Depression and Sex

Predictor Variable	R^2	F^a	Change in R^2	F^b
Duration of Illness	0,01	0,30		
Age at Onset	0,01	0,23	0,00	0,18
Present Age	0,29	5,43*	0,28	15,67**
Depression	0,41	6,60*	0,12	7,41**
Sex	0,42	5,35*	0,01	0,64

[a] - test of the null hypothesis that $R^2=0$ (df=k,N - k - 1)

[b] - test of the null hypothesis that change in $R^2=0$ (df=1,N - k - 1)

* p<0,05
** p<0,01

performed poorly on Linguistic Skills was the more depressed, older patient who had been ill for a longer period time, with disease onset having occurred at a younger age. This indicates that Linguistic Skills is a more emotionally vulnerable measure of cognitive functioning than both Intellect and Memory.

CHAPTER 8

DISCUSSION

The major findings of the present study indicate that cognitive functioning among PD patients is characterised by a continuous distribution, ranging from the intellectually intact to the severely impaired, with the level of functioning influenced by a complex of time-related variables. These variables are present age, age at onset and duration of illness.

Because of the high intercorrelation between these three variables, it is difficult to separate their respective effects. To examine the influence of any one of these variables involves the indirect examination of the others. Kerlinger (1973, p.622) points out: "The more independent variables are intercorrelated, the more difficult the interpretation (because) one has greater difficulty in telling the relative influences of the independent variables on the dependent variable".

The multiple regression analyses demonstrated the co-influence of these time-related variables on cognitive functioning. To add to the interpretation difficulties created by the close relationship between the three variables, no regular pattern of influence emerged from the analyses of their effects on different aspects of cognitive functioning. For instance, present age was shown to absorb the significant contribution of both age at onset and duration of illness to general intellectual functioning, yet the unique contributions of both age at onset and

duration of illness to linguistic skills functioning only became evident once present age had been controlled. The nature of the respective influences and relative importance of these three variables are difficult to determine and these complexities should be borne in mind as the results of the multiple regression analyses are discussed.

Firstly, as a general description of the patient sample, our older patients had experienced disease onset at a later age and had been ill for a shorter period of time. Conversely, our younger patients had experienced disease onset at a younger age and had been ill for a longer period of time.

Of the cognitive components examined here, general intellectual functioning (Intellect) embodied the "higher" or more intellectually demanding aspects of cognitive functioning. Although all three time-related variables produced significant contributions to variation in general intellectual functioning, present age was the only variable whose unique contribution remained significant once all other variables had been statistically controlled. The strongest predictor of general intellectual functioning was present age: the older the patient, the poorer his intellectual performance proved to be.

These findings are compatible with those of a number of other researchers (Celesia & Wanamaker, 1972; Garron et al. 1972; Marttila & Rinne, 1976). However, present age must not be regarded as simply reflecting chronological age. Several studies have shown PD patients to consistently perform worse than age-matched controls (Bowen et al., 1975; Horn, 1974; Loranger et al., 1972; Reitan & Boll, 1971). Present age in the PD context reflects disease-related phenomena and becomes a complex interaction of the disease process and the natural aging process, which is also statistically indicated by the high intercorrelation between the three time-related variables.

The descriptive trend mentioned previously would suggest that the older patient with poor general intellectual functioning is more likely to have experienced disease onset at a later age and been ill for a relatively short period of time. This does not mean that the length of time the illness has been in progress has no influence on cognitive impairment in PD, but rather indicates that the deleterious effects of the disease develop more rapidly when onset occurs at a later age. Lieberman et al. (1979) found dementia to rarely occur in those patients who experienced onset before age 60, and other studies have shown dementia to be particularly prevalent among late-onset patients (Garron et al., 1972; Marttila & Rinne 1976). In these studies duration of illness did not play a decisive role in cognitive dysfunction. However, Celesia and Wanamaker (1972) found demented patients to have been ill for longer than non-demented patients. The Garron study used a smaller sample and quite different assessment techniques, but the research procedures of the other two studies were essentially similar with no methodological reason to account for the differences in findings. The significant contribution of duration of illness to general intellectual functioning shown in the present study indicates that the effects of this variable demand consideration even though its role in cognitive dysfunction remain unclear.

In one particular aspect of physiological functioning, namely cerebral metabolism, the work of Lavy et al. (1979) suggests that disease duration is not a strong determinant of disease effects. They measured regional cerebral blood flow (rCBF) in PD patients and found it to be significantly reduced, particularly in elderly patients with dementia. The decreases in rCBF in the elderly PD patients far exceeded the "physiological" rCBF decline associated with advancing age as seen in normal control subjects. These researchers expected the reduction in rCBF to correlate

with the length of time the patient had been ill as a reflection of a combination of advancing age and disease effects, but rCBF was reduced regardless of disease duration. Rather, it was significantly linked to age and the presence or absence of dementia.

The importance of age at disease onset as a determinant of disease effects was further demonstrated in the results of the multiple regression analysis performed on the Memory component. In addition to present age, age at onset emerged as a significant predictor of memory span functioning. The patient with poor memory span was older and had experienced disease onset at a later age. This implies that, of the cognitive components examined here, memory span was the most affected by late onset which would suggest that those brain structures involved in memory span functioning are most vulnerable to the late development of PD. The hippocampus may become more susceptible to senile plaque and neurofibrillary tangle formation (or the cholinergic system may be more vulnerable to disruption) with advancing age, and therefore may be more easily damaged by late-onset PD.

