WHAT DOES THE TERM "DEPRESSION" MEAN IN PARKINSON'S DISEASE?

by

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TABLE OF CONTENTS

SUMMARY

The overlap of the features of Parkinson's disease (PD) and affective disorder is likely to produce an increased rate of diagnosis for depressive disorders in PD patients. Although the literature alludes to these problems, no systematic investigation of the extent of this has yet been undertaken.

A cross-sectional comparison of the Present State Examination (PSE) profiles and diagnoses between 52 PD subjects, 32 healthy control subjects and 30 depressed subjects was performed. The PSE profile of the PD group was very similar to that found by Brown and MacCarthy (1990), and consisted mostly of non-specific symptoms. The prevalence rate for depressive disorders in PD was 3.4%. The PSE profile of the PD subjects was similar to the profile of the control group rather than the depressed group.

When the diagnostic cut-off values on the Beck depression inventory (BDI), Hamilton depression rating scale (HDRS), Montgomery Åsberg depression rating scale (MÅDRS) and the Hospital anxiety and depression scale (HAD) were compared with the PSE diagnoses, the accepted cut-off values for the BDI, MÅDRS and HAD were found to be overinclusive producing a spuriously high prevalence rate. The accepted cut-off value for the HDRS may be acceptable. The excess was due to items on the rating scales contaminated by the features of Parkinson's disease. The DSM-III diagnostic criteria were also overinclusive.

The validated cut-off for the MÅDRS was applied to longitudinal data. Survival analysis revealed the incidence of depressive disorders in PD to be 43 per 1000 person-years.

ABBREVIATIONS

BDI:	Beck depression inventory.
DSM-III:	Diagnostic and statistical manual of the American Psychiatric Association (3rd edition).
DST:	Dexamethasone suppression test.
GNT:	Graded naming test.
GPRUIS:	General practice research unit interview schedule.
HAD:	Hospital anxiety and depression scale.
HDRS:	Hamilton depression rating scale.
H&Y:	Hoehn and Yahr staging for Parkinson's disease.
ICD-9:	International classification of disease (9th ed.).
MÅDRS:	Montgomery Åsberg depression rating scale.
MBHI:	Milton behavioural health inventory.
MMPI:	Minnesota multiphasic personality inventory.
MMSE:	Mini mental state examination.
MPI:	Maudsley personality inventory.
MSA:	Multiple system atrophy.
NART:	National adult reading test.
NUDS:	North-Western universities disability scale.
PD:	Parkinson's disease.
POMS:	Profile of mood states.
PSE:	Present state examination.
SCID:	Structured clinical interview for DSM-III-R
WAIS:	Wechsler adult intelligence scale.
WEBS:	Webster's scale for Parkinson's disease.
WMS:	Wechsler memory scale.
95%CI:	95% confidence interval.

1) INTRODUCTION.

In this thesis I shall examine the measurement and diagnosis of affective disorder in Parkinson's disease (PD). Firstly, I shall briefly summarise the accepted relationship between "depression" and PD. Then I shall review the concept of the diagnosis of affective disorder in general, and the particular problems which have been described in the assessment of affective disorders in elderly subjects, and in medically ill patients. This will emphasise the different ways that the term "depression" has been employed, and the differing approaches to the diagnosis of affective disorders that have been used. Then I shall critically review the literature referring to depressive symptoms and depressive disorders in PD, with particular emphasis on the methodology used.

I shall describe the cross-sectional assessment using various methods of assessment of mood of PD subjects who are taking part in a longitudinal assessment of cognitive functioning in PD. This will allow the performance of the commonly used rating scales for the assessment and diagnosis of depressive disorders to be compared in PD. The results from this cross-sectional study will then be applied to the longitudinal data, to determine the incidence of depressive disorder in PD. Finally I shall critically discuss the methodology and results in this thesis and relate them to the literature that already exists in this area.

2) PARKINSON'S DISEASE AND "DEPRESSION": THE PRESENT UNDERSTANDING.

Depression of mood in Parkinson's disease (PD) has been described as a "*frequently encountered enigma for clinicians*" (Blazer 1989), yet from reading the literature, it would appear that the nature and frequency of depressive disorders in PD are well understood. This chapter summarises the current accepted understanding. "Depression" is said to occur in 8% (Schiffer et al 1988) to 63% (Warburton 1967) of patients with PD, with an accepted figure being 40% (Baldwin and Byrne 1989). The clinical associations of depressive symptoms in PD have been variously reported. Horn (1974) and Robins (1976) found no sex difference, but Warburton (1967) and Celesia and Wannamaker (1972) found a higher prevalence in females with PD. Age of the patient and duration of illness have consistently shown no relationship with "depression". Dakof and Mendelsohn (1986) stated that l-DOPA does not act as an antidepressant, but "*may produce activation that some patients report as mood lifting*". l-DOPA improves "depression" in PD (Celesia and Barr 1970), makes "depression" worse (Cherrington 1970; Mindham et al. 1976) or has no effect (Marsh and Markham 1973; Mayeux et al 1981). Electroconvulsive therapy improves both affective disorders in PD and PD itself (Lebensohn and Jenkins 1975: Balldin et al 1980), as have tricyclic antidepressants (Strang 1965; Anderson et al 1980).

The prevalence rate for depressive disorders is 14.6% in medical in-patients (Feldman et al 1987); 11.5% for major depression in elderly medical hospitalised patients (Koenig et al 1988); 15% in non-institutionalised elderly (Berkman et al 1986); and 12.4% for major depression in institutionalised elderly (Parmelee et al. 1989). The prevalence rate for "depression" in PD is greater than these figures, and can be explained in differing ways. Firstly there may be a common neurochemical pathway resulting in both features of depressive disorder and of PD,

possibly representing a sub-type of PD. Studies have shown a decrease in 5-HT in the cerebrospinal fluid of PD patients who are "depressed" when compared to "non-depressed" patients with PD (Mayeux et al 1984a; Kostic et al 1987). Secondly disability due to PD may cause a psychological adjustment reaction resulting in depressive disorders (Taylor et al 1986). The third possibility to explain the increased prevalence of "depression" in PD is that methodological errors and inconsistencies occur throughout this literature, and have resulted in the over-estimation of the prevalence of depressive illness in PD.

That there is a relationship between the symptoms and signs of depressive illness and those of PD has been clearly demonstrated. Significant correlation between the features of depressive disorder and disability due to PD has been shown by Hoehn et al (1976): Mindham et al (1976); Singer (1976); Nissenbaum et al (1987); Santamaria et al (1986a: in patients who were considered not to have an affective disorder) and Brown et al (1988: with changes in disability correlating with changes in mood). Gotham et al (1986) found a somatic grouping in a factor analysis of the individual items of the Beck depression inventory (BDI). Santamaria et al (1986a) demonstrated a discrepancy between the diagnosis of depression by an experienced psychiatrist and the BDI, with the BDI scores being inflated by somatic symptoms.

If it is found that a common neurochemical pathway is responsible for the causation of PD and a type of depressive illness, much insight would be gained into the causation of "endogenous" type of depression and may suggest that the basal ganglia had a role in affective functioning. Conversely, if it was found that the depression was "reactive" in nature, this would provide a model for further investigation of the aetiology for this type of depression. However, it is my contention that despite methodological problems being referred to in the literature, insufficient examination of their role has been undertaken.

In summary, the literature concerning the relationship between "depression" and PD contains many contradictory results, and a wide range for the prevalence of depressive disorders in PD. Inconsistencies of this magnitude are often due to methodological factors.

Therefore, in the next section of this thesis, I will examine the usage of the term "depression", and will discuss the ways of diagnosing depressive disorder. I will then discuss how the methods for diagnosing depressive disorder can be affected by the patients being elderly or medically ill. I will then demonstrate the overlap of the symptoms and signs of depressive illness and PD, and finally discuss why this means that a re-evaluation of the relationship of depressive disorder and PD is required.

3) THE NATURE AND MEASUREMENT OF DEPRESSIVE ILLNESS.

A) WHAT IS "DEPRESSION" AND HOW CAN IT BE DIAGNOSED?

In this section I will discuss the ways in which the term "depression" is used and the methods by which affective disorders can be diagnosed. The term "depression" is used in several different senses, and leads to confusion in applying it, and "*the concept of the state is obscure*" (Snaith 1987). Veith and Raskind (1988) find "*depression*" a

> "*troublesome term that can be applied to an array of conditions that include a normal fluctuation in mood state, feelings of demoralisation, episodes of bereavement, a transient psychological reaction to injury or loss, or the neurovegetative syndrome that characterises a major depressive episode*".

The literature concerning affective disorder and PD uses the term "depression" inconsistently. Firstly the term is used as a symptom which subjects experience, and in this context the distinction between dysphoria, demoralisation and "depression" is not made clear. Secondly it is used to describe a general clinical impression of a morbid state as made following a routine interview. Thirdly it describes a state diagnosed by the summation of symptoms and signs greater than a cut-off score on an ordinal rating scale. Lastly, it describes a clearly defined syndrome such as is described in the Diagnostic and Statistical Manual (DSM-III: American Psychiatric Association) "Major Depression". The three latter uses of the term have areas of overlap in usage, and the clinical diagnosis, the diagnosis made by a rating scale and that made by a clearly defined syndrome should mostly be the same. In an attempt to standardise research diagnosis, the general clinical diagnosis has fallen out of favour, leaving research workers to either adopt a diagnosis made by a rating scale or by a clearly defined syndrome.

The distinction between these uses is unclear; not all people with dysphoria have sufficient symptoms to be diagnosed as having a major depressive disorder (Kathol and Petty 1981), and there is an "*arbitrary line dividing a case of affective disorder from a normal person*" (Murphy 1986). At present, the clearest definition of terms is provided in DSM-III or in the Present State Examination (PSE: Wing et al. 1974). Despite this clear definition, difficulties remain. For example, at what stage should a reasonable reaction to a chronic disabling disease such as PD be considered a pathological process?

The selection of an instrument to measure mood is very important but it is

> "*often an arbitrary decision undertaken without much thought concerning the characteristics of the scale or whether it is well suited to the study*" (Carroll et al 1973).

The overlap between the features of PD and those of depressive disorders means that the characteristics of any particular method of assessment of affective disorder in PD must be carefully considered.

Rating scales are often described as "valid and reliable", but this is an oversimplification as there are several indices of validity and reliability. These indices will not remain constant when used in conditions which differ from those in which the rating scale was originally tested. Reliability is the extent to which a test would give consistent results on being applied more than once to the same people under the same conditions, and relates to the re-administration of a scale (test-retest reliability); to the internal consistency of a scale; and to the repeatability between different administrators of the test (inter-rater reliability) (Morley and Snaith 1989).

The validity of a rating scale depends on several areas which include content and criterion validity. Content validity examines whether a rating scale adequately

probes the specific domain required, and is the extent to which a test is really measuring what the researcher intends it to measure. In other words, does the scale contain items attributable to outside influences or processes? Criterion validity examines the discriminatory power of a scale and can be subdivided into two areas: concurrent validity (when the measure and the criterion are measured at the same time) and predictive validity (where the criterion is measured later). Criterion validity is expressed in terms of sensitivity and specificity. The sensitivity of a test is the proportion of positive cases correctly identified, whereas the specificity is the proportion of non-cases correctly identified (see Table 1: Morley and Snaith 1992). The alteration of cut-off scores affects these parameters. The BDI and Hamilton Depression rating scale (HDRS: Hamilton 1960) both

> "*provide a general measure of the severity of the illness on the assumption that the sum of the severity of individual symptoms indicates the overall severity of the disorder*" (Snaith and Taylor 1985).

Ordinal rating scales used to diagnose affective disorder are particularly problematic in PD, because if the sum of the number of symptoms present is greater than a previously assigned cut-off, the "diagnosis" is made, irrespective of which symptoms and signs are present. Gurland (1976) found that symptom checklists elicit many depressive-type responses among older patients, but less than half those who scored highly were clinically depressed. Self-assessment questionnaires and observer-rated scales each possess advantages and disadvantages.

Self-rating scales do not require experience in eliciting psychopathology on the part of the investigator, and can be administered by post (as Gotham et al 1986). However, with a self-rating scale it is impossible to determine what criteria a person uses to give an answer. The answer will reflect the question that the subject thinks is being asked, and this may not be the same as that intended (unless

the question has been constructed with extreme care or luck!). The investigator will obviously be interested in the affective status of an individual, but the subject may relate all the questions to their PD. Golbe and Pae (1988) estimated the reliability (although they erroneously claimed it was validity) of postal administration of a self-rated scale for disability in PD by comparing it with the same questionnaire administered by a rater within one month of postal administration. They found that the kappa values were low and concluded that *"mail surveys in PD should either be avoided or rigorously pretested for validity"* (by which they mean reliability).

Vogel (1982) suggested that in PD *"hypomimia and a low voice"* may bias a rater to suggest a depressed mood, recommending self-rating scales *"because they are independent of the patient's reduced capacity for emotional expression"*. However a variety of factors may impair the ability of a patient to complete a self-rating form (e.g.: illiteracy, poor concentration, cognitive impairment etc.). Observer-rated scales require an experienced observer in order to perceive a global picture (or gestalt) of the patient's condition (Pichot 1972), and this may not be the case where raters are not psychiatrists or clinical psychologists (e.g. Williams 1988). Observer-rated scales are better overall in evaluating the presence and severity of psychopathology (Hamilton 1976). The observer can rate manifestations of the depressive illness of which the patient is unaware (such as loss of insight, depressed appearance or agitation), and has the experience to be able to rate a symptom or sign in comparison to that seen in other patients which an individual patient cannot do.

In summary, it is clear that the validity and reliability of a rating scale are dependent on many factors. It follows that when a rating scale is used in a different population from that in which it was originally tested, there will be problems. In the next section, examples of this found in the literature relating to

the assessment of affective disorder in medically ill patients and in the elderly will be discussed.

B) DEPRESSION IN THE MEDICALLY ILL AND ELDERLY.

Moffic and Paykel (1975) compared the clinical features of depression in a group of medically ill patients and a group of depressed patients. They found that depression in medical patients tended to be mild, with

> "*less suicidal feelings, and more feelings of pessimism, helplessness and anxiety, more retardation, agitation, self-pity and a distinct quality to the depression*". They comment that "*symptoms of medical illness must be distinguished from somatic symptoms characteristic of depression*". The "*special features of medical depression...*"

arise from the realistic appraisal of the specific situation to which the medical patient is exposed, whereas there is a striking discrepancy between the depressive's self-image and the facts.

The relationship between depression and medical illness has been critically reviewed by Kathol and Petty (1981). They comment that psychometric instruments and the commonly used interview check-list criteria for depression include "*physiologic items*". They show that somatic symptoms occur with significant frequency in the non-depressed medically ill population. Furthermore, severe medical disease leads to a greater frequency of these complaints. They conclude that these symptoms alone

> "*could account for or nearly account for a diagnosis of depression using symptom check-lists in the presence of medical illness*".

In his review of mood disorders after stroke, House (1987a) emphasises the need to consider the validity of a rating scale when it is used in a different population from

that originally intended. He further maintains that the use of screening instruments without additional clinical information has led to the term "*depression*" becoming a "*catch all for all varieties of mood disorder*".

Perhaps the clearest demonstration of the effects of physical illness on the performance of rating scales for depression on the diagnosis of depression has been made by Creed et al (1990). They used various measures of physical and psychiatric disability in patients suffering from rheumatoid arthritis, finding that a small increase in the diagnostic threshold for psychiatric conditions doubled the prevalence rate. Symptoms directly attributable to arthritis inflated the estimated prevalence of psychiatric disorder in rheumatoid arthritis and may indicate erroneously a direct relationship between severity of rheumatoid arthritis and psychiatric disorder. They caution that the increasing use of self rating scales for the diagnosis of psychiatric disorder in rheumatoid arthritis requires the ascertainment of the correct threshold for a particular instrument for use in rheumatoid arthritis.

In examining the role of ageing in depression, Pitt (1986) states that

> "*major depressive illness in the elderly is often much the same as in younger patients, but there may be features which mask, complicate or give an unusual quality to the underlying mood disorder*".

When Zung (1967) examined the individual items of his own rating scale for depression in an elderly group, he found the items that scored most severely were predominantly biological. Factor analysis[1] showed a "*loss of self esteem*" factor and three others of somatic symptoms. He concludes that the

[1]Factor analysis is a statistical technique used to identify a relatively small number of factors that can be used to represent relationships among sets of many interrelated variables. This assumes that underlying dimensions, or factors, can be used to explain complex phenomena. Observed correlations between variables result from their sharing these factors.

"baseline for depressive complaints in the normal aged is higher than that for a younger population, and that by using the same quantifying measure to determine depression, most geriatric subjects would be considered candidates for treatment".

McGarvey et al. (1979) compared the use of the Zung rating scale in three age groups. They found that there was a low total scale reliability in the use of the Zung scale in the elderly. Factor analysis showed three factors: well being and optimism; somatic symptoms; and depression and anxiety. In the oldest group there was little intercorrelation between these factors. They conclude that in the elderly, the simple addition of the item scores might result in a number of false positive scores. Both the Zung scale and the BDI have been criticised by Brink et al (1982). Using the Geriatric depression scale Yesavage and Brink (1983) found

"the items most poorly correlated with the total score were those dealing with somatic aspects of depression".

In an attempt to clarify the relationship between depression and morale, Blumenthal (1975) used the Zung scale and structured interviews about social activities and relationships in 160 married couples. Cluster analysis[2] resulted in four clusters, including a somatic symptom grouping. He suggests a higher baseline is required for the Zung scale in the elderly. Morris et al. (1975) performed factor analysis on results obtained from the Zung scale and morale scales which had been given to chronic patients (with no diagnosis specified) in a state mental hospital. They found that there was a large amount of overlap between these scales. However, because of the heterogeneous nature of the subjects, these results need to be treated with caution.

[2]Cluster analysis is a statistical technique to construct a sensible and informative classification of an initially unclassified set of data. It forms homogeneous groups from subjects that share similar characteristics (clusters). Group membership is unknown, as are the number of clusters. It groups results according to nearness and similarity.

Gurland et al. (1988) reviewed the relationship of depression and disability in the elderly. They state that "*in studying the correlation of depression with disability, every effort must be made to avoid confounding the measurement of one condition by the other*".

The main problem in this respect is distinguishing somatic symptoms due to depression from those due to disability or an accompanying physical illness. However, they list an extensive body of clinical lore which is of use in making the differential diagnosis of depression in the presence of physical illness. These are a change in the patient's behaviour; an increase in the patient's demands on carers; increased hypochondriacal complaints; withdrawal from normal activities out of keeping with the degree of disability; sleep disturbance accompanied by brooding or tense bouts of wakefulness; indecisiveness; increasing consumption of alcohol; and the development of persistent and unexplained pain. Unfortunately this clinical lore is difficult to convert into psychometric or criterion based methods to study the relationship between depression and disability.

In summary, somatic features have been found to be unreliable indicators of the presence of a depressive illness in the elderly and medically ill. A difference in performance of rating scales for the assessment of affective disorder in the elderly and the medically ill has been demonstrated. Can a case be put forward that there is an overlap of features between affective disorder and PD which will lead to differences in the performance of the scales in PD subjects? To examine this, the possible overlap of the features of PD and affective disorder will be considered.

C) THE OVERLAP BETWEEN THE FEATURES OF DEPRESSION AND PARKINSON'S DISEASE.

The features of PD have been summarised in many publications. A good general description was provided by Lishman (1987). The classical features are tremor, rigidity and hypokinesia; with other features such as fatigue, stooped posture, mask-like face and monotonous speech. When this description is compared with DSM-III major depression, there is a considerable overlap of symptoms and signs between PD and depressive illnesses. Case descriptions (Kearney 1964) report considerable clinical overlap between the features of PD and depressive illness.

The currently available rating scales for diagnosis or quantification of depressive illness utilise a wide spectrum of the features of depressive disorders. Carrol et al. (1973) stated there were "*no symptoms*" which are unique to depressive illness. Many of the features of affective disorder can occur in sufferers from PD as a part of the illness itself, or as a side effect of the treatment of the disease. One feature (e.g. difficulty in turning over in bed at night) may cause problems in one type of assessment (such as a self rating questionnaire asking about sleeping) but not in another (such as an observer rated scale where the cause of sleep disturbance is asked about and is felt to be due solely to PD). Some of the features of PD cause an understandable change in the person or their lifestyle which may be solely related to the disease, rather than due to an alteration in the persons mood per se: for example one patient persued a keen interest in ballroom dancing until forced to curtail his hobby by the onset of PD. Replying to a question about a change in his hobbies, he may reply that he had less interest or participated less in his hobbies (because he has had to give up ballroom dancing), although this may not caused by lowered mood. The significance of other items may be altered in PD. For example, a patient with PD is likely to be concerned about their physical condition,

but in most patients this concern will be appropriate, and will not be due to hypochondriasis.

D) WHY RE-EVALUATION OF DEPRESSION IN PARKINSON'S DISEASE IS REQUIRED.

In the preceding chapters, it has been demonstrated that the diagnosis of affective disorder is dependent on the method of assessment. The performance characteristics for a rating scale are specific to the situations in which the rating scale has been previously evaluated. In situations where a rating scale has not been evaluated, the performance characteristics can be changed by factors which confound content or criterion validity.

Being ill or elderly has an effect on the score of rating scales for depression, with many authors finding that depression rating scale scores have been spuriously raised by somatic symptoms secondary to illness and ageing. Consequently the threshold for the diagnosis of depressive illness in these groups may need to be raised. In PD, there are many features which are similar to or overlap with features of affective disorder. When used in PD (which is a physical illness and occurs mainly in the elderly), rating scales to assess affective disorder will not perform with the same characteristics as when the same scales are used in a younger physically well population.

In the next sections I shall review the literature referring to the presence of "depression" in patients suffering from PD. I shall group the recent papers according to the method of assessment used, and will describe the particular problems that may occur with the use of that particular method in PD. After briefly reviewing the early literature, I shall review studies in which clinical

observation was the method used, and subsequently I shall review papers which report the use of the BDI, the HDRS and finally various other methods.

4) DEPRESSION IN PARKINSON'S DISEASE: A REVIEW OF THE LITERATURE.

A) CLINICAL OBSERVATIONS OF DEPRESSION IN PARKINSON'S DISEASE.

James Parkinson (1817) first described the "shaking palsy", and it is questionable whether he recognised depression as a feature of the disease. He summarised the syndrome as follows:

> *"Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellect being uninjured".*

Mayeux et al (1981) proposed that Parkinson had recognised depression as a feature of PD because he referred to the "unhappy sufferer" and noted the "wished for release". Parkinson quoted Dr Maty who stated on seeing one particular patient for the first time:

> *"A more melancholy object I never beheld. The patient, naturally a handsome, middle-sized, sanguine man, of a cheerful disposition, and an active mind, appeared much emaciated, stooping, and dejected".*

It may be that this is a description of psychological changes, but in the context of the full passage, it is more likely that this is simply a comment on the man's appearance rather than a psychopathological formulation.

Shortly after Parkinson's description, a variety of mental changes were reported. Buzzard (1882) stated that

> *"there is an aspect of marked mental hebetude, or at all events an extremed slowness of expression".*

In the first edition of his textbook, Gowers (1888) wrote of paralysis agitans

"Often there is mental depression; it may be difficult to say whether this is more than the natural result of the physical ailment".

Patrick and Levy (1922) studied 146 cases of PD, and excluded cases of postencephalitic parkinsonism. They classified the mental symptoms observed into three groups. The first group had a "*history of acute mental symptoms following "shock" at or before onset of the first symptoms of the disease*", and comprised of 6 patients. The second group had a "*history of depression preceding onset*" and included 7 cases. The third "*less definite*" group were "*very nervous, highstrung, worrisome or of a nervous temperament*", and included 20 cases. This gives a prevalence of mental symptoms (mostly depression) of 34%, or of 9% if the "less definite" are excluded. This information was obtained retrospectively from case notes, and 22 of the patients developed parkinsonism following trauma.

In 1949 Mjönes performed a large clinical and genetic study of paralysis agitans. He examined 238 patients in Sweden. He found "nothing of note" regarding pre-morbid personality. He reported mental symptoms occurring as prodromes, coincident with the onset or during the course of the disease. He found "*reactive*" changes in which the patients became

> "*hyper-irritable, egocentric, exacting, discontented, hypochondriacal and querulent and lose to a great extent the realisation that their illness is a burden for their surroundings*".

He also found an "*organic*" group, characterised

> "*by the fact that the intellectual functions in the wider sense of the term suffer. Immediate memory becomes blunted and the process of thought retarded. A marked lack of concentration appears and -in particular- there is increased mental fatiguability. At the same time, the symptoms termed 'reactive' are frequently intensified.*"

The incidence for mental disorder (both reactive and organic) was 40%, with the organic type predominating. He found no evidence for a special paralysis agitans psychosis.

Schwab et al (1951) found four psychiatric syndromes associated with PD. Firstly, unrelated psychiatric disease antedating the onset of PD. Secondly, reactive mental disturbances. Thirdly, psychiatric symptoms attributable to medication. Finally, paroxysmal psychiatric disturbances probably directly related to PD, which includes attacks of anxiety; compulsive thinking; paroxysmal depression; paranoid attacks; paroxysms of strange feelings in the limbs; schizoid reactions; severe agitation and tension; and chronic fatigue states. Schwab and England (1958) in a general review of PD, emphasise the need for psychotherapy as an important component of treatment because sufferers "*sometimes go into a strong reactive depression*".

Mindham (1970) retrospectively examined the records of patients with PD admitted to a mental hospital. In addition to 36 patients suffering from "paralysis agitans", the sample included 19 cases of postencephalitic parkinsonism, 24 from arteriosclerotic parkinsonism and 10 from various other causes. Patients were classified using eight broad categories of psychiatric diagnosis. This study covers the period immediately prior to the introduction of l-DOPA to treat PD. Of the whole group of parkinsonism patients, 90% suffered from affective symptoms, and the frequency with which affective symptoms occurred was similar across all four types of parkinsonism. Depressive symptoms often responded to treatment without an accompanying improvement in the physical state.[3]

[3]This study is frequently quoted incorrectly as stating that the "general prevalence" of depression in PD is 90%.

Cherrington (1970) followed up 12 patients with idiopathic PD who were treated with l-DOPA of whom six developed mental depression (on unspecified criteria). Two of these patients had a history of a depressive disorder prior to the onset of PD, and two made suicide attempts. Only one patient (who had made a suicide attempt) was treated with a specific antidepressant therapy (electroconvulsive therapy), with the others receiving psychotherapy of an unspecified nature. The comment was made that at that time l-DOPA had received "*tremendously favourable publicity*", and that the expectations of some of the patients may have been unrealistic. Interestingly Cherrington found that

> "*family situations sometimes became worse as the patient's mobility improves. In 2 cases, the patient's wives became upset when their husbands were not at home as much as before*".

Rondot et al. (1984) examined 400 outpatients using clinical observation as their assessment procedure. They found 141 patients with psychiatric disorder, and classified these patients into four groups: dementia, anxiety, depression and psychotic disorders. They found that "*sadness is to be seen in almost all parkinsonians.....but it must not be confused with akinesia*".

Twelve per cent of their sample had depressive syndromes, and in 5.5% of cases this coincided with the onset of the syndrome. They

> "*only rarely observed (3 cases) a painful concentration on sad thoughts, a feeling of guilt, and constantly present suicidal ideas that led us to diagnose a melancholic state*".

Summary

Because of the change in usage of terminology over the years, and in the diagnosis of idiopathic PD from other causes of parkinsonism, the early reports can now only be used for general comment. Parkinson's writings are of little help in

answering the questions relating to the relationship between affective disorder and PD for several reasons (G.E.Berrios: Personal communication). His sample is too small to draw conclusions from (he only describes six patients, of whom three were seen as passers-by in the street), and it is likely that some of his cases did not have Parkinson's disease. His descriptions of PD are not complete, and are influenced by the debate to separate PD from the paralysis caused by strokes in which he was engaged at that time. Furthermore, it is unlikely that the original description of a disease can provide any information on the current state of the disease because for a disease, both the clinical language of the description and the biological processes it purports to describe are subject to secular change.

Clinical assessment was often performed with criteria for patient assignment to either the depressed or non-depressed group lacking systematic and/or operational definition, and may vary from study to study (see table 1 in Gotham, Brown and Marsden 1986). Depressive symptoms do occur, and there is a sizeable group in whom symptoms occur but their significance is unclear. Prodromal depressive symptoms are reported in several studies, although it is not possible to be clear if this is a genuine depressive illness or actually the prodromal features of PD itself. There is reported a dichotomy between reactive and organic syndromes. The study by Rondot et al. (1984) is of interest for several reasons. Firstly it is a study of an outpatient group of PD patients; secondly it based on recent classifications of depressive disorders; thirdly it shows that feelings of sadness are common in PD but it is necessary to separate features of lowered mood from the features of PD; and finally severe depressive episodes occur rarely.

B) THE BECK DEPRESSION INVENTORY IN PARKINSON'S DISEASE.

The Beck rating scale for depression (BDI: Beck et al 1961) is essentially a self rating scale (although its original administration was by an "observer" who read the items verbatim to subjects). Its 21 items, derived from clinical observation of depressed patients, have four statements (rated from 0 to 3) reflecting increasing severity of the features of affective disorder. Some of the items are clearly based on physical symptoms, and these relate to **sleep disturbance** (item p), **fatigueability** (item q), **loss of appetite** (item r), **loss of weight** (item s) and **decreased libido** (item u). Furthermore there are items which may reasonably be expected to be affected by a subject suffering from PD:

Item b: ***Pessimism.*** *This may reflect a realistic appraisal of an individual suffering from an illness which has no cure, will gradually progress and may leave the person severely disabled.*

Item c: ***Sense of failure.*** *Patients who are unable to fulfil their previous role in work, family or social commitments may well experience a sense of failure which is not unreasonable and in keeping with their enforced role change or loss of status.*

Item d: ***Reduced life satisfaction.*** *Similarly to item c, changes in role and lifestyle are likely to lead to dissatisfaction.*

Item l: ***Social withdrawal.*** *This could occur because an individual is too embarrassed by the tremor and other features of PD that they may avoid social contact, or some individuals may be so disabled they are unable to easily leave their homes to seek social contact.*

Item n: ***Body image.*** *PD causes both direct physical changes to a persons appearance such as mask-like facies, drooling and stooped posture, and indirect changes due to difficulty with personal hygiene and dressing. This may lead to an alteration of body image in some people.*

Item o: ***Work inhibition.*** *See comments on items b and c.*

Item t: ***Somatic preoccupation.*** *Sufferers from PD will be more aware of physical disabilities and sensations than "healthy" people.*

It can be seen that many of the individual items on the BDI have the potential for contamination by the features of PD. This possible overlap is mentioned by several authors. Cantello et al. (1984) felt the need to modify the BDI by the exclusion of the items "body image", "work inhibition", "fatiguability" and "somatic preoccupation", as it was felt that the response of a PD patient would "*automatically be positive*". The modified form of the BDI was not validated, and other items which were not removed have the same potential for overlap. Santamaria et al (1986a, 1986b) found that fifteen PD patients obtained a BDI score greater than ten, but in four of these patients no satisfactory criteria for mood disorder were found at interview. In these four patients, the scores were composed almost entirely of high scores on items o (work inhibition), q (fatiguability), t (somatic preoccupation) and p (sleep disturbance).

Huber et al. (1990) found a significantly higher BDI total score in the PD group compared to normal control subjects. The scores on the following individual items of the BDI were found to be significantly increased in the PD group: discouraged about the future; dissatisfied and bored; suicidal thoughts; interest in others; decision making; ability to work; fatigue; loss of weight; and concern over health. PD subjects were then split into two groups according to severity of PD. Post-hoc analysis comparing the control group and the two PD groups showed that symptoms of mood (items a, b, d, j, k, l) and self reproach (items c, e, f, g, h, i, m) were present in the early stages of PD and did not increase in severity with advancing disease. Somatic features of depression (items n, o, q, t) were evident early and increased with disease progression, and vegetative symptoms (items p, r, s, u) were only seen in the later stages of the disease. They comment that

"the different patterns of these depressive features with progression of PD may account in part for the variations seen in previous studies".

Brown et al. (1988) performed factor analysis on the individual items of the BDI, which resulted in three factors being identified: a "*guilt*" factor, a "*dysphoria*" factor and a "*somatic*" factor. It was found that the "*dysphoria*" and "*somatic*" factors correlated with the scores for activities of daily living, but that the "guilt" factor did not.

VALIDITY AND RELIABILITY.

Taylor et al. (1986) recognised the possibility that the signs of depression observed in PD are merely the "*natural reaction of the patients to their progressive and inevitable physical limitations and loss of independent function*".
They commented that the use in PD of depression rating scales and personality profiles has problems, as tests are often modified in a variety of ways without formal revalidation. They hypothesised that if an endogenous depressed state exists in PD, patients with it should perform in a similar manner to patients with endogenous depression on cognitive tests. They divided 30 PD patients into a depressed and a non-depressed group on the basis of scores on the BDI using a cut-off of 7 and above. They compared the performance of these groups on tests of short term memory with 15 patients with endogenous depression and 15 healthy controls. Regardless of the PD patient's depression state, both PD groups performed significantly better than the patients with endogenous depression on the tests of short term memory.

Because of the differences on short term memory from the group with endogenous depression, Taylor et al. conclude that depression in PD is not the same as endogenous depression. In particular, they formed the impression that

"*unlike endogenously depressed patients who remained tense and/or apathetic during the examination, it was possible to 'test through' the parkinsonian depressive mood state as these patients responded well to encouragement*".

Furthermore, the PD group endorsed BDI items which were

"*expected in terms of the realities of a progressive movement disorder*".

They concluded that

"*PD patients are frequently depressed when confronted with their behavioural limitations and that this reaction may be exacerbated by a form of emotional lability related to pathophysiological processes which may involve prefrontal areas*".

Levin, Llabre and Weiner (1988) administered the BDI to 119 PD patients and 76 healthy control subjects of similar age. They also administered the Milton Behavioural Health Inventory (MBHI). The individual items of the BDI were separated into a "*nonsomatic*" scale (the first fourteen items) and a "*somatic*" scale (the last seven items). The PD group reported higher scores on the BDI and the MBHI. Internal consistency reliability estimates were calculated for the whole BDI, and the somatic and the non-somatic subscales, which were found to be "*acceptable*". A principal axis factor analysis was performed from the results of 97 PD subjects using the somatic and non-somatic scores from the BDI, two subscales from the MBHI and scores for tremor, rigidity and bradykinesia. They interpreted this as giving a two factor solution (although three eigenvalues were greater than unity), with the somatic and non-somatic items from the BDI being grouped with the MBHI scales, and rigidity and bradykinesia in the second factor. These results are interpreted as suggesting the BDI "*including the somatic items is a reliable and valid measure of depression*" in PD.

Despite this claim, Levin, Llabre and Weiner have not adequately addressed the issue of validity or reliability. Firstly, they do not state which method to estimate

internal consistency they have used, making interpretation of the results difficult. Secondly, they wish to show content validity in the BDI (i.e. that it does not contain items that could be attributable to other processes) but do not demonstrate that the BDI scores are not dependent on the features of PD.

Ehman et al. (1990) examined 45 PD patients who were already participating in a treatment study, and with fairly recent onset of PD. A control group of 24 age and sex matched subjects was recruited, all of whom were chronically disabled (mostly with osteoarthritis). The BDI was administered, along with the research diagnostic criteria family history interview and measures of disability. Eight PD subjects had a past history of depression and 6 control subjects. The items on the BDI were separated into "somatic" (the last six items) and "cognitive/ affective" sections. The PD group scored higher than the disabled control group on both measures of these scales. The authors suggest this finding means that

> "*the higher depressive symptoms of the PD subjects were not merely a reflection of somatic complaints which could be attributed to PD symptoms or disability*". Whether the PD groups higher score in the "cognitive/ affective" section could be explained by the presence of two extra subjects with a past history of depression is unknown, but the presence of "somatic" items in both groups suggests overlap of symptoms occurs both in the PD and disabled control groups, but that it occurs more so in the PD group.

GENERAL CLINICAL FINDINGS USING THE BDI IN PD.

Mayeux et al. (1981) administered the BDI to 55 PD patients who were "*not overtly depressed*". They also administered brief measures of cognitive functioning. Thirty one spouses of the PD subjects acted as control subjects. The scores on the BDI were graded as follows: 0 to 9 was "not depressed"; 10 to 17 was "mild depression"; 18 to 24 was "moderate depression" and over 25 was

"severe depression". The PD subjects scored higher than the control subjects. Of the PD subjects 47.2% were depressed, and this included 30% who were mildly depressed, 12% who were moderately depressed and 3% who were severely depressed. 12.9% of the control subjects were depressed. There was a small but significant correlation between scores for PD and scores on the BDI, but this disappeared if PD subjects taking antidepressant medication were excluded. They also found a negative correlation between scores on the BDI and scores of cognitive functioning.

In two papers, Santamaria et al (1986a, 1986b) examined 34 PD patients of recent onset who were not on dopaminergic medication. The patients were assessed clinically to apply DSM-III criteria for major depression or dysthymic disorder. They also completed the BDI. A healthy age and sex matched control group was recruited from the spouses of the PD patients. They found that on DSM-III criteria, 32% of the PD group were depressed and 17% of the control group were depressed. Of the PD patients, one met the criteria for major depression, and ten for dysthymic disorder, whereas no controls met the criteria for major depression, one met the criteria for dysthymic disorder and three met the criteria for other types of DSM-III mood disorder. The mean BDI score was higher in the PD group than the control group. Non-depressed PD patients scored higher than non-depressed controls.

The BDI was used in a postal survey of PD subjects by Gotham, Brown and Marsden (1986). Two groups were approached: the first consisted of 200 PD patients attending an out patient department; the second group were 67 volunteers who responded to an advertisement placed in the national newsletter of the Parkinson's disease society. Altogether 189 replies were received, which means that 122 patients from the clinic replied. In addition, a group of out patient arthritis sufferers and a group of elderly subjects were recruited as control

subjects. All subjects completed the BDI, and in addition to this they also completed the Beck hopelessness scale, the Speilberger anxiety index and an activities of daily living questionnaire. They found both the PD and arthritis groups scored higher on the BDI than the healthy controls, but with no difference between the PD and the arthritis groups. There was a high intercorrelation between the BDI and the Beck hopelessness scale and the Speilberger anxiety index which suggests these tests are

> "*tapping some common feature, and that use of separate terms such as depression, hopelessness or anxiety may be misleading*".

The BDI items which scored significantly higher in the PD group as compared to the healthy control group were somatic items or items in which overlap between the features of PD and of depression was predicted.