The composite influence of the independent variables selected for investigation here, explained only 27% of variation in memory span, whereas they explained 41% of variation in general intellectual functioning and 42% of variation in linguistic skills. The remaining 73% of variation in memory span would be explained by error and variables not included in this study.

One would presume that impaired memory span would be a direct consequence of brain changes caused by aging and the disease process. If so, the disease-related predictor variables ought to reflect these brain changes and therefore produce higher contributions to variation in memory span than shown here. However, memory span is also a

strong measure of attention and freedom from distractability. Variables such as test-taking anxiety, tiredness and premorbid cognitive ability may be some of the variables contributing to the unexplained variation.

The profile of the patient who performed poorly on linguistic skills is quite different to the poor performer on the other two cognitive components. He is the older, more depressed patient, who suffered disease onset at an early age and has been sick for a longer period of time. This is the only component where duration of illness emerged as a significant predictor. It is unlikely that those brain structures responsible for the performance of linguistic skills are selectively more affected by the duration of PD than those involved in general intellectual functioning and memory span. As a component of cognitive functioning, linguistic skills is rather different to the other two components. Whereas both general intellectual functioning and memory span develop spontaneously, the acquisition of linguistic skills demands organised training. As trained skills, proficiency would depend to some extent on the practise of these skills which may be affected by the emotional status of the patient.

It is possible that the late-onset PD patient would have made some emotional adjustment to old age and have developed an acceptance of a general decline in health prior to PD onset, unlike the younger, early-onset PD sufferer who probably expected deteriorating functional ability to be a consideration for the future rather than of immediate import. The diagnosis of PD for the younger patient sets him apart from his relatively healthy peer group and the disease may disable him to the extent that his working life has to be cut short. The sufferer may become increasingly depressed at the progressive limitations placed on his lifestyle by the disease and the failure of antiparkinson drugs to offer a cure. As a

consequence of this emotional state, he is likely to become less interested in events around him. He will read less and find less reason to write. As he generally makes less use of his linguistic skills, his proficiency will decline.

This positions depression as reactive rather than being an integral part of PD. The views of other researchers, as to whether depression is a primary or secondary consequence of the disease, remain at variance. Riklan et al. (1973) suggested that it was psychogenic, yet Marsh and Markham (1973) said that it was probably not psychogenic. Markham et al. (1974) said that it was not clear whether depression was a primary or secondary effect, while Robins (1976) claimed that both primary and secondary elements were operative. It is difficult to evaluate depression in PD and the nature of this relationship seems open to the interpretation of the individual researcher.

The present study showed depression to be significantly related to one component of cognitive functioning, namely linguistic skills, but not to affect cognitive functioning as a whole. Mayeux et al. (1981) also found depression to be significantly related to aspects of cognitive functioning: calculations, digit span and visuomotor tasks. Besides sample size (the patient sample used in the Mayeux study was larger than the present sample - 55 patients as opposed to 43), there is little difference in the demographic profiles of the two samples to account for these differences. The source of the discrepancies may lie in the different assessment techniques utilised: Mayeux and his colleagues used the Beck Depression Inventory and a modified version of the Mini Mental State Examination.

Depression showed no significant relationship with present age, age at onset, duration of illness or sex. These results substantiate the findings of Horn (1974), Markham et al. (1974) and Robins (1976).

Depression in PD demands further examination. Definitive conclusions may, however, only be established by research in the biochemical area. The role of the loss of central monoamines in causing, or contributing to, depression in PD patients remains to be fully investigated.

Dementia would most reliably be indicated by severe impairment in general intellectual functioning and memory span rather than linguistic skills, the latter having been shown to involve trained cognitive operations which are more easily influenced by emotional factors. The time-related variables would, therefore, be stronger predictors of dementia in PD than depression and sex which exert only negligible inf[illegible]. Although at present the exact nature of the [illegible]ive influences exerted by the time-related varia[illegible]on cognitive dysfunction remains unclear, there is no indication that any subgroup of patients exists which responds differently to their influences.

The cluster analytic investigations failed to demonstrate the existence of a group of sufferers susceptible to dementia, or a group of sufferers resistant to dementia. The failure of major groups to emerge when the three cognitive components were explored separately and in combination suggests that subgroups do not exist in relation to aspects of cognitive functioning or overall cognitive functioning. The continuous distribution that was found to characterise cognitive functioning among PD patients indicates that demented patients, rather than constituting a subgroup of sufferers, represent the severely impaired extreme of the distribution.

It is a criticism of the present study, and in fact a drawback of research into cognitive functioning in PD in general, that although psychometric testing provides the most reliable method of mental status evaluation, the severely demented sufferers must be precluded from this form of assessment because of the nature and extent of their mental disability. We are therefore forced to draw conclusions based on the trends which emerge from the performance of less severely impaired sufferers.