The PD patients from the previous study were followed up between 6 and 20 months later (with a median of 14 months) (Brown et al. 1988). On this occasion, the BDI and a measure of activities of daily living were completed by 132 patients by post. Overall there was no difference in the BDI score between the two occasions. It was found that 61.4% remained not depressed on both occasions, and that 15.9% remained depressed on both occasions. In addition, 11.3% were depressed on the first occasion but not on the second, and a further 11.3% were not depressed on the initial occasion, but became so on the second. This gives a prevalence rate for each occasion of 27.2%. No linear relationship between depression and disability was found. A relationship was found between a change in disability (rather than absolute level of functioning) and a change in mood. The group which was permanently non-depressed had the least disability, and the permanently depressed group had the highest level of disability. The group who were initially depressed, and were later not depressed showed a small increase in disability, and the group who were not depressed initially and who became depressed showed a marked increase in disability.

This cohort of 138 PD patients was further examined by postal questionnaires by Nissenbaum et al. (1987). Patients were asked to rate features of their PD at their best and worst times (in terms of motor function) during the day. Similarly, they were asked to rate themselves for "*depression, anxiety and elation*" when at their best and worst. Thirty one patients (23%) were deemed to have significant "on-off" effects, and two thirds of these had parallel mood swings. In the same paper, they also reported results from a study of 10 PD patients with severe "on-off" fluctuations. Patients were interviewed when both "on" and when "off" using a semi-structured interview based on the BDI, the Montgomery Åsberg depression rating scale (MÅDRS: Montgomery and Åsberg 1979), Youngs mania questionnaire and the anxiety components from the clinical anxiety scale. Four patients were reported to have observable mood changes characterised by depression when "off", and four patients self-reported depressive mood changes from "on" to "off".

In a further paper on this sample, MacCarthy and Brown (1989) compared the postal scores on the BDI with other measures of self esteem, positive affect, social support and cognitions relating to illness. They found that

> "*a variable pattern of relationships between the different indices of psychological adjustment and physical illness emerged. Self esteem, coping style and practical support contributed significantly to the variance in psychological adjustment*".

Cantello et al. (1984) used a modified BDI (see above) in a group of 56 PD patients attending an out patient clinic. They identified 20 patients (39.2%) as depressed. Four of these patients were on antidepressant medication, three on neuroleptic medication, one on a benzodiazepine and eight on no psychotropic medication. They felt that depression was related to dementia. Cantello et al.

(1986) examined mood changes associated with "end-of-dose" deterioration (the "on-off" effect) in a group of 18 selected PD patients. Twelve patients with rheumatoid arthritis causing fluctuations in mobility were selected as a control group. The control subjects were matched for age, sex, education and length of illness, and were required to have no past psychiatric history or family history of psychiatric illness (although this stipulation was not made for the PD patients). Again, the modified form of the BDI was used, and in addition, "*depressive behaviour was evaluated and classified*" according to DSM-III criteria. In the mobile ("on") phase, the PD patients scored higher on the BDI than the rheumatoid arthritis group. Seven of the PD patients were diagnosed as depressed by the BDI and DSM-III criteria for major depression, and were reported to have been "*showing signs and symptoms of depression for several years*". In the immobile phase ("off"), both the PD and rheumatoid arthritis groups increased their scores on the BDI, but only in the PD group was this statistically significant. The obvious problem with this study is that by excluding depression from the rheumatoid arthritis group and not from the PD group, the study does not compare like with like. It follows therefore that the PD group will have higher scores on the BDI than the rheumatoid arthritis group because 7/18 are said to be depressed on DSM-III criteria.

Cantello et al. (1989) further examined major depression in PD by intravenous injection of methylphenidate (an "*amphetamine-like*" substance). This study attempts to test the hypothesis that depression in PD is due to a reduction in dopaminergic fibres derived from the ventral tegmental area (the mesolimbic dopamine system). Using an undescribed procedure, twenty four patients with PD were classified as suffering from DSM-III major depression or not. Thirteen patients met the criteria and eleven did not. They were also rated on the modified version of the BDI. A further fourteen patients suffering from DSM-III major depression but who were otherwise healthy, and twelve healthy subjects were

recruited as control groups. In a double blind randomised cross-over trial, all subjects were injected intravenously with methylphenidate and a placebo of saline three days apart. On each occasion they were rated on measures of activation, euphoria, depressed affect, dysphoria and somatic symptoms. They found that the depressed PD group showed little amelioration of mood, but that the other three groups did, suggesting that these patients represent a subtype of PD in which there is a reduction in dopaminergic fibres in the mesolimbic dopamine system.

SUMMARY.

Problems in the use of the BDI in medically ill or elderly patients have been clearly demonstrated (see section 2), and despite this comments are made in the literature on depression in PD such as the BDI

"*is gaining increasing recognition as a reliable measure in PD*" (Levin et al. 1988), and

"*has now been widely and authoritatively accepted*" (Cantello et al. 1989).

Taylor et al (1986) showed that depression in PD is not the same as endogenous depression. Santamaria et al (1986a) demonstrated a discrepancy between patients diagnosed as depressed on the BDI when compared with DSM-III diagnoses (despite the previously mentioned problems with the use of DSM-III criteria in the presence of physical illness). The group of studies from the Institute of Psychiatry (Gotham et al 1986; Brown et al 1988: Nissenbaum et al 1987) raise some interesting issues. The PD group scores higher than the healthy control subjects, and this is mainly in somatic items (or other items that could be predicted); a change in score on activities of daily living resulted in a corresponding change in depression scores; a somatic item was identified on factor analysis which correlates with change in scores of activities of daily living; and changes in motor function (the "on-off" effect) result in parallel mood changes. The prominence of the somatic items in these results and their relationship with virtually all the findings in

these papers suggests that the motor items are contaminating the assessment of mood. Despite the claims of Cantello et al (1989) for the use of the BDI in PD above, they found the need to omit four items because of possible contamination. In the study of the effects of methylphenidate in depression in PD, the use of the BDI and an undisclosed method of applying DSM-III criteria casts doubt on the reliability of the diagnosis of "depression" in the "depressed" group, making further interpretation of the results difficult.

C) THE HAMILTON DEPRESSION RATING SCALE IN PARKINSON'S DISEASE.

The Hamilton rating scale for depression (HDRS: Hamilton 1960) is an observer rated scale and was designed to quantify the severity of affective disorder, but has subsequently been validated as a diagnostic instrument. It originally contained 21 items, but this is commonly reduced to 17 because three items (depersonalisation, paranoia and obsessional symptoms) were less common and diurnal variation was considered to reflect the type of illness and not the severity. Most items are rated from 0 to 4 but some are rated from 0 to 2. Similarly to the BDI, the HDRS contains some physical items which are **early, middle and delayed insomnia** (items 4,5,6); **retardation** (item 8); **somatic anxiety** (item 11); **gastrointestinal somatic symptoms** (item 12); **general somatic symptoms** (item 13); and **genital symptoms** (item 14). As in the BDI, there are items which may reasonably be expected to be affected by a subject suffering from PD:

*item 2: **guilt;** see item (c) on BDI above.*

*item 7: **work and interests;** see item (o) on BDI above.*

*item 15: **hypochondriasis;** see item (t) on BDI above.*

*item 18: **diurnal variation;** a person with PD may find that they feel worse at particular times in the day due to fluctuations in response to l-DOPA medication (the "on-off effect").*

The BDI and HDRS have been shown to correlate highly (Bailey and Coppen 1976). The studies which use the HDRS in PD do not address the issues of the possible overlap of symptoms to anything like the extent of studies using the BDI. The second study reported below Robins (1976) comments that hypokinesia may contaminate the item retardation, and the paper by Starkstein et al (1990b) intends to address the problem of overlap. No papers relate to the validity or reliability of the HDRS in a PD group.

GENERAL CLINICAL FINDINGS USING THE HDRS IN PD.

Brown and Wilson (1972) examined 111 male PD patients who were admitted to hospital. The data was collected retrospectively from the records of the last admission. They rated patients on the HDRS from the patients notes, with

> "*no patient being considered as representing depression unless there was clear indication that these biological concomitants were present*".

They found that 52% of the all diagnostic categories of PD met their (unspecified) criteria for depression, and that 52% of their patients with a diagnosis of idiopathic PD also met the criteria for depression. They formed the impression that a correlation between rigidity and proneness to depression

> "*seemed likely but remained impressionistic because of the nature of the data*".

In this paper, no reference has been made to possible overlap of the features of PD and affective disorder, and, coupled with their requirement that biological symptoms are present, suggests that depressive disorders will be overestimated. Furthermore, they do not state the criteria by which a subject is deemed to have a depressive disorder or not.

Robins (1976) examined 45 PD patients who were living in institutions, and 45 age and sex-matched disabled patients who were living in the same institutions as the

PD subjects and were suffering from neurological or orthopaedic problems. The PD subjects were not demented, and were not taking l-DOPA. Subjects were rated on measures of disability and the HDRS. Higher HDRS scores were found in the PD group even though the control group had higher levels of disability. Analysis of the individual items showed there was a difference between the groups on the items depressed mood (even though the probability level quoted is 0.1); suicide; work and interests; retardation; psychic anxiety; general somatic symptoms and loss of insight: there was no difference on the other items. Because he felt that the item retardation may be contaminated by hypokinesia due to PD, it was removed from the analysis and did not affect the result. The choice of control group is of interest as it adequately controls for disability: however, there will be differences in the amount of overlap of symptoms between the control group and the PD subjects. The predictions at the start of this chapter suggest that of the items that Robins found a difference in, work and interests and general somatic items would be affected as well as retardation. I would speculate that with the removal of these three items, and the rather dubious difference on the item depression ($p=0.1$), that this would negate any difference between the two groups.

Vogel (1982) preferred the use of self-rating scales because they are "*independent of the patient's reduced motor capacity for emotional expression*". He examined 20 PD patients with early PD (Hoehn and Yahr stages I and II), of whom 4 had received treatment previously for "*compulsive and/ or depressive neurosis*" and 1 for "*compulsive suicidal tendencies without appropriate reason*". He rated features of the patients PD and also their perceptions of their own disability. They then completed a self-rating scale for depression (the "Befindlichkeitsskale"), and performed a semi-standardised interview from which items 1 to 18 of the HDRS were completed. From this interview he also calculated four syndrome scores from the AMP system (The "apathetic syndrome"; the "somatic-depressive syndrome"; the "inhibited-depressive syndrome"; and the "psycho-organic

syndrome"). He found that scores on both the HDRS and the self-reporting questionnaire were moderately raised, and that with respect to the AMP syndromes these patients were not significantly different from psychiatric in-patients undergoing antidepressant therapy. The HDRS scores did not correlate with the severity of motor symptoms, but tremor had a negative correlation with HDRS score. Interestingly in Vogel's group, 25% (5/20) had previously had features suggestive of depressive illness, and no comment is made about their present mental state: depressive symptoms in 25% of a group could easily produce "moderately raised" scores on measures of depression. No comment is made about the frequency of positive responses to somatic items on the HDRS.

Mayeux et al. (1984a, 1984b) postulated that depression in PD was not "reactive in nature" as there is little correlation between measurement of PD and depression. The lack of relation between depression and dopamine metabolism suggested that other biochemical systems be investigated. They examined 41 patients with idiopathic PD who were in-patients. They were rated on the HDRS and DSM-III diagnoses were made: this interview was performed by a psychiatric social worker. After an 8 day drug holiday, lumbar puncture was performed, and the cerebrospinal fluid was examined for 5HIAA, HVA and MHPG. In addition, 15 age matched patients with neuromuscular disorders or stroke (none of whom had a depressive disorder) were examined in the same manner as a control group. Sixteen out of the 41 (39%) PD patients were depressed according to DSM-III criteria, of whom 9 had major depression and 7 had dysthymic disorder. The control subjects had the highest mean level of 5HIAA; the PD subjects who were not DSM-III depressed had the next highest mean level; the PD subjects with dysthymic disorder had the next highest mean level; and the PD subjects with major depression had the lowest mean cerebrospinal fluid levels. Homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) did not relate to HDRS score. No relation was found between PD and HDRS score. There was a

considerable amount of scatter in some of these groups of 5-hydroxyindoleacetic acid (5HIAA) concentrations. If the scatter is examined, it can be seen that most of the concentrations of the PD patients are in the same range, with three outliers in the non-depressed group. No data or explanation is given as to why these subjects are outliers: are they very early in the course of PD? If instead of mean values, median values were employed there would be little difference between the PD groups. It therefore appears that there is no significant difference between the 5HIAA concentrations between the PD subjects whatever their affective status.

In an expansion of the previous study, Mayeux et al. (1986) analysed the results again but included an extra 8 subjects. They also report the results of a dexamethasone suppression test (DST) administered to the subjects. 43% of this expanded PD group met DSM-III criteria for affective disorder: 14 had major depression and 7 had dysthymic disorder. They report similar results of 5HIAA concentrations as the previous report, but report that the results of the dysthymic group were the same as the PD non-depressed group. They found that the following items were more prevalent in the depressed patients than the non-depressed patients: sleep disturbance; fatigue; psychomotor retardation; and loss of self esteem, and that psychomotor retardation and loss of self esteem correlated with the cerebrospinal fluid concentration of 5HIAA. The DST did not distinguish the groups. The glaring problem with these "expanded" results is that the symptoms which are more common in the "depressed" groups do not contain any symptoms of lowered mood or dysphoria *per se*, and can simply be described as somatic items. In summary, this pair of papers does not demonstrate a difference in cerebrospinal fluid 5HIAA concentrations between the depressed and the non-depressed PD subjects, nor does it demonstrate that the PD subjects in the depressed groups are actually depressed.

Sano et al (1989) report the further estimation of cerebrospinal fluid levels of 5HIAA in depressed and non-depressed PD subjects, in the context of an evaluation of the differences between dementia and depression in PD. They compared 46 non-demented or depressed PD subjects with 31 demented PD subjects; with 27 depressed PD subjects; and with 6 demented and depressed PD subjects. Depression and dementia were diagnosed according to DSM-III criteria. On this occasion they found no significant difference between the depressed and the non-depressed groups.

Pfeiffer et al. (1986) also reported the use of the DST and HDRS in a group of 46 PD subjects. They were also given a semi structured psychiatric interview. They found that 14 out of the 46 PD subjects were depressed as rated by the interview, and that this interview "*correlated well*" with the HDRS (no method of analysis stated). They found that the DST identified a similar percentage of depressed PD subjects as it had identified depressed patients in other (non-PD) studies. Unfortunately this paper is of little use for two reasons. Firstly, there is no stated method for correlating the HDRS with the clinical interview, and this phrase may just mean that both sets of results appeared similar. Secondly no reference is made to possible overlap between the features of affective disorder and PD, so it is likely that their "depressed" group will be overinclusive.

Kostic et al. (1987) examined 26 non-demented PD subjects using the HDRS. They also examined the cerebrospinal fluid of patients for 5HIAA levels. Fourteen of the PD subjects were deemed to be depressed because they scored higher than 17 on the HDRS. Like Mayeux et al (1984a) they found the 5HIAA concentration was lower in the depressed group than in the non-depressed group, and their scatterplot of 5HIAA levels appears to be more convincing than that of Mayeux et al. They imply that there is no problem due to overlap of the features of depressive disorders and PD by showing no correlation between depression and

disability scores. However, they use parametric statistics for data which is clearly non-parametric in distribution. Inspection of the scatterplot of HDRS score with motor disability suggests a low value of correlation, and if this data was analysed using a non-parametric test it is likely that this data would be statistically significant. This is exactly what would be expected to occur due to overlap of the features of PD and depressive disorders. Further evidence of contamination is present as the "depressed" PD group is older, has had PD for longer and has worse PD severity scores than the "non-depressed" PD group. It may be that the higher cerebrospinal fluid 5HIAA values in the "depressed" PD group are due to subjects assigned incorrectly to the depressed group and that the lowest values do occur in PD subjects who are suffering from a significant degree of affective disorder, but as the work has been reported it is impossible to determine.

Kostic et al (1990) examined 34 PD subjects using the HDRS and DSM-III criteria. They also performed the dexamethasone suppression test (DST). 16 PD subjects were diagnosed as depressed, and 18 as not depressed. They found that 75% of the "depressed" group had abnormal DST results, whereas 27.2% of the non-depressed group had abnormal results. The DST results may simply reflect more abnormal responses in more severe PD.

Huber, Paulson and Shuttleworth (1988b) examined 50 non-demented PD subjects for evidence of depression using the HDRS and for cognitive impairment using the Mini Mental State Examination (MMSE). No relationship between HDRS score and severity of PD nor intellectual performance was found. The mean score on the HDRS was 12 with a range of 3 to 30. In a further paper Huber et al (1988a) examined the relationship between severity of disease and the presence of depressive disorder. Sixty patients with idiopathic PD were assessed using the HDRS, and for the presence of DSM-III depression. No correlation was found between severity of depressive symptoms and any disease variable except dosage of

l-DOPA. Nineteen patients (32%) met DSM-III criteria for significant depression, and the other subjects were classified as "mild depression" (i.e.: no subjects were non-depressed). When compared to the non-depressed group, the depressed subjects showed greater HDRS scores, worse H&Y staging, a worse composite of PD symptom ratings and more bradykinesia, and had taken l-DOPA for longer and at a higher dose: there was no difference of age at the onset of PD, or rigidity. The non-depressed group showed more tremor than the depressed group.

Starkstein et al. (1989a) examined 78 subjects with idiopathic PD from 105 consecutive attendances at a neurology out-patient clinic. Subjects were administered a modified version of the PSE: this generated a total score for the number (and severity) of symptoms present, and was also used to generate a DSM-III diagnosis. The HDRS was also scored at the same time. The MMSE and various neuropsychological tests were also administered, and an assessment of social functioning was made. Patients were divided into those with major depression (15 subjects), those with "*minor depression*" (19 subjects); and those with no depression (44 subjects). Using a stepwise regression analysis, the only variable that accounted for variance between the groups was "*PSE score*". No difference was found between the non-depressed group and the group with minor depression on measures of PD, disability, demographic variables, neuropsychological measures or social functioning. The only difference found between the major depression group and the minor depression group was a worse performance on some neuropsychological tests in the major depression group.

In a subsequent paper (Starkstein et al 1990a), they comment that the

> "*frequency of depression was sometimes determined using cut-off scores on depression rating scales. Although these scales can quantitate the severity of depression, they are not intended to be diagnostic instruments and can lead to inaccurate assessments of the frequency of diagnosable depression*".

They report further analysis of a similar data set as the previous paper, but with the addition of the BDI to the assessment battery and with results from all 105 subjects. There were 21 subjects in the major depression group, 20 in the minor depression group and 64 in the non-depressed group. They then compared these groups on various variables. They found no differences on demographic details between the groups except that the major depression group had a higher frequency of a past history of a depressive episode before the onset of PD. There was a worse disability score in the major depression group, but no other variables were significantly different. HDRS and BDI scores were highest in the major depression group, and lowest in the non-depressed group. 19 patients were deemed to have right unilateral PD and 19 deemed to have left unilateral disease. The right sided group had more depressed subjects and higher depression scores. When the Hoehn and Yahr (H&Y) staging for PD was examined, it was found that patients with early (H&Y stage I) and late disease (H&Y stages IV and V) had higher levels of depression than stages II and III.

Early and late onset of PD as factors in depression were compared in a further paper on this data set (Starkstein et al 1989b). Subjects were divided according to whether the onset of PD was before or after the age of 55 years. In the early onset group, 14 patients (37%) had major depression and 10 (24%) had minor depression; in the older onset group 7 (10%) had major depression and 11 (17%) had minor depression: only the difference in the numbers of subjects with major depression was significantly different between the groups.