A continuous distribution of cognitive functioning among PD patients is in accordance with the findings of Pirozzolo et al. (1982). These researchers concluded that a continuum of cognitive deficits appears in PD patients. Deficits occur in a graded fashion throughout the patient population and are not restricted to any subgroup. Both the present study and the Pirozzolo study used psychometric measures, but the latter included a number of visual-spatial and timed motor response tests. The disadvantage of using visual-spatial and motor tests in assessing cognitive functioning in PD patients was discussed in Chapter 5. Their results are therefore contaminated and for this reason the present study cannot be regarded as providing unequivocal support for their findings.

It is difficult to compare the present findings with those studies which identified the existence of subgroups of sufferers because of differences in assessment techniques and research procedures. However, the careful examination of two of these studies in particular raises the possibility that their results may mask a continuous distribution of cognitive functioning among PD sufferer .

Lieberman et al. (1979) found two subgroups of patients and concluded that two separate disease disorders could be distinguished: one, exclusively a motor disorder

with a longer and more benign course occurring in a younger population, and the other, a motor followed by a cognitive disorder with a more fulminant course occurring in an older population. There are methodological limitations to this study which warrant discussion.

Firstly, these researchers used a subjective clinical interview technique to assess the mental status of their patients. This form of assessment technique is not suitable for research purposes, as noted earlier. Secondly, they separated the severely and moderately demented from the remainder of the sample and thereby experimentally manipulated the patient sample to create two groups. Lieberman (1974), when conducting an earlier study, wrote: "I have chosen to include only those patients with a moderate dementia (in one group) because as a group they can be clearly differentiated from normals without resort to detailed psychometric testing" (p.72). In the 1979 study, the same procedure was employed for presumably the same reason. Their research procedure may have produced two groups with significant group differences but in reality they may have disguised the existence of a single, homogeneous group of sufferers. Cognitive functioning assessed with sensitive psychometric techniques may have demonstrated a continuum with no true breakpoint.

Boller et al. (1980) correlated pathological data obtained at autopsy with clinical data of cognitive functioning obtained from hospital files. The fallibility of assessing intellectual status at time of death from historical data, gathered from interviews with clinical staff, is clear. The patient sample was divided into three groups: the severely demented, the mildly demented and those of normal status. Boller and his co-workers found a significant incidence of pathological pointers characteristic of AD (namely, senile plaques and neurofibrillary tangles) in the brains of those patients assessed as being demented. The demented

group differed from the non-demented group in having a significantly higher mean senile plaque density. (It should be noted that the non-demented group was not totally free of senile plaque formation, as will be discussed later.)

These findings lead these researchers to propose that two forms of PD may exist: the first with neuropathological changes limited to the basal ganglia and no dementia, and a second form with subcortical PD changes and cortical AD changes with dementia. However, the evidence of two groups of sufferers is not distinct. Firstly, a range of cognitive functioning among the patient sample was evident, and it must be acknowledged that the points of division between the severely demented, the mildly demented and normal status categories would, of necessity, have been arbitrary. Secondly, some patients who were classified as being of normal status showed AD changes while some patients with mild dementia had none of these changes. So, although a significant number of severely demented patients showed AD changes, and a significant number of patients with normal status showed no AD changes, there is a blurring of barriers.

Other studies have identified subgroups of sufferers by examining cognitive functioning in relation to motor deficits. Mortimer et al. (1982) correlated cognitive functioning deficits with measures of bradykinesia, tremor and rigidity. They found a significant relationship between severity of bradykinesia and decline in intellectual performance. The same relationship was not shown between severity of other motor symptoms and intellectual performance. Rather, tremor showed a significant inverse relationship with scores on a test of spatial orientation memory. These researchers then proposed that there are two forms of PD: one with predominant tremor and relatively intact intellectual functioning, and another with marked bradykinesia and cognitive impairment.

The inferential leap from results to conclusion is unfounded for a number of reasons. The correlation between motor symptoms failed to reach significance. Their study did not prove that PD patients show predominant bradykinesia or tremor to the extent that patient subgroups could be distinguished on the basis of predominant motor symptoms. Also, bradykinesia showed significant correlations only with measures of visual-spatial behaviour and psychomotor tasks, and failed to show significant correlations with measures of "higher" intellectual functions such as "fund of information" and "verbal memory". These results therefore show a significant relationship between the impairment of motor and visual-spatial behaviour, which is predictable as both behaviours are controlled by the same subcortical structures damaged by PD (Boller, 1982). Sparse evidence is provided for the existence of two forms of PD. Also, Marttila and Rinne (1976) found tremor to be more severe, rather than less severe, in patients with dementia.

No major methodological criticisms can be levelled at Garron et al. (1972). They found that they could divide PD patients into a "fast" and a "slow" group on the basis of combined motoric and intellectual response time. The distribution of response time scores "tended" to be bimodal. The two groups which emerged from this bimodality showed significant group differences with respect to age at testing and age at onset. The "slow" group was older and had experienced late onset of the disease. The researchers failed to report on the distribution of the number of items correctly answered. If bimodality had been demonstrated, patient subgroups based on cognitive functioning differences would have been suggested.

Garron and his co-workers investigated aspects other than the status of cognitive functioning. By examining the speed of intellectual functioning, a qualitative

dimensions of cognitive functioning was measured. Also, a motoric component was introduced in combination with the cognitive component as patients were required to manually operate the self-testing apparatus. Their study raises the interesting possibility that subgroups of patients may exist with respect to the interaction of PD disease symptomotology.

The question of patient subgroups may be approached from two premises. Firstly, subgroups of patients could indicate patient subtypes which, by virtue of individual attributes resulting from constitutional, environmental or psychological factors, respond differently to the same disease process. Secondly, subgroups could provide evidence for disease subtypes which produce varied disease symptomotology.

The present findings have implications for both premises. No subgroup of sufferers appears to exist that is particularly susceptible to, or resistant to, dementia. The continuous distribution of cognitive functioning that emerged suggests a wide variability of patient responses to the dementing process associated with PD. The effects of this process appear to be dependent on individual attributes which are not identifiable as the collective features of patient subgroups. An homogeneous patient group suggests the effects of a single disease process. The range of differential functioning probably reflects varying stages of degeneration. For example, when disease damage is confined to subcortical regions, little or no cognitive impairment is produced, but with progressive involvement of cortical regions more extensive and severe impairment becomes evident. This would support the views of Boller et al. (1980), Botez and Barbeau (1973), Hakim and Mathieson (1979), Lieberman (1974), Mayeux et al. (1983) and Sweet et al. (1976).

It may be challenged that the *continuum* of cognitive impairment may be *consequent* upon subcortical damage *alone and* that we are examining a subcortical dementing condition. It cannot be refuted that the influence of subcortical damage is reflected in the cognitive impairment in PD sufferers. However, there is no evidence to substantiate only subcortical *involvement* at a functional level. Boller et al. (1980) write:

> In PD...lesions of deep subcortical nuclear structures may be responsible for the changes in mental status sometimes referred to as subcortical dementia. However, our patients with mild dementia do not fit the clinical description of subcortical dementia, and they had neither the marked personality changes nor (specifically) the defective ability to manipulate acquired knowledge characteristic of that condition. (p.333)

Also, Mayeux et al. (1983) found no *significant* differences between the *neuropsychological* functioning of AD patients (*supposedly* cortically demented) and PD patients (supposedly subcortically demented). The failure of motor symptom severity to significantly correlate with the severity of impairment in aspects of cognitive functioning historically accepted to be cortically controlled *suggests* subcortical and cortical *involvement* in PD (Mortimer et al., 1982).

The cognitive changes seen in subcortical dementias are described as resembling those seen in the cortical dementias with the prominent exception of preserved *language* function. "Almost all *aspects* of language function are *undisturbed including* reading, writing, speaking and *comprehension*" (Heilman & Valenstein, 1979, p.486). If we evaluate the performance of our patient sample on the measures of reading, writing and comprehension used here, it is clear that these aspects of language are not undisturbed. A range of *language functioning* from

intact to impaired is evident which would suggest that impairment reflects more extensive neurological damage than the subcortex alone.

When subcortical and cortical dementias are discussed, the criteria for dementia must be clarified. As Mayeux et al. (1983, p.282) point out: "If dementia refers to an acquired intellectual impairment, then...PD should be so characterised. However, if more stringent criteria are applied, such as the presence of aphasia and agnosia, then (PD) might be exempt in (its) early stages". As aphasia and agnosia are symptoms of cortical dementia, Mayeux's words intimate a progression of the Parkinson dementia to cortical structures.

On a structural level, the neuropathological evidence gathered by Hakim and Mathieson (1979) and Boller et al. (1980) indicates subcortical and cortical involvement. Strong support for these findings is offered by the work of Whitehouse et al. (1983) and their discovery of the loss of cholinergic neurons in the basal forebrains of demented patients with PD which provides a morphological link between subcortical and cortical degeneration in PD. Whitehouse and his colleagues say:

> Since demented patients with PD have plaques and neurofibrillary tangles and show loss of neurons in the nucleus basalis of Meynert, we believe that similar pathophysiological mechanisms may operate in the dementias of AD and PD. Clinically, the cognitive symptoms in AD and PD have been referred to as examples of cortical and subcortical dementias, respectively. The overlap in clinical, pathological and neurochemical features between AD and PD, coupled with the demonstration of neuron loss in the nucleus basalis of Meynert in both diseases, may require reworking of this concept. (p.246)

Theoretically, the PD process may observe a neurological "pathway" of degeneration. The PD degenerative process

has a particular affinity for the dopaminergic neurons of the substantia nigra (Rinne, 1978) and this is where the process begins. Then it spreads, with Lewy body formation and neuronal loss in the caudate nucleus, globus pallidus and putamen (Pearce, 1978) as well as the hypothalamus (Mayeux et al., 1981). A striatal dopamine depletion occurs and an increase in acetylcholine activity takes place (Pearce, 1978). The characteristic motor symptoms are manifested together with visual-spatial perception and behaviour deficits (Boller, 1982). It is possible that at this point there may be other subtle changes in aspects of cognitive functioning in which these subcortical brain structures are involved, either on an individual basis or in a systemic arrangement with cortical structures. The degeneration then spreads further, resulting in a loss of cholinergic neurons in the basal forebrain and particularly in the nucleus basalis of Meynert which forms the pathological substrate for the loss of presynaptic cholinergic markers in the cortex (Whitehouse et al., 1983). Cortical acetylcholine activity is reduced, cortical senile plaques and neurofibrillary tangles form, and progressive cognitive dysfunction occurs.