In a further paper, Starkstein et al. (1990b) addressed the problems of the overlap of the features of depression and PD. They matched depressed PD subjects (both major and minor depression) with non-depressed PD subjects on the basis of H&Y stage and length of time since the onset of PD. There were no differences between these groups on demographic or neurological variables. The PSE items were

clustered into autonomic and affective groupings, and the frequencies of the occurrence of these groups of symptoms was compared. The depressed group showed higher scores for both autonomic and affective symptoms. The following items occurred more frequently in the depressed group than the non-depressed group: worrying; brooding; loss of interest; hopelessness; suicidal tendencies; social withdrawal; self depreciation; ideas of reference; anxiety symptoms; loss of appetite; initial and middle insomnia; and loss of libido. No difference was observed for anergia; motor retardation; or early morning awakening. Patients with recent myocardial infarction were used as a control group and showed the same frequency of both autonomic and affective symptoms as the non-depressed PD group.

The last paper in this series (Starkstein et al. 1990c) reports a follow-up study on 49 of the 70 patients described in Starkstein et al. (1989a), three to four years later. Patients were divided into depressed or non-depressed using a cut-off score of 6 or below on the HDRS to represent "depression". Examining the neurological variables, they found a worsening over time of tremor, rigidity and akinesia, and that in each case this was worse in the depressed group when compared to the non depressed group. The depressed group showed higher HDRS scores. The HDRS scores in the depressed group were better at the later assessment and those of the non-depressed group were worse. Ten of the 18 depressed group were no longer depressed at follow-up, and 8 of the 31 non-depressed subjects had become depressed. Improvement in HDRS score was not dependent on treatment with antidepressants.

The basic methodology of these papers from this group has been criticised (Madeley et al 1991). Firstly, on some occasions they define depression using DSM-III criteria, but arrive at this diagnosis by using the PSE which generates diagnoses from ICD-9 rather than DSM-III. This procedure should be validated

itself as the two classificatory systems differ radically in regard to depressive syndromes. Secondly, on other occasions they used a very low cut-off (7 and above) on the HDRS (which was validated against DSM-III diagnostic criteria). The use of this very low cut-off is likely to result in significant numbers of subjects being diagnosed incorrectly as "depressed" because of the overlap of features between depressive disorders and PD. Hence "depression" as diagnosed by Starkstein et al. may bear little resemblance to any condition diagnosed by psychiatrists. The finding of significantly more tremor, akinesia and rigidity in the depressed group is consistent with the notion that higher HDRS scores are associated with more severe PD, and do not necessarily reflect the presence of a depressive disorder. The low levels (in numbers and dosage) of treatment in the "depressed" group suggests that the overall degree of morbidity was low. Thirdly, parametric statistics are used for data which is non-parametric in nature. At the core of these papers is the separation into depressed and non-depressed groups, but the manner in which this has been done does not produce a meaningful diagnostic separation. Therefore any interpretations based on this diagnostic procedure are invalid.

D) OTHER METHODS OF ASSESSMENT OF DEPRESSION IN PARKINSON'S DISEASE.

The Minnesota Multiphasic Personality Inventory.

The Minnesota Multiphasic Personality Inventory (MMPI) (Hathaway and McKinley 1951) was designed to

> "*provide an objective assessment of some of the major personality characteristics that affect personal and social adjustment*".

It is self-administrated with the subject responding true or false to statements. It consists of three validity scales which assess the subjects test-taking attitudes, and

ten clinical scales: depression; hysteria; psychopathic deviate; masculinity-femininity; paranoia; psychasthenia; schizophrenia; hypomania; social introversion-extroversion; and ego strength. It contains many items which may arise from PD alone, such as inability to work, disturbed sleep, lack of energy and general poor health.

Marsh and Markham (1973) compared 27 subjects with PD with volunteers using the MMPI. PD subjects were tested before starting l-DOPA, and at three and fifteen months subsequently: control subjects were tested initially and three months later. The MMPI scores did not show significant change with time in either the PD or control subjects. The PD subjects score higher than the controls on the following scales: hysteria; depression; hypochondriasis; psychasthenia; schizophrenia; social introversion; and ego strength. They interpreted this as suggesting

> "*considerable maladjustment with complaints of physical illness, depression, and hopelessness which would appear to be to a large extent a reality-based response to the progressively debilitating nature of Parkinson's disease*".

Horn (1974) used the depression scale of the MMPI (D30) (along with other neuropsychological tests) in a group of PD patients, a group of paraplegic patients and a healthy control group. The PD group had greater scores on the D30 than the control group and the paraplegic group. Horn concluded that

> "*depressive symptoms as measured by the D30 scale are significantly related to the presence of Parkinson's disease*".

Hoehn, Crowley and Rutledge (1976) administered the MMPI to 25 subjects who had not taken their l-DOPA medication for one week. They found the depression, schizophrenia and hypochondriasis scores were elevated. Bradykinesia correlated

with decreased ego strength, and with increasing scores for schizophrenia, depression, psychasthenia, hypochondriasis and paranoia. Rigidity correlated with increased psychasthenia and schizophrenia, and with lowered ego strength. Most of these correlations would be predicted by the overlap of the features of PD and depressive disorder.

Beilauskas and Glantz (1987) administered the depression scale of the MMPI (60 items), the Mini-Mult shortened version (20 items) and the HDRS to 35 patients with idiopathic PD. The overall scores on these three measures correlated significantly. There was little difference between the MMPI D scale and the Mini-Mult in the numbers of subjects that were identified as "depressed" (74% and 69% respectively). Using a cut-off of 11, the HDRS classified 67% of the PD subjects as depressed. In a further report (Beilauskas and Glantz 1989), they analyse the individual items of the Mini-Mult scale. They found five items which differentiated between the "depressed" and the "non-depressed" PD subjects, as follows:

1. *Are you more nervous than others?* (yes; "depressed" patients).
2. *Do you worry often about health?* (yes; "depressed" patients).
3. *Have you periods when you couldn't get going?* (yes; "depressed" patients).
4. *Do you enjoy different kinds of recreation?* (yes; "non-depressed" patients).
5. *Are you full of energy at times?* (yes; "non-depressed" patients).

They comment

> "*These items are not basically vegetative or anhedonic in nature. Rather, they generally indicate a concern with the disease and a preoccupation with the impact on life style that the disease causes*".

In fact these items include no features which would be regarded as pathognemonic of affective disorder, and are highly suggestive that overlap of the features of PD and depressive disorder is occurring.

Other Psychological Measures.

Diller and Riklan (1956) examined 108 patients with PD who had been referred for neurosurgery. Using a clinical interview, observation of the patients on the ward and various psychological tests (including the Rorschach ink-blot test; the Bender-Gestalt; and a modified version of the Thematic Apperception test), 59% of subjects were classified as "*normal-neurotic*"; 21% as "*severely disturbed*" (which includes borderline psychotic, free floating anxiety states, severe obsessive compulsive disorders, paranoid states and severe chronic depression); 5% as "*schizophrenic*" and 14% as "*organic*". They found no evidence of a "parkinsonian personality", but they reported a

> "*tendency for the group to describe their childhood as unhappy, to attribute the cause of illness to stress, and to emphasise withdrawal and self-consciousness in reaction to the disease*".

Warburton (1967) examined 140 PD patients who had been referred for thalamotomy, and 140 age and sex control subjects with a variety of medical, surgical or gynaecological conditions. He used the Maudsley personality inventory (MPI), and classified subjects into 3 categories of depression:-

First degree. Fleeting symptoms of depression experienced within a month of interview. Never lasting more than a few hours and being dispelled by undertaking some activity. Not severe enough to interfere with the patient's life in general.

Second degree. A sustained feeling of depression present for weeks or months before interview. Severe enough to prevent the patient making a realistic adjustment to his illness but never reaching the point of suicidal contemplation.

Third degree. A sustained feeling of depression severe enough for the patient to contemplate suicide and warranting psychiatric treatment at the time of the interview.

He found a significantly higher prevalence of depressive disorder in the PD subjects when compared to the control subjects, particularly in female patients. He also found a significant relationship between depressive symptoms and neuroticism scores which "*suggested a reactive aetiology in vulnerable patients*". The MPI has been criticised because many of the items that compose "neuroticism" are in fact

> "*expressions of the state of emotional distress, and probably reflect the subjects level of minor psychiatric symptoms*" (Snaith 1991).

Celesia and Wannamaker (1972) calculated the prevalence of depressive disorder in Warburton's study as 63% overall, which must be compared with a figure of 40% for control subjects. The classification of depression used will be overinclusive as almost any degree of distress in the previous month will qualify a subject for first degree depression. These subjects had been referred for thalamotomy: this suggests that they will have severe PD (and more potential for overlap of the features of PD and affective disorder). It may be the case that subjects referred for a possible operative procedure will over-emphasise their symptoms to ensure they will receive the treatment.

The same criteria for grading depression used by Warburton (1967), were used by Celesia and Wannamaker (1972) in a study of 153 subjects with idiopathic PD. 37% of the subjects were categorised as depressed before receiving l-DOPA therapy, and 24% in subjects receiving l-DOPA. Five subjects had a history of depressive disorder prior to the onset of PD. No relationship was found between the severity of motor disability and grade of depression.

Mindham, Marsden and Parkes (1976) used the General Practice Research Unit Interview Schedule (GPRUIS) to examine 50 PD out-patients who were taking part in a treatment study comparing groups taking anticholinergics; l-DOPA; and l-DOPA with a peripheral decarboxylase inhibitor. The GPRUIS is a standardised psychiatric interview designed to assess minor degrees of psychiatric disturbance over the previous week and at the time of interview. The GPRUIS was completed in full at the beginning and end of the trial, and at intervals between only the mental state portion of the GPRUIS was completed. 24 of the subjects had a past psychiatric history, and in 18 this was depressive in nature. There was initially a high psychiatric morbidity, and during the course of the treatment 22 subjects developed a depressive disorder. The development of a depressive disorder was associated with a previous history of depressive disorders and treatment with l-DOPA (despite the l-DOPA groups showing greater improvement in the symptoms and signs of PD). The severity of the physical signs of PD and affective symptoms were shown to be related at several stages during follow-up.

Andersen et al. (1980) used their own rating scale for depression in a double-blind cross-over trial comparing the effects of nortriptyline to placebo in a group of 19 PD patients with depressive symptoms. They found no change in the neurological signs, and the depression score improved more in the treatment group than the placebo group. Six items of the rating scale were excluded because of possible overlap of the features of PD and affective disorders, but a further eight or nine items may also show contamination. However, the most pronounced effect of nortriptyline was in items which were unlikely to be contaminated by any cross-over.

Menza et al (1990) examined ten consecutive PD subjects with "on", "off" and "on with dyskinesia" phases in their response to l-DOPA, using the bipolar form of the Profile of Mood States (POMS). The POMS measures 6 "mood states" and was

developed for the assessment of subjective responses to medication. No subject was demented or taking antidepressant medication. On day one subjects completed the POMS when "off"; on day two when "on"; and on day three when "on with dyskinesia". This process was repeated five times, and the mean scores for each subject for each state were used in the analysis. They found little difference between the "off" and the "on with dyskinesia" states, but the scores were elevated in the "on" state. They interpret this as meaning that subjects in the "off" phase are "depressed" due to biochemical deficits, and that in the "on" phase these deficits are corrected. The lowering of mood in the "on with dyskinesia" phase is felt to be due to a reaction to the disabilities caused by the dyskinesias.

Schiffer et al (1988) compared 16 depressed subjects with PD with 20 depressed subjects with rheumatoid arthritis. These subjects were from out-patient samples of several hundred patients who were interviewed using the Schedule for Affective Disorders and Schizophrenia (SADS). This gives a prevalence for depressive disorder of 16/200 (8%). They found that 12 of the 16 PD subjects with depressive disorder also met the criteria for past or present generalised anxiety disorder or panic disorder. In 7 of the 8 subjects with panic disorder, the onset of panic occurred after the onset of neurological symptoms, and the initiation of treatment with l-DOPA. In 4 subjects there was a temporal relationship between motor "on-off" phenomena and panic attacks. They concluded that this demonstrated that "depression" in PD is "*atypical*".

The Hospital Anxiety and Depression scale (HAD: Zigmond and Snaith 1983) is a self rating scale. It contains seven items which rate depressive symptoms and seven which rate anxiety. The two scales are independent of each other. The depression scale was constructed specifically to exclude somatic items, and most items are intended to indicate the presence of anhedonia. Of the items related to depressive disorders, there are no items which are directly somatic in nature.

However when used to assess subjects with PD, there are items which may be unreliable:

*Item: "**I feel as if I am slowed down**". As bradykinesia is virtually a* sine qua non

for PD, virtually all PD subjects ought to respond positively to this.

*Item: "**I have lost interest in my appearance**". see item (n) on BDI.*

*Items: "**I still enjoy the things I used to enjoy**" and*

*"**I look forward with enjoyment to things**". see items (d) and (l) on BDI.*

The HAD has been validated for use in an adult population (Zigmond and Snaith 1983), in a general medical out-patient setting (Alyard et al. 1987) and in the elderly (Kenn et al 1987). It has been shown to correlate highly with the MÅDRS (Snaith and Taylor 1985).

Use of the HAD in PD has been reported by MacMahon and Fletcher (1989, 1990) in two preliminary communications. In a community sample, the HAD was administered to 100 PD patients and their carers. They found that 28.9% of PD subjects were diagnosed as suffering from anxiety and that 16.7% suffered from depressive disorder. There was no significant difference in the prevalence of anxiety and depressive disorder between the carers and the PD subjects. Similarly, there was no significant difference in the prevalence of anxiety and depressive disorder between the carers of PD subjects and healthy controls: this implies that there was no difference between the PD subjects and the healthy controls. Neither anxiety nor depression correlated with the stage of PD or disability. Both anxiety and depression levels in the PD subjects correlated with the levels in their carers.

The Montgomery-Åsberg depression rating scale (MÅDRS: Montgomery and Åsberg 1979) is an observer rating scale which has 10 items, which were refined from the comprehensive psychopathological rating scale. Each of the items is rated on a six point scale with "anchor" points being provided to guide the rater in his

choice. Of the 10 items, **reduced sleep** (item 4); **reduced appetite** (item 5) and **lassitude** (item 7) reflect somatic symptoms. The following items may be affected by the subject suffering from PD:

*item (1): **apparent sadness.*** *Most patients with PD have a depressed and/ or anxious facies. Care must be taken by the rater to ensure that he is not simply rating a feature of PD.*

*item (8): **inability to feel.*** *see item (d) in BDI above.*

*item (9): **pessimistic thoughts.*** *see item (b) on BDI above.*

The MÅDRS has been shown to have acceptable inter-rater reliability, but to have poor item-subtotal correlations for the items relating to suicidal ideation, and disturbance of sleep and appetite (Davidson et al 1986). Kearns et al (1982) compared the use of the HDRS and the MÅDRS and found that the HDRS was good for the overall assessment of "depression", but the MÅDRS was better in the presence of physical illness. Only a brief report of the use of the MÅDRS in PD exists (Hovenstadt and Kooij 1991). They question the validity of the use of scales of depression in PD. They found that 66% of the scores obtained by PD subjects could be accounted for by somatic items.

E) THE PRESENT STATE EXAMINATION IN PARKINSON'S DISEASE.

The Present State Examination (PSE) (Wing et al 1974) was designed "*to assess the* 'present mental state' *of adult patients suffering from one of the neuroses or functional psychoses*".

It has three main purposes:-

1) To provide a reliable method of examining the present mental state of an individual at a given time;

2) To allow the investigation of diagnostic rules and practices;

3) To provide a clear-cut basis for teaching and clinical work.

"*A consideration of the degree of concordance and type of discrepancy between two classifications should throw light on the processes of clinical diagnosis and suggest how they might be improved*" (Wing et al 1974).

Interviewing and Scoring.

The PSE is a structured interview examining symptoms experienced during the previous four weeks. A check list (schedule) which systematically covers all phenomena likely to be considered during a present state examination, and indicates how they are to be coded. A form of questioning is suggested for items, but may depend on answers given previously. The intention is for a flexible interview while preserving a "*substantial degree of standardisation*". The Catego computer program sorts the items into syndromes, which are "units upon which diagnostic rules can operate", and allow descriptive profiles to be formed visually. The next stage of the program incorporates rules for the combination of the syndromes to produce a number of descriptive categories. Finally, a classification is produced which, where the symptoms and signs of the present mental state constitute most of the information on which a diagnosis would be based, is equivalent to a diagnosis (Wing 1983). The diagnosis is given in the form of an ICD-9 diagnosis. An index of definition is allocated to each subject, which reflects the degree of confidence in the presence of key symptoms: the threshold is level 5.

Use of the PSE in Medical Patients.

When used in the assessment of patients treated at a renal unit, difficulties were found in the use of questionnaires which emphasised the value of interview based assessments (House 1987b). The PSE was found to have acceptable inter-rater reliability in stroke patients (House et al 1991). Some studies (Feldman et al 1987,

House et al 1991) have adopted the practice of rating all symptoms without assumptions as to their cause.

In the PSE interview there are items which either deal with physical symptoms, or may be subject to possible contamination. In the section "*health, worrying, tension*", the subject is asked about their physical health, but also the presence of physical illness in the opinion of the rater is also recorded. Other items in this section refer to worries about health (among other worries), exhaustion, difficulty in relaxing, and restlessness which may occur in physical illness. Physical symptoms are included in the section "*autonomic anxiety*", but are unlikely to be confused with PD. The question referring to anxiety about meeting other people must be distinguished from embarrassment due to the problems of PD when in public situations (as must questions in the section "*self and others*"). Further physical symptoms are enquired about in the section "*appetite, sleep, retardation, libido*".

It appears there is considerable scope for contamination of the assessment of affective state by the PSE by the features of PD. However, there are reasons why this is less likely to be the case than with ordinal rating scales. Firstly, people using the PSE are trained to standardise the rating procedure. Secondly, there is a comprehensive glossary of definitions and terms giving directions on the principles that should be adopted to rate responses. Thirdly, positive ratings are not made unless the symptoms are definitely present and have been so for most of the previous four weeks, and at a significant level of intensity. Fourthly, the responses to items are combined by the Catego program in the manner above using clearly defined rules that ensure that a diagnosis is only made if symptoms of sufficient severity are present and in the correct constellation. If the PSE is effective at assessing depressive disorders in PD without problems of overlap of the features of affective disorder and PD, it would be expected that relatively large

numbers of symptoms would be identified, but that few diagnoses would be made. Therefore I shall now discuss the only report of the correct use of the PSE in PD.

Brown and MacCarthy (1990) used the 10th edition of the PSE to interview 40 subjects with PD. Subjects had responded to a previous study (see Brown et al 1988), were living with another person (usually spouse) and lived within 50 miles of London. These included 25 females and 15 males, with a mean age of 65.8 years and a mean duration of disease of 11.4 years. Using Hoehn and Yahr's staging for PD, no subjects were in stage I; 12 were in stage II; 20 were in stage III: and 12 were in stage IV. When rating symptoms that may be due to either PD or affective disorder,

> "*evidence was sought to determine (a) whether a symptom could be judged to be out of proportion to the severity of the motor symptoms, (b) whether the symptom had worsened recently without any accompanying deterioration of the physical symptoms of the Parkinson's disease, or (c) whether the symptom was concordant with other features not related to physical aspects of the disease*". Such ratings were "*always conservative*".