It would be an oversimplification of a highly complex disease process to propose that this pattern of degeneration occurs in all PD patients and that dementia is the inevitable outcome. Any experienced clinician will confirm the observation that while some PD patients become demented, others remain remarkably intact. With reference to the present findings, the intellectually intact and demented patients would be representatives of the extreme ends of our continuous distribution rather than being members of separate groups.

The objective of PD research is to establish the boundaries of the primary disease process. Once the brain structures and biochemical systems disrupted by disease damage are known, the behavioural manifestations of the disease can be evaluated in relation to disease pathology, the ultimate goal being the development of new and more effective therapeutic approaches. Unfortunately, as is well-known, human behaviour often defies reductionism and this is no less evident in PD.

The work of Hakim and Mathieson (1979) and Boller et al. (1980) has been mentioned before but will be discussed further. Not only does the work of these researchers illustrate the complexities of PD and the issue of behaviour in relation to brain changes, but it also provides some neuropathological support for the present findings of a continuous distribution of cognitive functioning in PD patients.

Hakim and Mathieson (1979) examined the brains of 34 patients meeting neuropathological criteria for PD (Lewy bodies in the substantia nigra or locus ceruleus). They found evidence of histological changes characteristic of AD in 33 of the 34 patients. Specifically, these changes were senile plaques in the hippocampus (85% of patients), neurofibrillary tangles in the pyramidal cells of the hippocampus (85% of patients) and granulovacuolar changes in the hippocampal neurons (88% of patients). Age- and sex-matched controls showed a significantly lower incidence of these changes than the PD patients.

A number of histopathological and behaviour anomalies were found when comparing the autopsy findings with clinical notes concerning the cognitive functioning of the patients prior to death. The one patient free of all AD signs was a 70-year old man who had been ill with PD for many years and who had displayed symptoms of dementia for many years.

(Exact figures were not on file.) Fourteen patients had no descriptions on file of demented behaviour yet all of these patients showed evidence of AD brain changes. Many of the patients noted as having florid dementia showed markedly less severe AD histological features than a large proportion of those patients who showed no dementia. Unfortunately, the clinical criteria for dementia were not given.

Boller et al.'s 1980 proposal of the existence of two forms of PD distinguishable by differences in pathology and symptomotolgy was not supported by their findings. On autopsy, they examined 36 cases with a pathologically confirmed diagnosis of idiopathic PD. (Criteria for PD were neuron loss and Lewy bodies in the substantia nigra.) A search for senile plaques and neurofibrillary tangles was made in sections of the cerebral cortex and hippocampus.

Twenty patients (56% of the sample) showed some evidence of AD changes: senile plaques and/or neurofibrillary tangles. Fifteen of these patients (42% of the sample) met the criteria for a pathological diagnosis of AD. Of these 15 patients, 3 had been clinically assessed as being of normal mental status until death. Of the 16 patients showing no AD lesions, 4 were clinically described as being mildly demented. (The assessment of intellectual status was based on interviews noting alertness, affect, orientation, language functions, immediate, recent and long-term memory, insight and abstract reasoning.)

These studies demonstrate the high incidence of AD changes in PD patients which would explain the high incidence of dementia in PD patients. They show that these cortical changes vary in quantity and quality and could produce a gradation of cognitive functioning among the PD population. These studies also indicate the complexities of correlating

morphological changes with manifest behaviour because some patients assessed as being demented (albeit mildly) showed no cortical involvement while other patients assessed as normal would have been diagnosed, on pathological grounds, as being AD sufferers.

Dementia in PD is strongly age-related as it has been shown to be prevalent among those older patients who suffered late disease onset (Garron et al., 1972; Lieberman et al., 1979; Marttila & Rinne, 1976). This age-related trend is supported by the present findings although the evidence is not conclusive.

A number of brain changes that occur as the natural result of the aging process are similar to those occurring as the pathological result of PD. With respect to subcortical aging, a marked decrease in striatal dopamine has been shown to occur with advancing age in normal humans (Lavy et al., 1979), and it is the major biochemical correlate of PD. Mann and Yates (1982) point out that in old age there is an obvious loss of pigmented nerve cells from the substantia nigra and atrophy of those that remain, which is a major structural change occurring as a result of PD. With respect to cortical changes occurring with natural aging, regional cerebral blood flow levels are reduced and cholinergic levels may be reduced, not to pathological levels but to the extent of predisposing the aging brain to pathological changes should aggravating factors (like PD) intrude (Mann & Yates, 1982).

Early-onset PD has been associated with a slow evolution of the disease (Pollock & Hornabrook, 1966) and this may be due to the disease attacking a younger, healthier brain. Late-onset PD produces an acceleration of the disease process so that within a relatively short period of time the patient becomes severely disabled in all aspects of the disease (Pederzoli et al., 1983). Early-onset PD may

be described as "premature aging" of the central nervous system (Mann & Yates, 1982) with aging changes occurring earlier than in normals. Late-onset PD may be described as "accelerated aging" as it produces an increase in age-related changes already in progress. When onset occurs later in life, the aging brain is particularly vulnerable to disease attack and pathological changes are facilitated in both the subcortex and the cortex placing the elderly patient at a much higher risk of dementia.

Dementia in PD is a reflection of the extensive neurological damage brought about by the progressive degenerative disease process. The present study has identified the age of the patient, the age at which disease onset occurs and the length of time the disease is in progress as important determinants of cognitive dysfunction. In my opinion, it is the task of future research to separate their effects. A series of studies involving the experimental control of these variables will be required to establish the relative importance and nature of influence of each individual variable.

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APPENDIX I

ABBREVIATED FORMS OF LURIA'S NEUROPSYCHOLOGICAL INVESTIGATION

MEMORY SUBSCALE

1. I am going to say seven words. After I finish saying them, I want you to repeat as many of them back to me as you can remember. (Present words at the rate of one per second.)

   house forest cat night table needle pie

   (Have subject recall as many of the words as possible. Go on to next trial if subject is unable to recall another word, or if subject has recalled all seven words.)

   You remembered __ words out of the seven on that trial. I am going to say the same seven words again and I want you to try to recall as many as you can. Please begin only after I have finished. However, before I begin, I want you to tell me how many words you think you will remember this next time after I finish saying the words again. Remember, you got __ out of seven on the last trial. (Do this for each trial until subject reaches two perfect trials in a row or five trials.)

	predict	actual	house	forest	cat	night	table	needle	pie
1									
2									
3									
4									
5									

2. I want you to remember some words that I am going to say:

house tree cat

Repeat them. Now look at this picture. What do you see? (Present Card A and have subject describe picture for 15 seconds.) Now can you tell me, what were the words I asked you to remember?

house (__) tree (__) cat (__)

---

3. I want you to remember some other words:

table carpet flower

Repeat them. Now look at this picture. What do you see? (Present Card B and have subject describe picture for 15 seconds.) Now can you tell me, what were the words I asked you to remember?

table (__) carpet (__) flower (__)

---

4. Now I am going to say some words and I want you to try and remember them:

man hat door

Now please repeat those words to me. (If incorrect, say once before proceeding: "Remember the words are man, hat, door".) Now try to remember these words:

light stove cake

Tell me, what were the three words I said first?

man (__) hat (__) door (__)

What were the three words I said second?

light (__) stove (__) cake (__)

---

5. Now I am going to read two sentences to you and I want you to remember them.

"The sun rises in the east." *Please repeat that.*
"In May the apple trees blossom." *Please repeat that.*

What was the first sentence?
(The sun rises in the east. ___)
What was the second sentence?
(In May the apple trees blossom. ___)

---

6. Now I am going to show you some pictures. With each picture, I am going to say a word. When I finish, I will show you the pictures and I want you to say the word that goes with it. For example, I will show you this picture (present Card A) and say "horse". When I show you the picture later, what would you say? (Prompt subject if necessary.) You will have five seconds to look at each picture.

Card C (energy)	___	Card G (family)	___
Card D (employment)	___	Card H (project)	___
Card E (party)	___	Card J (pollution)	___
Card F (happy)	___		

RECEPTIVE SPEECH SUBSCALE

1. (Place a pencil, a key and a comb clockwise in a triangle before the subject.)

   Point at the pencil. ___
   Point at the key. ___

---

2. (Keep the triangle of pencil, key and comb on the table.)

   Point with the key to the pencil. ___
   Point with the pencil to the key. ___

---

3. (Keep the triangle of pencil, key and comb on the table.)

   Point to the *pencil with the key*. ___
   Point to the comb with the pencil. ___

---

4. Will you tell me whether the "father's brother" and the "brother's father" are two people or the *same person*?

   Same ___ Two ___

---

5. What would you call your "father's brother"? (Uncle ___)

   What would you call your brother's father"? (Father ___)

   (Give subject response paper.)

6. I would like you to draw a cross beneath a circle. (___)

---

7. I would like you to draw a circle to the right of a cross. (___)

RECEPTIVE SPEECH SUBSCALE

1. (Place a pencil, a key and a comb clockwise in a triangle before the subject.)

   Point at the pencil. ___
   Point at the key. ___

---

2. (Keep the triangle of pencil, key and comb on the table.)

   Point with the key to the pencil. ___
   Point with the pencil to the key. ___

---

3. (Keep the triangle of pencil, key and comb on the table.)

   Point to the pencil with the key. ___
   Point to the comb with the pencil. ___

---

4. Will you tell me whether the "father's brother" and the "brother's father" are two people or the same person?

   Same ___ Two ___

---

5. What would you call your "father's brother"? (Uncle ___)

   What would you call your brother's father"? (Father ___)

(Give subject response paper.)

6. I would like you to draw a cross beneath a circle. (___)

---

7. I would like you to draw a circle to the right of a cross. (___)

---

8. Tell me which is right:

   "Spring comes before summer" OR "Summer comes before spring"?