They felt that

> "*The major advantage of interviews is that additional information can be obtained to clarify any ambiguity or uncertainty*"

They found that 70% of patients obtained a positive rating on at least one syndrome. The syndromes observed represented disturbances of affect, anxiety and non-specific features. The most common syndromes were "*loss of interest and concentration*" (IC: 40%); a non-specific grouping of worry, nervous tension and brooding (WO: 32.5%); "*irritability*" (IR:27.5%); "*simple depression*" (SD 25%); and "*tension*" (TE 25%). These syndromes formed the "*core features*" of the profile shown by the PD subjects.

These syndromes translated into 6 Catego subclasses, with 67.5% of subjects being allocated to a subclass and associated major class. The most common subclass with 13 subjects was "*simple depression*" (SD) which produced the major class of "*neurotic depression*" (N). Two patients received the subclassification "*retarded depression*" (RD) and the corresponding major classification (R). Two subjects were allocated to the subclass "*phobic neurosis*" (PN), and two to "*anxiety neurosis*" (AN) which both led to the class "*anxiety state*" (A). Eight patients were in the subclass "*residual neurosis*" (XN), and the corresponding class X ("*residual*").

Four patients received an ICD-9 diagnosis with an index of definition of 5 or greater. Two were classified as "*neurotic depression*" (300.4); one as "*anxiety state*" (300.0), and one as "*phobic depression*" (300.2).

Several points of interest are raised in the discussion section of this paper. Morbidity at the level of PSE syndromes was "*widespread*", with 70% of subjects having at least one syndrome present. However, depressed mood was not associated with "*many of the other symptoms that characterise depressive illness*". This was felt to explain why so few patients were assigned to an ICD-9 diagnosis of a depressive illness. Brown and MacCarthy comment that this "*suggests that analysis at the level of diagnostic category is probably unsuitable when considering patients with Parkinson's disease*". They compare their PSE profile of PD subjects with those from two large international studies employing the PSE, and conclude that the PSE PD profile is most similar to that of allocated to class N (neurotic depression). They further comment

> "*Several other features of depressive illness were also uncharacteristic of the present sample, even those showing mood disturbance. These included depressive delusions and hallucinations, diurnal variation or persistent depression, appetite disturbance and weight loss. Sleep disturbance was*

common, but was generally linked to the physical symptoms of parkinsonism. Some patients reported that, at times, they felt 'life was not worth living' (tedium vitea), but the thoughts were not translated into suicidal ideation or action. In these respects, the present sample was clearly atypical of patients receiving diagnoses of affective psychosis (ICD-9 classification 296)".

This seems to raise contradictions. Brown and MacCarthy argue that the PSE generates a large number of symptoms, and because this does not generate a large number of diagnoses, the PSE must be unsuitable for use in PD as it somehow generates false negatives. On the other hand, the symptom profile in PSE is not felt to be like that of affective psychosis, and most closely resembles that of neurotic depression. Then Brown and MacCarthy present a figure contrasting their data with data obtained from a general population , demonstrating that the PD group show an increased frequency in only three PSE syndromes, namely simple depression, loss of interest and concentration, and (slightly) irritability. They also report a similar prevalence of caseness at an index of definition of five or above. They comment that at this level of analysis "*there is no evidence for increased psychiatric morbidity*", although they do point out that 17.5% of subjects obtained an index of definition of four, just below the threshold for caseness.

SUMMARY OF LITERATURE REVIEW.

This thesis set out to examine the measurement and diagnosis of depressive disorders in PD. The review of the literature undertaken has covered several areas. The concepts of "depression", and the methods by which it can be diagnosed have been discussed, and been shown to be inconsistently employed. It has been demonstrated that the use of ordinal rating scales to diagnose depressive disorders are overinclusive in medically ill and elderly subjects. The symptoms and signs of PD and depressive illness have been shown to have many similarities.

The combination of the three factors above suggest that there may be problems in the use of ordinal rating scales to diagnose depressive illness in PD because they are overinclusive due to the overlap of features between the conditions. Therefore the literature examining the relationship between "depression" and PD has been critically re-examined. The clinical observations proved inconclusive due to changes in terminology and diagnostic classifications. When rating scales are used, little work has been done to examine their performance in PD, despite frequent comments concerning the potential for overlap, or (unvalidated) changes being made to rating scales because of potential problems of overlap perceived by authors. Critical review of the studies using rating scales to evaluate and/ or diagnose depressive illness reveals problems in the manner the scales have been used. The PSE is a structured interview which provides computerised analysis of results and provides a diagnosis only if the features of psychiatric illness are present at a sufficient severity, and with the correct constellation of features. Use of the PSE in PD records many symptoms, but only generates a few diagnoses. I believe that the paper by Brown and MacCarthy (1990) demonstrates the PSE is capable of overcoming the problems of overlap of the features of depressive disorders and PD, and can therefore be used to assess the functioning of other rating scales in a group of PD subjects. The specific hypotheses to be tested are now listed.

HYPOTHESIS ONE.

Null hypothesis:

When Parkinson's disease subjects are compared with normal healthy control subjects, there are similar numbers of subjects diagnosed as "depressed" using scores obtained from ordinal rating scales for depression as compared with subjects diagnosed as suffering from a depressive disorder by the Present State Examination.

Alternate hypothesis:

When Parkinson's disease subjects are compared with normal healthy control subjects, there is an excess of subjects diagnosed as "depressed" using scores obtained from ordinal rating scales for depression as compared with subjects diagnosed as suffering from a depressive disorder by the Present State Examination.

HYPOTHESIS TWO.

Null hypothesis:

When Parkinson's disease subjects are compared with normal healthy control subjects using ordinal rating scales for the assessment of "depression", there is **no** excess of the somatic features of "depression" when compared to the psychic features of "depression".

Alternate hypothesis:

When Parkinson's disease subjects are compared with normal healthy control subjects using ordinal rating scales for the assessment of "depression", there is an excess of the somatic features of "depression" when compared to the psychic features of "depression".

HYPOTHESIS THREE.

Null hypothesis:

When Parkinson's disease subjects are compared with control subjects suffering from a depressive disorder but who are otherwise healthy, using ordinal rating scales for the assessment of "depression", there is **no** excess of the psychic features of "depression" when compared to the somatic features of "depression" in the depressed group.

Alternate hypothesis:

When Parkinson's disease subjects are compared with control subjects suffering from a depressive disorder but who are otherwise healthy, using ordinal rating scales for the assessment of "depression", there is an excess of the psychic features of "depression" group when compared to the somatic features of "depression" in the depressed.

5) A CROSS-SECTIONAL STUDY OF AFFECTIVE DISORDER IN PARKINSON'S DISEASE.

The work for this thesis was performed as part of a collaborative research project based in the Department of Psychiatry at the University of Leeds. In this section, I shall describe a cross-sectional study of affective disorder in Parkinson's disease that was undertaken specifically for this thesis. In section 6, I shall describe an analysis of results obtained from the longitudinal data obtained from the existing project, based on the results of the cross-sectional analysis.

METHOD.

Subjects.

1) Parkinson's disease subjects.

All subjects still participating in the existing study of cognitive functioning were assessed. Patients with idiopathic PD had been referred to the study from a local neurological clinic. This represented all existing patients at the time the study was initiated in 1985, and all subsequent referrals until September 1990. No PD patients refused to be seen initially. A small number of patients were volunteers from other neurological clinics, and although the number of patients who were approached and refused is unknown, there is no evidence that patients suffering from dementia or affective disorders are over-represented in this group (Biggins et al 1992).

Subjects were considered suitable for inclusion into the study if they had at least two of the three major features of PD (rigidity, tremor and bradykinesia), and a

history of insidious onset and progression of symptoms. Patients were excluded from the study if they met any of the following criteria:

(i) a history of stroke, transient ischaemic attack, hypertension, syphilis, encephalitis, epilepsy, cerebral tumour, alcoholism, diabetes mellitus or head injury resulting in loss of consciousness;

(ii) the presence or history of any neurological sign not compatible with a diagnosis of PD (e.g. cerebellar signs, impairment of downward gaze, oculogyric crises etc.);

(iii) the presence of any illness associated with chronic confusional states or of any chronic disabling disease other than PD:

(iv) surgery in the previous six months or neuroleptic medication in the previous three months.

Whenever a subject was assessed during the course of the existing study, the diagnosis of idiopathic PD was reviewed, and a small number of subjects were later excluded when it became apparent that the diagnosis of idiopathic PD was incorrect. When subjects were assessed specifically for this cross sectional study, the inclusion and exclusion criteria were re-applied. At the time the existing study was conceived, there were no existing criteria for the diagnosis of PD as opposed to parkinsonism, that were entirely satisfactory. Gibb and Lees (1989) have since formulated criteria which have been adopted by the United Kingdom Parkinson's Disease Society Brain Bank. Therefore the PDS Brain Bank criteria were applied to PD subjects with the exception of the requirement for CT scanning. Most of the subjects have been assessed over a period of several years, and in no case has the progression of the disease been such as to suggest a diagnosis of multiple system atrophy (MSA).

Because this thesis concerns the interpretation of self rating questionnaires, and requires that subjects are able to describe their subjective experiences adequately to

be rated by an observer, it was decided that patients suffering from a dementing process should be excluded. Therefore, all subjects who had been deemed to be diagnosed as demented up to the previous visit (i.e. before August 1990) were excluded from the study (see Biggins et al 1992). Furthermore, at the assessment visit subjects were required to complete the MMSE, and were included only if they scored 23 or higher (Anthony et al 1982). Half the subjects in this group were tested by Dr P Madeley and half by Dr C A Biggins.

2) The healthy control group.

In addition to the PD subjects, a control group was recruited from the spouses or other relatives of the PD patients, from a local general practice or from a local day centre for the elderly. Control subjects were required to be healthy apart from transient minor ailments, and in addition to showing no evidence of having PD, they were also subject to the same exclusion criteria as the PD subjects. Half the subjects in this group were tested by Dr P Madeley and half by Dr C A Biggins.

3) "Depressed" control group.

In order that the pattern of scores of PD patients on the rating scales could be compared with that obtained with subjects diagnosed as suffering from a depressive illness, a group of subjects who were in-patients from all the acute admission psychiatric wards in the Leeds psychiatric service and diagnosed as "depressed" were tested. In an attempt to avoid any bias in the selection of subjects, all patients who met the criteria on any ward were approached.

The inclusion criteria for the "depressed" group were as follows:-

(i) Being an in-patient on an acute admission psychiatric ward.

(ii) Having a formal or informal diagnosis of "depression". This includes all ICD and DSM diagnoses relating to lowering of affect, and all other informal diagnoses of lowered mood. This was required to be the main diagnosis, and no other diagnosis except one related to personality was allowed. This rather broad definition was intended to cover all diagnoses relating to lowered mood and not to be prejudicial with regard to any concept of identification of or classification of affective disorder. The intention was to include the full spectrum of the features and severity of lowered mood as seen in psychiatric in-patients. Patients were tested at any time during their stay as an in-patient.

(iii) The subject should have no other psychiatric diagnosis, except one relating to personality. The exclusion diagnoses include schizophrenia, schizo-affective disorder, mixed affective states, substance abuse, eating disorders or acute or chronic confusional states.

(iv) The subject should be otherwise well and otherwise meet the exclusion criteria for the healthy control group.

All these subjects were tested by Dr P Madeley.

Procedure.

All the PD and healthy control subjects were seen at home. The depressed control group were seen on the wards on which they were in-patients. Subjects were first assessed neurologically, and the PD subjects were rated on the measures of PD. All visit were performed during 1990 or 1991. For subjects who were participating in the existing study, this testing procedure replaced the normal testing procedure (as described in the next chapter).

The neurological assessment consisted of:-

(i) Hoehn and Yahr's staging for PD (H&Y) (Hoehn and Yahr 1967), which gives a general but rather crude overall assessment of the severity of PD (see table 2);

(ii) Webster's scale (WEBS) (Webster 1968), which measures various symptoms and signs of PD, and thus reflects the physical features of PD;

(iii) North-Western Universities Disability Scale (NUDS) (Diamond 1983), which measures disability due to the effects of PD rather than the features of the disease per se.

Details of family, personal, medical, psychiatric and drug histories were reviewed in-patients participating in the longitudinal study, and were collected for all other subjects. The Mini Mental State Examination (Folstein et al 1975) was then performed. Subjects then completed the BDI and HAD self rating scales. Subjects were required to complete the forms without assistance, and any requests for advice on how to complete the items or general comments made while filling in the forms were interrupted to prevent the assessors being influenced in the later stages of the assessment procedure. The forms were then collected without the assessors being aware of the contents. When the forms were eventually analysed, it was decided that any response which was ambiguous or missing would be rated as 0 on both the BDI and the HAD.

The subjects were then given an interview which was based on the PSE interview, and was recorded on modified PSE forms (see appendix). These modified forms consisted of the PSE scoring chart with the items from the HDRS, MÅDRS and DSM-III inserted at the appropriate point. This enabled items from the PSE and the rating scales to be completed at the same time, and from the same information in the interview. All items on the PSE relating to a possible diagnosis of depressive states were asked. The replies were recorded in the standard manner for the PSE, and items on the rating scale were completed in accordance with the

instructions for that diagnostic interview. In particular, responses which were felt to be due to PD and not to a putative depressive illness, were rated as "0". Similarly, when rating the MÅDRS and HDRS, the assessors attempted not to rate positively any features which were felt to be due to PD alone or to other physical problems. The version of the PSE used was PSE9, and of the Catego program was Catego4. Catego categories required an index of definition of 5 or greater.

This therefore generated a (possible) PSE Catego category, and scores on the BDI, HAD, HDRS and MÅDRS, and also allowed DSM-III (possible) diagnoses to be made. The results were analysed using the SPSS-X statistical package.

RESULTS.

The results section of this thesis consists of two main parts. In this chapter, results of the cross-sectional investigation performed specifically for this thesis are reported. In the next chapter, these results will be used to interpret the data collected previously as part the main project.

1) Subjects.

Table 3 shows the basic details of each group. There are 52 subjects in the Parkinson's disease group (the "PD" group); 32 subjects in the healthy control group (the "control" group) and 30 subjects in the depressed control group (the "depressed" group). The mean ages of the three groups are not statistically different, nor is the proportion of male subjects in each group.

The Hoehn and Yahr (H&Y) staging for the PD group is as follows: 2 subjects (3.8%) were H&Y stage I; 13 subjects (25.8%) were H&Y stage II; 32 subjects (61.5%) were H&Y stage III; and 5 subjects (9.6%) were H&Y stage IV. The

mean score on Webster's scale was 11.0 (95% CI: 10.0 to 12.0), and the mean score on the NUDS was 39.6 (95% CI: 38.2 to 41.0). The mean age of onset of PD was 56.5 years (95% CI: 53.4 to 58.6), and the mean length of time since the onset of PD was 10.8 years (95% CI: 8.5 to 12.9).

The PD group were taking the following medications. 45 subjects were taking l-DOPA preparations (mean daily dose l-DOPA was 505 mg; 95% CI: 410 to 600); 35 subjects were taking selegeline; 23 were taking anticholinergic preparations; 7 were taking bromocriptine; and 2 were taking amantidine. In addition to the antiparkinsonian medication, 6 subjects were taking tricyclic antidepressants; 8 subjects were taking minor tranquillizers; but no subjects were taking major tranquillizers.

How representative are the sample?

As will be described in the section on the longitudinal study, the subjects in this study were representative of an out-patient population of PD patients. During the course of the longitudinal study, and also the assessments for this cross-sectional study, some subjects "dropped out" from the testing procedure. It is therefore important to determine whether the remaining sample is still representative of an out-patient population of subjects with PD.

Sixteen PD subjects had died since joining the study. A further fifteen of the subjects with PD had become lost to follow-up. This group included subjects who refused further testing, who moved from the locality, or who were unable to be contacted. In order to determine whether the people who had died or become lost to follow-up were different in any characteristics to the remaining subjects, Mann-Whitney "U" tests were performed for all variables as measured at the initial visit. This revealed that the group who dropped out were older than the subjects

remaining, and had worse disability scores as measured by NUDS. They did not have worse scores on the other measures of PD (Webs or H&Y), nor did they have worse depression scores or verbal IQ scores (see Table 4).

Among the control subjects, 18 subjects were lost to follow-up. Five of these subjects had died, and the rest refused further testing, moved from the locality, or were unable to be contacted. Using Mann-Whitney "U" tests, the subjects who dropped out were found to be older than subjects remaining in the study, but were otherwise no different (see Table 5).

In addition, 12 of the PD subjects had become demented during the course of the longitudinal study, and were not included in the cross-sectional analysis. The demented patients had previously been shown not to differ from non-demented subjects on MÅDRS scores (Biggins et al 1992).

2) THE PRESENT STATE EXAMINATION.

a). Syndrome Profile.

Figure 1 shows the percentage of PD patients receiving a definite rating for each of the syndromes (i.e. a rating of + or ++). In the PD group, 67% of subjects had at least one syndrome rated positively; 48% of subjects had at least two syndromes; 29% had three; and 23% had four. The syndromes that were rated positively in the PD group are characteristically those that occur in depressive disorders and anxiety. Only two syndromes were present in at least 20% of the subjects. These were worry (WO) which occurred in 44% and tension (TE) which occurred in 21%.

In the control group, 16% of subjects had at least one syndrome rated positively (see fig 2); 16% at least two syndromes; 13% at least three syndromes; and 9% four or more syndromes. Only one syndrome was present in more than 10% of the subjects: this was worry (WO) which occurred in 13%. Most of the syndromes which were positively scored, occurred in no more than one subject (3%).

In the depressed group, 100% of subjects had at least four syndromes (see fig 3). Eleven syndromes were scored positively in at least 25% of the subjects, and five syndromes were present in at least 70% of the subjects. These syndromes were all characteristic of affective disorders.

b) Catego Subclasses.

The syndromes above were then combined by the Catego program to produce subclasses and major classes. In the Parkinson's disease subjects, nine subclasses were produced, and 68% of PD subjects were allocated. The most common was "residual neurosis" (XN) with an allocation of 30%; "simple depression" (SD) was the next most frequent with 18%; the remaining subclasses allocated were "phobic neurosis" (PN) with 10%; "obsessional neurosis" (ON) with 6%; and "anxiety neurosis" (AN), "neurotic depression" (ND), "psychotic depression" (PD), and "paranoid psychosis" (DP) with 2%.

In the control group, 84% of subjects were not allocated a subclass, and 4 subclasses were produced. The most frequent subclass was "residual neurosis" (XN) with an allocation of 6%; and "obsessional neurosis" (ON), "phobic neurosis" (PN), and "simple depression" (SD) were each allocated 3%.

In the depressed group, all subjects were allocated to one of 4 subclasses. These were "reactive depression" (RD) with an allocation of 50%; "simple depression"

(SD) with 40%; "neurotic depression" (ND) with 10%; and "psychotic depression" (PD) with 3%.

c) Catego Major classes.

The 68% of PD subjects who were allocated to a Catego subclass were allocated to one of 6 Catego major classes. The most frequent class was "residual class" (X) with 29% of subjects allocated; "neurotic depression" (N) had 19% allocated; "anxiety state" (A), "obsessional neurosis" (B) "paranoid psychosis" (P) both had 12% allocated; and "retarded depression" (R) had 2% allocated.

The most frequent class allocated in the control group was "residual class" (X) with 6%; the other classes "anxiety state" (A), "obsessional neurosis" (B), and "neurotic depression" (N) were each allocated 3%.

The most frequent class allocated in the depressed group was "retarded depression" (R) with 50%; "neurotic depression" (N) was allocated 47%; and "depressive psychosis" (D) was allocated 3%.

d) ICD-9 Classifications.

In the PD group, four subjects were allocated an ICD-9 diagnosis by the Catego program. Two subjects were placed in the class 300.4 (neurotic depression), one in class 297.9 (other paranoid psychosis), and one in class 300.2 (phobic state). Only one subject in the control group was allocated an ICD-9 class: 300.4 (neurotic depression). In the depressed group, two subjects did not merit an ICD-9 class at an index of definition of 5 or greater. Twelve of the depressed group were allocated to class 300.4 (neurotic depression), one subject was allocated to class

296.2 (depressive psychosis), and fifteen subjects were allocated as being either class 296.2 (depressive psychosis) or 300.4 (neurotic depression).

2) DSM-III Criteria for Major Depression.

At the same time as rating subjects on the PSE and the ordinal rating scales for depression, the DSM-III criteria for major depression were also applied. In the PD group 6 patients met the criteria, along with 1 subject in the control group and all 30 subjects in the depressed group.

In the PD group, the DSM-III diagnosis of major depression was compared to the PSE diagnosis of any type of affective disorder. The two subjects who obtained diagnoses from the Catego program that were not of affective disorder were excluded from this part of the analysis. Forty five subjects were diagnosed by both systems as "not depressed". Two subjects were diagnosed by both systems as "depressed", and three subjects were diagnosed by the DSM-III criteria for Major Depression as depressed, but diagnosed as "not depressed" by the Catego program. Thus when the DSM-III criteria for Major Depression are compared to Catego diagnosis of any type of "depression", the DSM-III criteria have a sensitivity of 100% but a specificity of 40%.

3) The Ordinal Rating Scales for Depression.

The median and range of total scores obtained from the ordinal rating scales for depression (including the anxiety subscale of the HAD) are shown in table 6, and the distribution of the scores is shown in figures 4-7. In all the scales the median score is lowest in the control group, slightly higher in the PD group, and much higher in the depressed group. There is a large overlap in the range of total scores

between the PD and control groups, and some overlap between the PD and control groups with the depressed group.

Tables 7a, 7b and 7c show matrices of intercorrelation (using Spearman's rank correlation coefficient) for the depression rating scales in the PD, control and depressed groups. In each of the three groups, the two observer rated scales (MÅDRS and HDRS) show a high degree of correlation with each other. The two self rated scales for depression (HAD and BDI) show moderate correlation with each other in the three groups. The degree of correlation between the self rating scales and the observer rated scales is moderate in the PD and depressed groups, but very poor in the control group.

In the PD group, there is moderate to good correlation between the measures of PD. The value for H&Y and WEBS is 0.65 ($p<0.001$); for NUDS and WEBS -0.72 ($p<0.001$); and for NUDS and H&Y -0.71 ($p<0.001$). The inverse correlations between NUDS and the other measures is because decreasing NUDS scores reflect greater disability, whereas increasing scores on the other scales reflect greater disease severity. Table 8 shows the intercorrelation matrix between the measures of PD and the depression rating scales. Only one correlation is greater than 0.5 (MÅDRS with H&Y), and most correlation coefficients are suggestive of a moderate degree of correlation. The correlation coefficients between WEBS with HADD and WEBS with HDRS are both poor.

In order to determine if the totals obtained on the depression scores in the three groups were from different populations, a series of Kruskal-Wallis one way analyses of variance were performed, with post hoc comparisons to determine which group(s) were different (where applicable) (Siegel and Castellan 1988). A level of significance of $p=0.01$ was adopted for the Kruscal-Wallis ANOVA, and of $p=0.025$ (one tailed) for the post-hoc comparison. For all depression rating

scales (including both the HADD and HADA subscale of the HAD), it was demonstrated that the totals did not come from the same populations. The rankings for the PD group were higher than the control group, but not as high as in the depressed group. The post hoc comparisons demonstrated that the totals for the depression rating scales were from different populations both for the PD and control groups, and the PD and depressed groups.

A similar procedure was performed using the scores of the individual items from each of the rating scales. This revealed that for most of the individual items on the rating scales there was no difference for the scores between the PD and control groups. However, there were some items where this was not the case. Of the items on the HAD, the items "*I feel as if I am slowed down*"; "*I get a sort of frightened feeling as if something awful is about to happen*"; and "*I can sit at ease and feel relaxed*" were not from the same population, and scored higher in the PD group. Similarly the item "*somatic preoccupation*" (item t) on the BDI; "*concentration*" on the MÅDRS; and "*somatic symptoms*" (item 13) on the HDRS also scored higher in the PD group.

Conversely for the scores between the PD and depressed group, almost all the individual items were found to represent different populations. The exceptions to this pattern were as follows. On the HAD, no difference was found on the items "*I feel as if I am slowed down*"; "*I get a sort of frightened feeling as if something awful is about to happen*"; "*I feel restless as if I have to be on the move*"; "*I get sudden feelings of panic*"; and "*I can sit at ease and feel relaxed*". On the other scales, the items "*somatic preoccupation*" (item t) on the BDI; "*anxiety*" on the MÅDRS; and "*psychic anxiety*" and "*somatic symptoms*" on the HDRS also showed no difference between the PD and depressed groups.

These analyses demonstrated that the total scores on the depression rating scales in the PD group were significantly higher than in the control group, but the individual items comprising the scales were not greater, except for a few cases. In order to determine if these items were responsible for the differences between the PD group and the control group, further Kruscal-Wallis ANOVAs were performed using the total scores for the depression scales with these items which are more frequent in the PD group not included. This showed that the totals on the depression rating scales remained greater in the PD group than the control group for each of the scales. It is possible that the two PD subjects who were diagnosed as depressed by the PSE/ CATEGO may account for the increase in the scores of the PD group. Therefore a Kruscal-Wallis ANOVA was performed between the PD and control groups, but with all PSE diagnosed subjects excluded. The PD group still ranked higher that the control group on all the rating scale totals ($p=0.01$ one tailed).

4) Criterion Validity of the Depression Rating Scales.

In order to establish the degree of criterion validity, expressed in terms of sensitivity and specificity, the effects of changes in the diagnostic cut-off scores used on the various rating scales was examined. The diagnosis of any type of depressive disorder made by the Catego program from the PSE interviews was used as the "gold standard" against which the performance of the rating scales was judged. The results of the effect of changing the cut-off score on the sensitivity of the rating scales are given in the sections below, and the changes in specificity are shown in Figure 8 and in the sections below.

Various cut-off values to "diagnose depression" ranging from 8 and above to 26 and above on the BDI were examined to determine the effect on the sensitivity and specificity. At all these cut-off values, the sensitivity was 100%. However the values of specificity ranged from 53% (at 8 and above) to 100% (at 23 and above).

When cut-off scores from 8 and above to 17 and above were applied to the HDRS, the sensitivity remained 100%. The specificity at the cut-off of 8 and above was 88% and rose to 100% at 14 and above. Cut-off values of 11 and above up to 20 and above were applies to the MÅDRS, with a sensitivity of 100% at all these values. The specificity was 88% at 11 and above, and rose to 100% at 18 and above. In the HAD, the cut-off range was from eight and above to 12 and above, and the sensitivity was 100% for these values. At eight and above the specificity was 92%, and rose to 100% at 11 and above.

5) The Reliability of the Depression Rating Scales.

There are four basic methods for estimating the reliability of empirical measurements. These are the retest method, the alternative-form method, the split-halves method and the internal consistency method. The retest method involves the administration of the test on two occasions over a period of time. However, this may not always be possible to do; there may be a change over time in the concept being measured, and the administration on the first occasion may alter the individuals perception for the second. The alternative-form method involves two alternate forms of the same test being given. However, it can be difficult to construct an alternate form which is parallel to the original. Both the above methods require two administrations with the same group of people. The split-halves method can be conducted on one occasion. The items are split into halves which are used to estimate reliability. However, there are many ways that an individual test can be split, and the reliability estimates obtained will be different for each split. This limitation is overcome by using the internal consistency method of which Cronbach's alpha is the most popular method. Cronbach's alpha provides an excellent technique for assessing reliability (Carmines and Zeller 1979), because the practical limitations of the alternative-form method is avoided by randomly dividing the items in half to form two randomly parallel tests.

As a general rule, reliability values "*should not be below 0.8 for widely used scales*" (Carmines and Zeller 1979). At that level, the calculations are attenuated very little by random measurement error. At the same time it is often too costly in terms of time and money to try to obtain a higher reliability coefficient.

Table 9 shows estimates of Cronbach's alpha of the rating scales for depression in the three subject groups. Most of the values are either 0.8 or greater, or are close to 0.8. However, some values are less than 0.7. When the scores on the rating scales obtained in all three groups are combined, the values of Cronbach's alpha are all greater than 0.8 (as would be expected due to the greater variability of scores).

6) What scale items cause the excess in PD?

The analyses above have demonstrated that although the total scores of the depression rating scales are greater that those of the control group, only a small minority of the individual items that combine to form the depression scales are greater in the PD group. Furthermore, the specificity of the rating scales has been shown to be low when low diagnostic cut-off scores are employed. It would be expected that the scores of PD subjects whose scores on rating scales are in the band of lowered specificities will reflect an excess of somatic items. Therefore the distribution of scores on individual items of subjects whose total score on the depression rating scales is in the range band of lowered specificity were examined, and the results are shown in figure 12 (for the BDI) and figure 13 (for the HDRS). As no cut-offs have been used for the MÅDRS or HAD in PD, no figures are shown for the items on these scales.

In both figures 12 and 13 it can be seen that almost no "non-somatic" items rated higher than "1", and that the items in which scores of "2" or "3" were obtained were those which are "somatic" in nature. (NB: items from the HDRS which are not included in figure 13 are not shown because all subjects were rated on these items as "0").

HYPOTHESES TESTED: HYPOTHESIS ONE.

Null hypothesis:

When Parkinson's disease subjects are compared with normal healthy control subjects, there are similar numbers of subjects diagnosed as "depressed" using scores obtained from ordinal rating scales for depression as compared with subjects diagnosed as suffering from a depressive disorder by the Present State Examination.

Alternate hypothesis:

When Parkinson's disease subjects are compared with normal healthy control subjects, there is an excess of subjects diagnosed as "depressed" using scores obtained from ordinal rating scales for depression as compared with subjects diagnosed as suffering from a depressive disorder by the Present State Examination.

Result:

The null hypothesis was rejected, and the alternate hypothesis therefore upheld. At most values that have been adopted as cut-off scores diagnostic for depressive illness on the ordinal rating scales, the ordinal rating scales for depression identify an excess of affective disorder.

HYPOTHESES TESTED: HYPOTHESIS TWO.

Null hypothesis:

When Parkinson's disease subjects are compared with normal healthy control subjects using ordinal rating scales for the assessment of "depression", there is **no** excess of the somatic features of "depression" when compared to the psychic features of "depression".

Alternate hypothesis:

When Parkinson's disease subjects are compared with normal healthy control subjects using ordinal rating scales for the assessment of "depression", there is an excess of the somatic features of "depression" when compared to the psychic features of "depression".

Result:

The null hypothesis was rejected, and the alternate hypothesis therefore upheld. The PD group scored higher than the control group on only 6 items, and these were somatic in nature. Furthermore, examination of the frequency distributions of the items of the rating scales in subjects who are diagnosed as "depressed" by the ordinal rating scales, but not by the PSE show that the items which score highly are somatic in nature.

HYPOTHESES TESTED: HYPOTHESIS THREE.

Null hypothesis:

When Parkinson's disease subjects are compared with control subjects suffering from a depressive disorder but who are otherwise healthy, using ordinal rating scales for the assessment of "depression", there is **no** excess of the psychic features of "depression" when compared to the somatic features of "depression" in the depressed group.

Alternate hypothesis:

When Parkinson's disease subjects are compared with control subjects suffering from a depressive disorder but who are otherwise healthy, using ordinal rating scales for the assessment of "depression", there is an excess of the psychic features of "depression" when compared to the somatic features of "depression" in the depressed group.

Result:

The null hypothesis was rejected, and the alternate hypothesis therefore upheld. The PD group did not score as highly as the depressed group on almost all the individual items of the rating scales. The items on which the PD group scored as highly as the depressed group were almost all somatic in nature.

6) A LONGITUDINAL STUDY OF AFFECTIVE DISORDER IN PARKINSON'S DISEASE.

The work presented in this chapter was performed as part of a collaborative research project based in the Department of Psychiatry at the University of Leeds. In this section, I shall describe an analysis of results obtained from the longitudinal data obtained from the existing project, based on the results of the cross-sectional analysis.

METHOD.

Subjects.

1) Parkinson's disease subjects.

Patients with idiopathic PD had been referred to the study from a local neurological clinic. This represented all existing patients at the time the study was initiated in 1985, and all subsequent referrals until September 1990. No PD patients refused to be seen initially. A small number of patients were volunteers from other neurological clinics, and although the number of patients who were approached and refused is unknown, there is no evidence that patients suffering from dementia or affective disorders are over-represented in this group (Biggins et al 1992).

Subjects were considered suitable for inclusion into the study if they had at least two of the three major features of PD (rigidity, tremor and bradykinesia), and a history of insidious onset and progression of symptoms. Patients were excluded from the study if they met any of the following criteria:

(i) a history of stroke, transient ischaemic attack, hypertension, syphilis, encephalitis, epilepsy, cerebral tumour, alcoholism, diabetes mellitus or head injury resulting in loss of consciousness;

(ii) the presence or history of any neurological sign not compatible with a diagnosis of PD (e.g. cerebellar signs, impairment of downward gaze, oculogyric crises etc.);

(iii) the presence of any illness associated with chronic confusional states or of any chronic disabling disease other than PD:

(iv) surgery in the previous six months or neuroleptic medication in the previous three months.

Whenever a subject was assessed during the course of the existing study, the diagnosis of idiopathic PD was reviewed, and a small number of subjects were later excluded when it became apparent that the diagnosis of idiopathic PD was incorrect. At the time the study was conceived, there were no existing criteria for the diagnosis of PD as opposed to parkinsonism, that were entirely satisfactory. Gibb and Lees (1989) have since formulated criteria which have been adopted by the United Kingdom Parkinson's Disease Society Brain Bank. Therefore the PDS Brain Bank criteria were applied to PD subjects with the exception of the requirement for CT scanning. Most of the subjects have been assessed over a period of several years, and in no case has the progression of the disease been such as to suggest a diagnosis of multiple system atrophy (MSA).

2) The healthy control group.

In addition to the PD subjects, a control group was recruited from the spouses or other relatives of the PD patients, from a local general practice or from a local day centre for the elderly. Control subjects were required to be healthy apart from

transient minor ailments, and in addition to showing no evidence of having PD, they were also subject to the same exclusion criteria as the PD subjects.

Procedure.

The neurological assessment procedure carried out is the same as described in the previous chapter, and consisted of Hoehn and Yahr's staging for PD (H&Y), Webster's scale (WEBS), and the North-Western Universities Disability Scale (NUDS).

The neuropsychological assessment consisted of:-

(i) National Adult Reading Test (NART) (Nelson 1982), which provides an estimate of premorbid intelligence, and was administered at the first assessment only.

(ii) The verbal scale and the picture completion subtest of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler 1958).

(iii) The mental control, logical memory and associate learning subtests of the Wechsler Memory Scale (WMS) (Wechsler 1945).

(iv) The Graded Naming Test (GNT) (McKenna and Warrington 1983).

The psychiatric assessment consisted of:-

(i) The Montgomery and Åsberg Depression Rating Scale (MÅDRS).

(ii) The Mini Mental State Examination (MMSE).

Most subjects were assessed at their own homes, although a small number preferred to be assessed in the research office in the Department of Psychiatry. The testing took on average between 90 and 120 minutes to complete, and the assessment were performed at approximately nine monthly intervals. The manner in which the test battery was interpreted is described fully elsewhere (Boyd et al.

1991, Biggins et al. 1992). The essence of these reports is that there is an increased prevalence of impairment over a range of cognitive functions was observed at the first visit in the PD subjects as compared to age and sex matched control subjects (Boyd et al. 1991). Using survival analysis with the onset of dementia as the survival event, a cumulative period incidence of dementia of 19% in PD was found over a 54 month period, while none of the control subjects became demented (Biggins et al 1992).

The assessments as described above were performed at nine-monthly intervals. At each assessment, enquiries were made as to any change in the person's health (including mood and memory), and any changes in medication were recorded. There was no specific mechanism for visiting subjects who may have developed a depressive illness between visits. Inspection of the records of subjects who reported possible depressive episodes since the previous visit were all associated with increased scores on the MÅDRS at the assessment in question.

Data Collection.

The work described above was part of a collaborative study which was initiated by Professor R H S Mindham, and many people were involved in the collection of data. From 1985 to 1987, all neurological and psychiatric assessments were performed by Drs C A Cruickshank, F M Harrop, C W Kenn, and A G Oswald and Prof. R H S Mindham. From January 1988 until August 1989, all neurological and psychiatric assessments were performed by Dr P Madeley, and from August 1989 these assessments were performed equally by Drs P Madeley and C A Biggins.

From 1985 until 1987, Neuropsychological assessment was performed by Mr R J Smith; from 1987 until 1989 by Mrs J L Boyd (nee Hulley); in 1989 by Dr J I Randall; and from 1990 by Drs P Madeley and C A Biggins.

RESULTS.

This section is comprised of an analysis of data collected as part of an on-going longitudinal study of cognitive impairment in PD. The results in the previous chapter are used to interpret data on depression collected incidentally as part the longitudinal project.

SURVIVAL ANALYSIS.

The cross-sectional analysis revealed that the MÅDRS had 100% sensitivity and specificity when a cut-off of 17 and greater was adopted. This cut-off was used to determine whether a subject was likely to be suffering from a depressive illness using data from the longitudinal study. It was thus adopted as the criterion by which a probable depressive illness was deemed to be present and hence the "terminal event" for the survival analysis. Survival time was calculated as the time from the first assessment when subjects entered the study, to the assessment when subjects first met the criterion for the probable presence of a depressive illness (i.e. a MÅDRS score of 17 or greater). The first occasion that the terminal event occurred was the only occasion that any one subject figured as an event in the survival analysis, and a second score of 17 or greater on the MÅDRS was not recorded as a further episode for the purpose of the survival analysis.

The results of the survival analysis are shown in table 10 and figure 14. Five PD subjects were found to have a probable affective disorder at the first assessment, and were not included further in the survival analysis. A further ten developed a

probable depressive illness during follow-up. The cumulative incidence of probable depressive illness during the follow-up period is 10.9%; this is equivalent to 43 per 1000 person-years. In the control group, one subject was found to have a probable depressive disorder at the first visit, and one further subject developed a probable depressive disorder during follow-up.

Predictors of depressive illness.

In order to determine if any factors predict whether a PD subject will develop a depressive illness, the 11 PD subjects who developed a probable depressive illness during the course of follow-up (i.e. who were not deemed to have a probable depressive illness at the first visit) were compared to a group of PD subjects (n=20) who did not develop a probable depressive illness during follow-up, and who had been followed-up for at least 27 months, using Mann-Whitney "U" tests. Because this involves over 50 estimations of "U", a significance level of p=0.001 (two-tailed) was adopted. None of the scales to rate PD were different between the groups. Neither the initial MÅDRS total, nor the scores on any of the individual items of the MÅDRS were significantly different between the two groups. Similarly, none of the age scaled scores of the subtests from the WAIS, nor the IQ scores showed any difference.

Consequences of depressive illness.