   (Spring comes before summer. ___)

---

9. Which boy is shorter if Tom is taller than Arnie?

   (Arnie. ___)

---

10. Please listen to this statement:

    "The woman who worked at the store came to the school where Mary studied to give a talk."

    Who gave the talk? (The woman. ___)

    What was Mary doing? (Studying, attending school. ___)

EXPRESSIVE SPEECH SUBSCALE

1. I am going to show you some cards with sentences that have a word missing. Please give me a word that you think can fill in each sentence.

   Card K _____ (___)

   Card L _____ (___)

   Card M _____ (___)

---

2. Here is a card that has three words on it. Make up a sentence that includes all three of these words. (Present Card N.)

   Response: _____ (___)

---

3. Now I am going to give you a card on which the words are mixed up. If they are arranged correctly they can make a sentence. I want you to arrange them so that they do make a sentence. (If subject responds incorrectly, say: "That is not quite right. Keep trying.")

   Present Card O. (I spoke to the doctor about my headache. ___)
   Present Card P. (I feel much better today than I did yesterday.___)

READING SUBSCALE

1. Now I am going to show you cards with sentences on them. Please read them to me. (Present Card Q, then Card R.)

   Card Q: The man went out for a walk. ___

   Card R: There are flowers in the garden. ___

---

2. Now read these sentences carefully.
   (Present Card S, then Card T.)

   Card S: The sun rises in the west. ___

   Card T: The boy went to bed because she was ill. ___

---

3. Now I am going to show you a card with a paragraph on it. Read it out aloud to me quickly but carefully.
   (Present Card U. Circle missed words.)

   John was a boy who liked apples - especially if they were stolen. One dark night he went into an orchard, plucked what he took to be an apple and set his teeth in it. It was, however, a very unripe pear and his loose front tooth stuck in the fruit. Now he only steals apples in the daytime.

WRITING SUBSCALE

(Hand subject response paper.)

1. I would like you to write your name for me.

---

2. I am going to dictate a sentence to you, and I want you to write it down on your sheet of paper.

   "All of a sudden it began to rain."

---

3. Now would you please write:

   "Jack and Jill went up the hill."

---

4. *(Hand subject mock-up of cheque.)*

   Now would you please complete this for me as you would a real cheque. Make the cheque out to the value of one hundred rand. You can make it payable to whomever you wish, but I want you to sign your own name at the bottom.

---

5. Now would you please write a sentence for me. Make up one of your own.

WRITING SUBSCALE

(Hand subject response paper.)

1. I would like you to write your name for me.

---

2. I am going to dictate a sentence to you, and I want you to write it down on your sheet of paper.

   "All of a sudden it began to rain."

---

3. Now would you please write:

   "Jack and Jill went up the hill."

---

4. (Hand subject mock-up of cheque.)

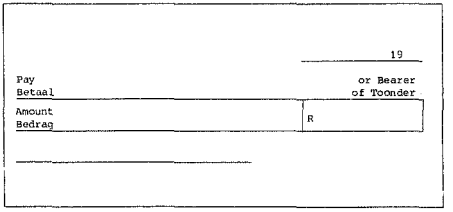
   Now would you please complete this for me as you would a real cheque. Make the cheque out to the value of one hundred rand. You can make it payable to whomever you wish, but I want you to sign your own name at the bottom.

---

5. Now would you please write a sentence for me. Make up one of your own.

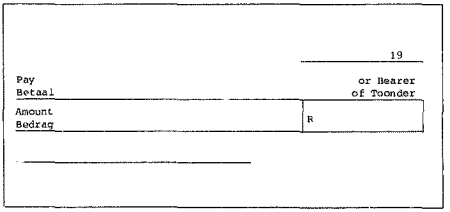
Writing Subscale

Item 4



Writing Subscale

Item 4



The cards used here correspond to the following cards from Luria's Neuropsychological Investigation:

Card A - M7
B - H28
C - M10
D - M11
E - M12
F - M13
G - M14
H - M15
J - M16
K - J32
L - J33
M - J34
N - J35
O - doctor - my - spoke - the - about - headache - I - to
P - today - feel - much - did - I - than - better - yesterday - I
Q - K18
R - K20
S - K21
T - K22
U - K23

APPENDIX II

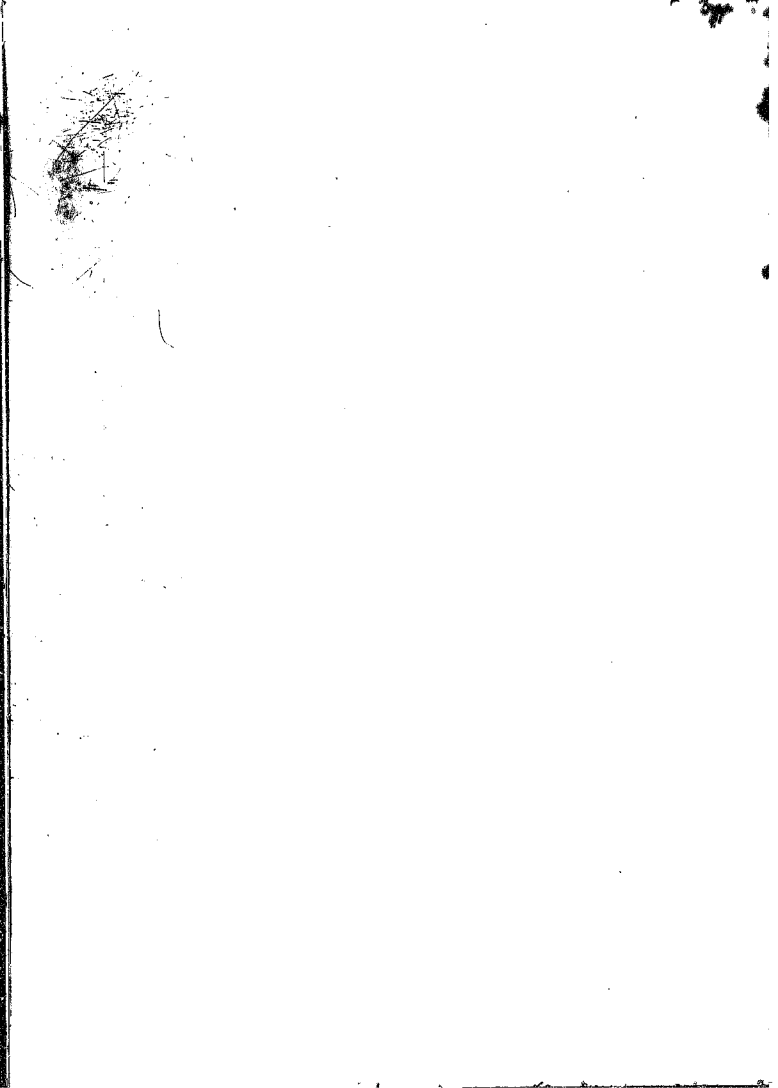
PEARSON PRODUCT-MOMENT CORRELATION MATRIX

	Sex	Age	Time	Onset	Info	Digits	Similar
Sex	1,000						
Age	0,0904 p=0,263	1,000					
Time	-0,1931 p=0,120	-0,3160 p=0,019	1,000				
Onset	0,1617 p=0,150	0,8887 p=0,000	-0,7158 p=0,000	1,000			
Info	-0,1181 p=0,725	-0,5921 p=0,000	0,0085 p=0,479	-0,4399 p=0,002	1,000		
Digits	-0,0194 p=0,451	-0,1982 p=0,101	-0,1433 p=0,180	-0,0767 p=0,313	0,4741 p=0,001	1,000	
Similar	0,0242 p=0,439	-0,3843 p=0,005	0,1674 p=0,246	-0,3348 p=0,014	0,7027 p=0,000	0,4984 p=0,000	1,000
Vocab	0,1547 p=0,141	-0,4568 p=0,001	-0,0282 p=0,426	-0,4226 p=0,017	0,8044 p=0,000	0,3752 p=0,007	0,7146 p=0,000
Memory	-0,1309 p=0,201	0,2237 p=0,075	0,0367 p=0,408	0,1469 p=0,174	-0,3811 p=0,006	-0,5598 p=0,000	-0,5500 p=0,000
RecSp	-0,1067 p=0,248	0,1628 p=0,148	0,0617 p=0,347	0,0900 p=0,283	-0,4795 p=0,001	-0,4252 p=0,002	-0,4836 p=0,001
ExpSp	-0,1024 p=0,252	0,6543 p=0,000	-0,0991 p=0,264	0,5294 p=0,000	-0,6263 p=0,000	-0,4604 p=0,001	-0,5415 p=0,000
Read	0,0165 p=0,458	-0,1912 p=0,122	0,0675 p=0,334	-0,1660 p=0,144	-0,2036 p=0,095	-0,2493 p=0,053	-0,4410 p=0,002
Write	-0,2004 p=0,099	0,1418 p=0,182	0,0762 p=0,314	0,0675 p=0,334	-0,4492 p=0,001	-0,4740 p=0,001	-0,4765 p=0,001
Depress	-0,0353 p=0,411	-0,0430 p=0,392	-0,0707 p=0,326	0,0026 p=0,493	-0,1326 p=0,198	-0,1618 p=0,150	-0,1617 p=0,150

PEARSON PRODUCT-MOMENT CORRELATION MATRIX cont.

	Vocab	Memory	RecSp	ExpSp	Read	Write	Depress
Vocab	1,000						
Memory	-0,4551 p=0,001	1,000					
RecSp	-0,5660 p=0,000	0,5406 p=0,000	1,000				
ExpSp	-0,6230 p=0,000	0,4483 p=0,001	,4547 p=,001	1,000			
Read	-0,1877 p=0,114	0,3188 p=0,019	0,3466 p=0,011	0,0[illegible] p=0,4[illegible]	1,000		
Write	-0,4810 p=0,001	0,3711 p=0,007	0,6076 p=0,000	,5243 p=,000	[illegible] p=0,001	1,000	
Depress	-0,2418 p=0,059	0,2610 p=0,045	0,4650 p=0,001	0,1305 p=0,202	0,1680 p=,139	0,2[illegible] p=0,070	1,000





Author Basnett Denice
Name of thesis Dementia In Long-term Parkinson's Disease Patients Receiving Chronic Levodopa Therapy. 1985

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