The current status of all subjects who entered the longitudinal study was categorised according to whether they were demented or not (as in Biggins et al. 1992); whether they were dead or not; whether they had disappeared from follow-up and their current status was unknown; and whether they had developed a probable depressive illness or not.

Subjects who developed a probable depressive illness during the course of the study were not over-represented in the group of subjects who died or had dropped out of the study. There was an over-representation of subjects who developed a probable depressive illness in the group of subjects who became demented during the course of the study (chi-square=5.99 p=0.014).

7) DISCUSSION.

In this section, I will discuss the methodological issues raised by the two studies, and in particular those arising from the use of the PSE. Then I shall discuss the results obtained by the two studies and compare and contrast them with the existing literature.

a) Methodological Issues.

i) Subjects.

The sample of subjects in this investigation was recruited primarily from one out-patient clinic. The diagnosis of idiopathic Parkinson's disease has been made according to the most exacting criteria currently available, those of the Parkinson's Disease Society Brain Bank (with the exception of the requirement for computerised tomographic scanning). As most subjects have been observed over a number of years, the evolution of the disease has confirmed the diagnosis as that of idiopathic PD and not a condition with a similar presentation (e.g. multiple system atrophy).

PD patients were excluded if they scored less than 23 on the MMSE. This was for the following reasons. Firstly, it was felt that subjects with dementia should be excluded so that the responses to questions would not be contaminated by inappropriate or muddled responses due to cognitive impairment. Secondly, there is a possibility that there may be a neurochemical relationship between PD and depressive disorder, and the added presence of a dementia syndrome would further confuse matters due to the possible involvement of other neurochemical systems. However, there are potential problems posed by this approach. It is possible that a score of less than 23 on the MMSE could be due to a depressive pseudodementia

which had been missed. I feel this is unlikely for two reasons. Firstly, the subjects were taking part in a longitudinal study of cognitive functioning in which each subjects "normal" level of cognitive functioning had previously been established, and each subject scoring less than 23 on the MMSE, this was part of a gradual decline and not a sudden change. Secondly, the clinical interview established that these subjects were not giving the typical "I don't know" responses to questions typical of a depressive pseudodementia, and their answers corresponded to the patterns seen in dementia.

The effects of the medication being taken by the PD subjects warrants consideration. Six subjects were taking tricyclic antidepressants at the time the cross-sectional study was undertaken. It is difficult to estimate the effect of this. In addition to being prescribed for depressive disorders, tricyclic antidepressants are also prescribed for emotional incontinence, and are readily prescribed by some neurologists as their anticholinergic (side) effects may be beneficial to the patients PD itself as well as their depression or emotionalism. Antidepressants do reduce the risk of a relapse of a depressive illness when continued after the initial episode resolves, so may reduce the occurrence of depressive disorder during the longitudinal study. Thirty five subjects were taking selegeline, which is a monoamine-oxidase B inhibitor, and could theoretically have the potential to elevate mood. However, at the dose used for the treatment of PD (i.e. 5 or 10 mg daily), no improvement has been observed on the depression scales in patients with PD (Lees et al 1977; Przuntek et al 1987).

The repeated assessment by psychiatrists may have induce a Hawthorn effect[4] by sensitising subjects and their carers to the possible presence of depressive symptoms causing them to seek treatment, and on rare occasions where the

[4]The Hawthorn effect is the unwitting introduction of extraneous variables through the social interaction of human experimenters and human subjects.

presence of severe depressive illness was detected, and (with the subjects permission) its presence communicated to their general practitioner who may have instigated antidepressant treatment.

The choice of the composition of the two control groups used for comparison merits some discussion. The "healthy" control group consisted of the spouses and other close relatives of the PD subjects, some subjects recruited from the age and sex register of a local general practice, and volunteers from a day centre for the elderly. When the Leeds PD project was initiated, the control subjects were matched for age and sex as part of the study design, and were found to have a similar premorbid IQ (Boyd et al 1990). However as subjects dropped out from the study, this initial matching was not possible to maintain. Although some PD and control subjects participating in the longitudinal study dropped from follow-up, they showed few differences to subjects who continued their participation. The PD subjects who did not participate in the cross-sectional study because they dropped out from the longitudinal study were older in age and had more disability due to PD than the remaining subjects, and the control subjects who dropped out were older, but otherwise no different to the control subjects who remained.

The use of the carers of PD subjects has been criticised by MacMahon and Fletcher (1990) on the grounds that carers of PD patients have higher levels of depression than occur in the community (as measured by the HAD). However, when the PSE scores of the control group are examined, few symptoms were recorded and few diagnoses made. It was not possible to analyses the data to determine whether the symptoms were predominantly reported by the relatives of the PD subjects, or by all control subjects. The incidence of probable depressive disorder in the healthy control group was 2.2 per 1000 person-years. It does not appear therefore, that probable depressive disorder occurred in the control group more frequently than would be expected.

The depressed control group was designed to collect all patients who were depressed on the acute admission wards in Leeds. The intention was to assess patients who had been diagnosed as having a serious depressive illness necessitating admission to hospital. Some subjects were seen within 24 hours of admission, whereas others were seen when "much improved" and due for discharge. It is to be emphasised that all "depressed" subjects were assessed, and that no subjects with less severe depressive illness (e.g. "neurotic depression", "reactive depression" etc.) were excluded. The intention in choosing this group was to demonstrate the pattern and severity of symptoms of PSE syndromes which occurs in depressive illnesses of sufficient severity to warrant in-patient assessment and treatment. This also allowed comparison with the PSE syndrome profile in PD subjects, to determine whether the profiles were similar or not.

Unfortunately, both control groups are smaller in size than the PD group. Subjects with PD are on the whole motivated to try to help research into "their" disease, and this attitude is actively promoted by the Parkinson's Disease Society, which the majority of our PD subjects belonged to. Where health control subjects were recruited from the spouses and carers of the PD subjects, this positive attitude to research was also present. Healthy controls are much more difficult to recruit, and do not have the motivation of suffering from a disease, but only the more abstract motivation of being able to help with "medical research". This probably accounts for the higher proportion of drop-outs (not due to death) in the healthy control group when compared to the PD group. The presence of lassitude and decreased motivation due to affective disorder is an obvious problem when trying to recruit depressed control group, even for a one-off assessment. When the number of control subjects is limited, a trade-off is required between rigidly insisting on careful matching of control with the PD group on the one hand, and being less rigid about matching to achieve a numerically large control group on the other.

The degree of matching and sample size in this thesis represents, in my opinion, a reasonable compromise between these two pressures.

ii) The Assessment Process.

There are methodological issues to discuss in the use of the PSE and the four rating scales for depression. There may be bias introduced by the PSE and the four rating scales being completed by one rater. This is a difficult issue, but I believe that the structure of the assessment forms means that this possible bias is kept to a minimum. A copy of the assessment schedule is included in the appendix, and from this it can be seen that the items from the MÅDRS and HDRS were completed at the same time that these symptoms and signs were probed by the PSE. I believe that this format means that there should be a consistent approach to scoring an individual symptom reported by a patient, whilst at the same time it is difficult for the rater to keep a running total of the MÅDRS and HDRS scores. Bias on the part of a rater would also be reduced because the PSE symptoms are analysed by the Catego program, and during the course of an interview it would be difficult for a rater to predict the eventual outcome of the Catego analysis. I would suggest that these factors would result in a consistency of rating of items that would reduce the effect of rater variability, without introducing a significant effect of rater bias.

A possible way to examine for possible bias would be to compare the results of the observer rated scales (i.e. the MÅDRS and HDRS) with those obtained from the self-reported rating scales (i.e. the BDI and the HADD), which will not be subject to observer bias as they are completed by the subjects themselves immediately prior to the PSE interview, but the completed forms were not examined until after the PSE interview. Examination of Table 7 shows the following: firstly the MÅDRS and HDRS correlate highly in all three groups; secondly the BDI and

HADD correlate weakly in the PD and depressed groups but not in the healthy control group; thirdly the MÅDRS and HDRS correlate well with the BDI in the PD and depressed groups but not in the healthy control group; and finally the MÅDRS and HDRS correlate weakly with the HADD in the PD and depressed groups but not in the healthy control group. The difference in performance between the BDI and the HADD can be explained by the HADD relying on the presence or absence of anhedonia which the BDI does not. I believe this pattern of results is consistent with the presence of little observer bias.

When subjects with physical illnesses are assessed on the PSE, two strategies have been reported to accommodate symptoms that could be due to the physical illness alone. One strategy is to take all symptoms in a "non-prejudicial" manner, and to rate without reference to cause (e.g. Feldman et al 1987, House 1987b). The other strategy which is recommended by the authors of the PSE, and the one adopted in this study, is not to rate positively when a physical cause for the symptom is obvious. As both raters were experienced psychiatrists and both members of the Royal College of Psychiatrists, it was felt they were of sufficient experienced to be able to perform this task. Although few difficulties were experienced, raters felt this experience was necessary to perform this task. I feel it is doubtful whether a person with little or no training in psychopathology would be able to perform this task adequately. It may be that neurologists, clinical psychologists, psychiatric nurses or psychiatric social workers could be trained to differentiate between a physical or a psychological cause for a symptom, but it would be necessary to demonstrate that this was the case.

b) PSE Results.

My use of the PSE in the cross-sectional study is very similar to the use of the PSE by Brown and MacCarthy (1990), and it is therefore interesting to compare the two

sets of results. Both sets of subjects were out-patient populations with idiopathic PD. Brown and MacCarthy's subjects were of comparable age to my subjects, but had earlier onset of the disease, and had worse staging of the disease on Hoehn and Yahr's classification.

A comparison of the syndrome profiles obtained from the PSE between Brown and MacCarthy's study and mine is shown in figure 15. The syndrome profiles are very similar indeed. There were no syndromes present in Brown and MacCarthy's sample that were not present in mine, but there were five syndromes present in mine that were not present in theirs. These were depressive delusions and hallucination (DD) in 10% of my sample; depersonalisation (DE) in 2.5%; lack of energy (LE) in 17.5%; social unease (SU) in 12.5%; and hypochondriasis (HY) in 5%. Of these items, LE, SU and HY were among the items that Brown and MacCarthy found

"*some problem or ambiguity in making ratings owing to the presence of motor symptoms or the effects of medication*". The most likely explanation for the presence of these syndromes is that in their study, Brown and MacCarthy did not rate these symptoms as positive if there was any suggestion that they may be due to contamination by the effects of PD, but that in my study, these symptoms were rated if they were present but probably not due to possible contamination. There appears to be little effect on the Catego diagnosis due to these "disputed" syndromes, as the rate of Catego diagnoses made is identical in the two studies.

As the syndrome profile in figure 15 has now been produce by two studies, it is likely this represents the syndrome profile that is typical of subjects with PD, and that the syndromes that rate positively are the "core features" of the PSE profile in PD. These "core features" can be divided into four groupings. Firstly there are those related to lowering of mood: simple depression (SD); special features of depression (ED); and other symptoms of depression (OD). Secondly there are

those related to anxiety: situational anxiety (SA); general anxiety (GA); and possibly obsessional neurosis (ON). Thirdly there are those related to non-specific symptoms of worry: tension (TE); lack of energy (LE); worry (WO); irritability (IT); and hypochondriasis (HY). Finally there are symptoms of social unease: social unease (SU); and ideas of reference (IR). Syndromes which feature in schizophrenic illnesses were not found in either study. As shown in figure one and three, there is little similarity between the syndrome profile in PD subjects and subjects who are in-patients with "depression".

The PSE diagnoses obtained by the two studies are very similar (but this is not surprising given the similarity of the syndrome profiles). Brown and MacCarthy found two subjects with "neurotic depression", one with "anxiety state" and one with "phobic state": I found two subjects with "neurotic depression", one with "phobic state" and one with "other paranoid psychosis".

Brown and MacCarthy interpreted their findings of many symptoms but few PSE diagnoses as suggesting the level of diagnosis of the Catego program was not appropriate in PD, and should be lower. What is the reason for this apparent mismatching of the number of symptoms with the number of diagnoses?

The PSE interview and the analysis of this by the Catego program is designed to reflect the principles and practice of standard psychiatric practice in the diagnosis of psychiatric conditions. The Catego program makes a standard psychiatric diagnosis only if the correct constellation of symptoms is present. My impression of subjects tested was that the PSE/ Catego diagnosis was at the correct level, in that few subjects were clinically depressed, but many reported symptoms of dysphoria. Hantz et al (1994)[5] using the Structured Clinical Interview for DSM-

[5]This paper was published after the original submission of this thesis. As it has bearing on this discussion it is included briefly here, but has not been reviewed in full

III-R (SCID) in PD subjects, which performs in a similar manner to the PSE/ Catego system except it generates DSM-III diagnoses, also found a low prevalence rate for major depression. They suggest that "*minor degrees of psychiatric morbidity are common but that when they are assessed by means of strict diagnostic criteria they fall short of defined psychiatric syndromes*", and feel their results are consistent with those of Brown and MacCarthy (1990). They conclude that "*Parkinson's disease itself does not appear to confer a greater risk for a psychiatric diagnosis than do old age or physically disabling, chronic conditions*". I agree with this statement in terms of affective disorder (although I disagree if they are intending to imply that the risk for dementia is not increased).

There are conditions which are present in PD which do not amount to standard psychiatric diagnoses, but do cause symptoms. These conditions are states such as demoralisation due to the presence of a chronic physical illness (see chapter two). The presence of prominent tearfulness (emotionalism) has been described in 10% of subjects with PD (Madeley et al 1992), and this condition produces symptoms but no standard psychiatric diagnosis. Although these conditions do not produce a "standard psychiatric diagnosis", they do cause distress and suffering to subject with PD. It is important that these "non-diagnosable states" are recognised, and appropriate strategies developed to manage them. Epidemiological models of depression demonstrates that although "diagnosable" depressive disorders are seen in psychiatric settings, there are many people with depressive symptoms who are seen by general medical practitioners. Terms such as "*secondary depression, demoralisation and neurotic depression*" (Klerman 1989) are applied to these people, implying that their depression is less an illness than in patients with bipolar disorder or other major affective conditions. Despite this, these people show significant impairments of functional and social status. A very important aspect of the management of these conditions is the provision of support, both for the patient and their carer. The model of service provision of "community neurology" in

which support is an important factor, similar to that provided by MacMahon and colleagues in Cornwall may be an appropriate way to deal with these "non-diagnosable states".

c) Discussion of the Hypotheses Tested.

The null hypothesis for hypothesis one was rejected, and the conclusion reached that there was an excess of PD subjects diagnosed as suffering from a depressive disorder by ordinal rating scales compared to by the PSE. This was shown by the excess subjects diagnosed as "depressed" using virtually all the cut-off scores that have been employed in studies using ordinal rating scales. The proportion of PD subjects diagnosed as having a depressive illness obtained in this study is comparable with that obtained by the use of the PSE by Brown and MacCarthy (1990) and Hantz et al (1994). This begs the question whether these standardised instruments (e.g. PSE and SCID) are more accurate than the ordinal scales, but it should be remembered that these standardised scales are designed to reflect the processes involved in psychiatric diagnostic practice whereas the ordinal scales were designed to measure one specific psychiatric condition on the assumption that the individual item scores reflected the presence and severity of that condition, and that condition alone.

The null hypothesis for hypothesis two was rejected, and the conclusion reached that there was an excess of the somatic features of depressive illness relative to the psychic features of depressive illness in the PD subjects compared to healthy control subjects. The null hypothesis for hypothesis three was rejected, and the conclusion reached that there was an excess of the psychic features of depressive illness relative to the somatic features of depressive illness in the depressed control group compared to PD subjects. The overall effect of these two hypotheses was that the PD group resembled the healthy control group in the psychic features of

depression (i.e. not depressed in nature), whereas they resembled the depressed control group only in somatic items (i.e. not depressed in nature but with many physical features). When the scores of individuals in the PD group who scored between the lower and higher cut-off scores used by investigators using the BDI and HDRS were examined, most of the items scoring highly were somatic in nature.

d) Depression Rating Scales and PD.

A weak but significant correlation was found between measures of PD and scores obtained on the rating scales for depression. When the distribution of scores on the individual items of the depression rating scales was compared between the PD, control and depressed groups, it was found that the PD group was similar to the control group rather than the depressed group. The total scores on the depression rating scales were higher in the PD than the control group. Even when the few individual items of the scales that were higher in the PD group than the control group were excluded from the analysis, the total scores of the depression rating scales remained higher in the PD group than the control group. This suggests that the scores of the individual items are higher in the PD group than the control group, but that this difference is not statistically significant, and that the summation of a large number of non-significant differences produces total scores which are significantly different. Furthermore, although the difference between the PD and control groups is found to be statistically significantly different, it does not necessarily follow that the difference is clinically significantly different.

Only two PD subjects were diagnosed by the PSE as suffering from a depressive illness. When the PSE diagnoses were compared with varying cut-off scores on the depression rating scales, no subjects were diagnosed as suffering from a

depressive illness by the rating scales when the PSE did not diagnose them (False positive scores). This would be predicted by the strict criteria that the Catego program imposes. However, it means that in this sample, the specificity is always 100% (except at very extreme values). Normally the characteristics of a rating scale in terms of sensitivity and specificity are best displayed using ROC curves, but as the constant value for sensitivity makes this inappropriate, specificity scores were displayed.

The diagnosis of only 2 PD subjects as suffering from a depressive illness also makes the selection of cut-off scores difficult. There is a band of scores for each depression rating scale for which the specificity and sensitivity scores are 100%. For the purposes of the Longitudinal study, the lowest score where both specificity and sensitivity were 100% was adopted. The presence of this band of scores where sensitivity and specificity are 100% demonstrates that the subjects diagnosed by the PSE as having a depressive disorder are outliers, rather than the upper end of a continuum.

From these results it can be seen that the BDI and HAD need higher cut-off scores than those which have been already used. The status of the HDRS is less clear: it may be that the cut-off of 17+ may be acceptable or it may need to be at a higher value: the wide band where sensitivity and specificity are 100% make this difficult to assess. The validation of a cut-off value for the use of the MÅDRS in PD made it possible to examine the patterns of probable depressive disorder sequentially over a six year period. This produced an incidence for probable depressive disorder of 43 per 1000 person years in PD. No predictors for the later development of depressive disorders were found.

e) Methodological Issues Concerning the Survival Analysis.

The cross-sectional study using the PSE was used to determine an acceptable cut-off score for the MÅDRS for use in PD. This cut-off score was then applied retrospectively to the results from the ongoing Leeds study which had collected scores on the MÅDRS to obtain a classification of probable depressive disorder. Five PD subjects were found to have a probable depressive disorder at the first assessment, and were therefore excluded from the rest of the analysis. As the aim of the analysis was to determine the incidence of new cases of probable depressive disorder in PD, only the first occasion on which a subject scored above the cut-off score was included in the survival analysis, and subjects who remained depressed or who recovered and then scored above the cut-off score on a second occasion were not included a second time in the survival analysis (as they had already reached the "terminal event").

The use of a survival analysis depends on all episodes of the terminal event being detected and included in the analysis. As our subjects were assessed at approximately nine monthly intervals, is it possible that some episodes of probable depressive disorder were missed? There was no mechanism by which subjects would notify the project if they became "depressed" between the periodic assessments. However, at each assessment, the subjects were questioned as to the state of their health since they were last assessed, and whether they had had any change in their prescribed medications (of any type: not solely for PD). No subject reported an episode of low mood or being prescribed antidepressant medication unless they scored above the cut-off score on that visit. It is possible that some episodes may have been missed, but I consider this unlikely considering that subjects were sensitised to be aware of the symptoms of depressive disorders by the testing process.

f) Placing These Results in Context.

Depression and PD has recently been the topic of review articles (Ring and Trimble 1991; Cummings 1992). However, these reviews have not been critical in nature, and have taken the published results at face value, with little consideration to the methodological issues I have raised in this thesis. For example, Ring and Trimble referred to the overlap of the features of affective disturbance and PD said

> "*But despite these observations, the consensus is that there is a specific association between PD and depression*".

Cummings justifies the use of the BDI by citing Levin et al (1988), and Starkstein et al (1990); two papers which require critical re-evaluation. Cummings feels the wide range of prevalence rates that have been obtained is due to

> "*different definitions of depression, thresholds for identification of a mood disorder and assessment strategies*".

It is of interest to note that the three reports that use a standardised rating instrument (Brown and MacCarthy 1990; Hantz et al 1994; this study), and the one clinical study using recent classification for depressive disorders (Rondot et al 1984) give a consistently low prevalence for depressive disorders in PD. The interpretation of these results differ, but I believe that these consistently low results in conjunction with the arguments expounded in this thesis clearly demonstrate that depressive disorders in PD require a critical re-evaluation of the literature.

g) Speculation as to the Nature of "Depression" in PD.

I believe it is difficult to draw on much of the published literature to speculate on the nature of "depression" in PD due to the methodological problems I have

discussed. This is perhaps most clearly demonstrated in the paper by Mayeux et al (1981) who examined PD subjects who were "*not overtly depressed*", and despite this found that 48% of the subjects were "*depressed*" according to the BDI.

Despite this, it is possible to speculate to an extent. At the start of this thesis I raised three possible explanations as to why PD and depressive disorders may be associated. I feel the evidence presented above is suggestive that depressive disorders have been overdiagnosed in PD. However there is no doubt that severe affective disorder does occur in PD. Rabins (1982) described the symptoms of PD subjects who had been admitted to a psychiatric hospital. Some patients presented with "*classical depressive delusions, self-blame and guilt, as well as somatic delusions*". Other patients had no vegetative symptoms, did not experience depressive or somatic delusions, did not improve with tricyclic antidepressants, and as their symptoms could be understood in light of their disability, fulfilled the criteria for "adjustment disorder with depressed mood".

As affective disorders do occur in PD, can the other two mechanisms for their occurrence be relevant. These are that there is a common neurochemical pathway for depressive disorders in PD, and that there is an adjustment reaction that is due to the presence of a chronic disabling disease. Cummings (1992) proposed a model for the pathogenesis of depression in PD (see figure 16), which combines these two approaches. However, the basis for the neurobiological part of the model comes form his uncritical reading of the literature. Ring et al (1994)[6] used PET scanning in a group of PD subjects who did not have a depressive disorder, a PD group that did have DSM-III major depression, a control group and a DSM-III major depression group (but otherwise healthy). They found that the PD DSM-III major depression group and the healthy DSM-III depression group PET scan

[6]This study was not published when Cummings wrote his review, nor when this thesis was originally submitted. Because of it's relevance I am including it briefly here, but am not fully reviewing it.

findings were virtually identical; namely that there was impairment of blood flow in the anteromedial regions of the medial frontal cortex and the cingulate cortex. They conclude that the "*depression of PD shares a common biological substrate with that of primary depression*".

Given that the picture of severe depression in PD resembles severe depression in healthy individuals in frequency of prevalence (Rondot et al 1984; Brown and MacCarthy 1990; Hantz et al 1994; this study), in phenomenology (Rabins 1982), and PET scan appearance (Ring et al 1994), I conclude that severe depression in PD is the same as severe depression in healthy subjects: this has been the area of concern for this thesis.

However, there do remain a large number of symptoms in PD sufferers who do not correspond to the picture of severe depression. I would speculate that these symptoms correspond to dysphoria and demoralisation, although I have not specifically explored this area. The use of group therapy to treat PD (Chafetz et al. 1955; Szekely et al. 1982) may have been directed to these lesser states. Horn (1974) found that subjects with PD appeared to have premature ageing is sociological terms.

8) CONCLUSIONS.

This thesis set out to examine whether depressive disorders were overdiagnosed in PD, and if this was the case, if this was due to the problems of overlap of the features of PD and affective disorders when ordinal depression rating scales were being used. Using the MÅDRS, the incidence of depressive disorders was 10% over a five year period, and using the PSE diagnosis from the cross-sectional study gives a prevalence rate of 3.4%. Even after differences in prevalence rates between populations with differing severities of PD is taken into account, it is difficult to explain prevalence rates which are significantly higher than this, except by ascribing this difference to overdiagnosis by the use of ordinal rating scales.

The aim of clinical research is to benefit patients. This can be achieved in two ways: firstly by improving patient care directly; and secondly by facilitating further research. This thesis will hopefully perform both tasks. It is essential that clinicians who treat patients with PD consider the possibility that their patient may be depressed. A clear diagnosis should be made (including distinguishing between severe affective disorder and adjustment reactions). Whatever the diagnosis, social interventions and supportive psychotherapy are likely to improve the situation. Adjustment reactions are unlikely to respond to physical treatments. In severe affective disorder in PD, tricyclic antidepressants (Anderson et al 1980) and ECT (reviewed by Abrams 1989) have been shown to be effective in the treatment of the mood disorder and also the motor symptoms of PD. Indeed, there are five studies in which ECT was administered to non-depressed PD subjects, and in four of these studies improvement in the motor symptoms of PD was reported. Finally, consideration should also be given to the carers of PD subjects, who have been shown to have higher rates of depressive symptoms than the general population (Fletcher et al 1990).

From the research point of view, it is essential that the methodological flaws are overcome. This will require the formulation of clear definitions of lowered mood states, especially the "less severe" depressive disorders. It will also require the use of standardised interview schedules such as the PSE and SCID or ordinal rating scales which have been validated for use in PD.

REFERENCES.

Abrams R. (1989) "ECT for Parkinson's disease." American Journal of Psychiatry. 146: 1391-1393.

Alyard PR, Gooding JH, McKenna PJ, Snaith RP. (1987) "A validation study of three anxiety and depression self-assessment scales." Journal of Psychosomatic Research. 31: 261-268.

American Psychiatric Association. (1980) Diagnostic and Statistical Manual of Mental Disorders, 3rd edn. American Psychiatric Association: Washington DC.

Andersen J, Aabro E, Gulman N, Hjelmsted A, Pedersen HE. (1980) "Anti-depressive treatment in Parkinson's disease." Acta neurologica Scandinavica. 62: 210-219.

Anthony J C, LeResche L, Niaz U, von Korff MR, Folstein MF. (1982) "Limits of the 'Mini-Mental State' as a screening test for dementia and delirium among hospital patients." Psychological Medicine. 12: 397-408.

Bailey J, Coppen A. (1976) "A comparison between the Hamilton rating scale and the Beck inventory in the measurement of depression." British Journal of Psychiatry. 128: 486-489.

Baldwin RC, Byrne EJ. (1989) "The psychiatric aspects of Parkinson's disease." British Medical Journal. 299: 3-4.

Balldin J, Eden S, Granerus A-K, Modigh K, Svanborg A, Walinder J, Wallin L. (1980) "Electroconvulsive therapy in Parkinson's syndrome with "on-off" phenomenon." Journal of Neural Transmission. 47: 11-21.

Beck AT, Ward CH, Mendelson M, Mork S, Erbaugh S. (1961) "An inventory for measuring depression." Archives of General Psychiatry. 4: 561-571.

Beilauskas LA, Glantz RH. (1987) "Use of the mini-mult D scale in patients with Parkinson's disease." Journal of Consulting and Clinical Psychology. 55: 437-438.

Beilauskas LA, Glantz RH. (1989) "Depression type in Parkinson's disease." Journal of Clinical and Experimental Neurology. 11: 597-604.

Berkman LF, Berkman CS, Kasl S, Freeman DH Jr, Leo L, Ostfield AM, Cornoni-Huntley J, Brody, JA. (1986) "Depressive symptoms in relation to physical health and functioning in the elderly." American Journal of Epidemiology. 124: 372-388.

Biggins CA, Boyd JL, Harrop FM, Madeley P, Mindham RHS, Randall JI, Spokes EGS. (1992) "A controlled longitudinal study of dementia in Parkinson's disease." Journal of Neurology, Neurosurgery and Psychiatry. 55: 556-571.

Blazer D. (1989) "Depression in late life." Current Opinion in Psychiatry. 2: 515-519.

Blumenthal MD. (1975) "Measuring depressive symptomatology in a general population." Archives of General Psychiatry. 32: 971-978.

Boyd JL, Cruickshank CA, Kenn CW, Madeley P, Mindham RHS, Oswald AG, Smith RJ, Spokes EGS. (1991) "Cognitive impairment and dementia in Parkinson's disease: a controlled study." Psychological Medicine. 21: 911-921.

Brink TL, Yesavage JA, Lum O, Heersema PH, Adey M, Rose TL. (1982) "Screening tests for geriatric depression." Clinical Gerontologist. 1: 37-43.

Brown GL, Wilson WP. (1972) "Parkinsonism and depression." Southern Medical Journal. 65: 540-545.

Brown RG, MacCarthy B. (1990) "Psychiatric morbidity in patients with Parkinson's disease." Psychological Medicine. 20: 77-87.

Brown RG, MacCarthy B, Gotham A-M, Der GJ, Marsden CD. (1988) "Depression and disability in Parkinson's disease: a follow-up of 132 cases." Psychological Medicine. 18: 49-55.

Buzzard T. (1882) "A clinical lecture on the shaking palsy." Brain. 4: 473.

Cantello R, Aguggia M, Delsedime M, Chiardo Cutin I, Riccio A, Mutani R. (1989) "Major depression in Parkinson's disease and the mood response to intravenous methylphenidate: possible role of the "hedonic" dopamine synapse." Journal of Neurology, Neurosurgery and Psychiatry. 52: 724-731.

Cantello R, Gilli M, Riccio A, Bergamasco B. (1986) "Mood changes associated with "end of dose deterioration" in Parkinson's disease: a controlled study." Journal of Neurology, Neurosurgery and Psychiatry. 49: 1182-1190.

Cantello R, Riccio A, Scarzella L, Leotta D, Bergamasco B. (1984) "Depression in Parkinson's disease: a disabling but neglected factor." Italian Journal of Neurological Sciences. 5: 417-422.

Carmines EG, Zeller RA. (1979) Reliability and validity assessment. Sage Publications. Beverly Hills.

Carroll BJ, Fielding JM, Blashki TG. (1973) "Depression rating scales." Archives of General Psychiatry. 28: 361-366.

Celesia GC, Barr AN. (1970) "Psychosis and other psychiatric manefestations of levodopa therapy." Archives of Neurology. 23: 193-200.

Celesia GC, Wannamaker WM. (1972) "Psychiatric disturbances in Parkinson's disease." Diseases of the Nervous System. 33: 577-583.

Chafetz ME, Bernstein N, Sharpe W, Schwab RS. (1955) "Short-term group therapy of pateints with Parkinson's disease." New England Journal of Medicine. 252 (22): 961-964.

Cherrington M. (1970) "Parkinsonism, L-DOPA and mental depression." Journal of the American Geriatric Society. 18: 513-516.

Creed F, Murphy S, Jayston VJ. (1990) "Measurement of psychiatric disorder in rheumatoid arthritis." Journal of Psychosomatic Research. 34: 79-87.

Cummings JL. (1992) Depression and Parkinson's disease: a review. American Journal of Psychiatry. 149: 443-454.

Dakof GA, Mendelsohn GA. (1986) "Parkinson's disease: the psychological aspects of a chronic illness." Psychological Bulletin. 99: 375-387.

Davidson J, Turnbull CD, Strickland R, Miller R, Graves K. (1986) "The Montgomery-Asberg depression scale: reliability and validity." Acta Psychitrica Scandinavica. 73: 544-548.

Diamond GJ. (1983) "Evaluating the evaluations: or how to weigh the scales of parkinsonian disability." Neurology. 33: 1098-1099.

Diller L, Riklan M. (1956) "Psychosocial factors in Parkinson's disease." Journal of the American Geriatric Society. 4: 1291-1300.

Ehman TS, Beninger RJ, Gawel MJ, Riopelle RJ. (1990) "Depressive symptoms in Parkinson's disease: a comparison with disabled control subjects." Journal of Geriatric Psychiatry and Neurology. 3: 3-9.

Feldman E, Mayou R, Hawton K, Arden M, Smith E. (1987) "Psychiatric disorder in medical In-patients." Quarterly Journal of Medicine. 63: 405-412.

Fletcher P, Maguire R, MacMahon DG. (1990) "The prevalence of anxiety and depression in elderly Parkinson's disease patients and carers." Movement Disorders. 5 Supp: 70.

Folstein SE, Folstein MF, McHugh. (1975) "'Mini mental state': a practical method for grading the cognitive state of patients for the clinician." Journal of Psychiatric Research. 12: 189-198.

Gibb WR, Lees AJ. (1989) "A comparison of clinical and pathological features of young- and old- onset Parkinson's disease." Neurology. 38: 1402-1406.

Golbe LI, Pae J. (1988) "Validity of a mailed epidemiological questionnaire and physical self-assessment in Parkinson's disease." Movement Disorders. 3: 245-254.

Gotham A-M, Brown RG, Marsden CD. (1986) "Depression in Parkinson's disease: a quantitative and qualititive analysis." Journal of Neurology, Neurosurgery and Psychiatry. 49: 381-389.

Gowers WR. (1888) A manual of the disease of the nervous system. London. MacMillan.

Gurland BJ (1976) "The comparative frequency of depression in various adult age groups." Journal of Gerontology. 31: 283.

Gurland BJ, Wilder DE, Berkman C. (1988) "Depression and disability in the elderly; reciprocal relations and changes with age." International Journal of Geriatric Psychiatry. 3: 163-179.

Hamilton M. (1960) "A rating scale for depression." Journal of Neurology, Neurosurgery and Psychiatry. 23: 56-62.

Hamilton M. (1976) "Comparative value of rating scales." British Journal of Clinical Pharmacology. 3: 58-60.

Hantz P, Caradoc-Davies G, Caradoc-Davies T, Weatherall M, Dixon G. (1994) Depression in Parkinson's disease. American Journal of Psychiatry. 151: 1010-1014.

Hathaway S, McKinley J. (1951) The Minnesota Multiphasic Personality Inventory Manual. Minneapolis: University of Minnesota Press.

Hoehn MM, Crowley TJ, Rutledge CO. (1976) "Dopamine correlates of neurological and psychological status in untreated parkinsonism." Journal of Neurology, Neurosurgery and Psychiatry. 39: 941-951.

Hoehn MM, Yahr MD. (1967) "Parkinsonism: onset, progression and mortality." Neurology. 17: 427-442.

Horn S. (1974) "Some psychological factors in parkinsonism." Journal of Neurology, Neurosurgery and Psychiatry. 37: 27-31.

House A. (1987a) "Mood disorders after stroke: a review of the evidence." International Journal of Geriatric Psychiatry. 2: 211-221.

House A. (1987b) "Psychosocial problems of patients on the renal unit and their relation to treatment outcome." Journal of Psychosomatic Research. 31: 441-452.

House A, Dennis M, Mogridge L, Warlow C, Hawton K, Jones L. (1991) "Mood disorders in the year after first stroke." British Journal of Psychiatry. 158: 83-92.

Hovestadt A, Kooij JG. (1991) "Measuring depression in Parkinson's disease." Abstracts from the 10th International Symposium on Parkinson's disease, Tokyo.

Huber SJ, Freidenberg DI, Paulson GW, Shuttleworth EC, Christy JA. (1990) "The pattern of depressive symptoms varies with the progression of Parkinson's disease." Journal of Neurology, Neurosurgery and Psychiatry. 53: 275-278.

Huber SJ, Paulson GW, Shuttleworth EC. (1988a) "Relationship of motor symptoms, intellectual impairment and depression in Parkinson's disease." Journal of Neurology, Neurosurgery and Psychiatry. 51: 855-858.

Huber SJ, Paulson GW, Shuttleworth EC. (1988b) "Depression in Parkinson's disease." Neuropsychiatry, Neuropsychology, and Behavioural Neurology. 1: 47-51.

Kathol RG, Petty F. (1981) "Relationship of depression to medical illness: a critical review." Journal of Affective Disorders. 3: 111-121.

Kearney TR. (1964) "Parkinson's disease presenting as depressive illness." Journal of the Irish Medical Association. 54: 117-119.

Kearns NP, Cruickshank CA, McGuigan KJ, Riley, SA, Shaw SP, Snaith RP. (1982) "A comparison of depression rating scales." British Journal of Psychiatry. 141: 45-49.

Kenn C, Wood H, Kuczy M, Wattis J, Cunnane J. (1987) "Validation of the hospital anxiety and depression rating scale in an elderly psychiatric population." International Journal of Geriatric Psychiatry. 2: 189-193.

Klerman GL. (1989) "Depressive disorders: further evidence for increased medical morbidity and impairment of social functioning." Archives of General Psychiatry. 46: 856-858.

Koenig HG, Meador KG, Cohen HG, Blazer DG. (1988) "Depression in elderly hospitalised patients with medical illness." Archives of Internal Medicine. 148: 1929-1936.

Kostic VS, Djuricic BM, Covickovic-Sternic N, Bumbasirevic L, Nikoloc M, Mrsulja BB. (1987) "Depression and Parkinson's disease: possible role of serotonergic mechanisms." Journal of Neurology. 234: 94-96.

Kostic VS, Covickovic-Sternic N, Beslac-Bumbasirevic L, Ocic G, Pavlovic D, Nikoloc M. (1990) "Dexamethasone suppression test in patients with Parkinson's disease." Movement Disorders. 5: 23-26.

Lebensohn ZM, Jenkins RB. (1975) "Improvement of parkinsonism in depressed patients treated with ECT." American Journal of Psychiatry. 132: 283-285.

Lees AJ, Shaw KM, Kahout LJ, Stern GM, ElsworthJD, Sandler M, Youdim MBH. (1977) Deprenyl in Parkinson's disease. Lancet. 2: 791-795.

Levin BE, Llabre MM, Weiner WJ. (1988) "Parkinson's disease and depression: psychometric properties of the Beck depression inventory." Journal of Neurology, Neurosurgery and Psychiatry. 51: 1401-1404.

Lishman WA. (1987) Organic Psychiatry. Blackwell Scientific Publications. Oxford.

MacCarthy B, Brown RG. (1989) "Psychosocial factors in Parkinson's disease." British Journal of Psychological Medicine. 28: 41-52.

MacMahon DG, Fletcher PJ. (1989) "Psychiatric aspects of Parkinson's disease." British Medical Journal. 299: 388-389.

MacMahon DG, Fletcher PJ. (1990) "Depression in Parkinson's disease." Journal of Neurology, Neurosurgery and Psychiatry. 54: 666.

Madeley P, Biggins CA, Boyd JL, Mindham RHS, Spokes EGS. (1991) "Cognitive impairments and depression in Parkinson's disease." (letter) Journal of Neurology, Neurosurgery and Psychiatry. 54: 941.

Madeley P, Biggins CA, Boyd JL, Mindham RHS, Spokes EGS. (1992) "Emotionalism in Parkinson's disease." Irish Journal of Psychological Medicine. 9: 24-25.

Marsh GC, Markham CM. (1973) "Parkinsonian patients' self-reports of levo-DOPA effects on cognitive and memory changes." Psychosomatics. 12: 114-116.

Mayeaux R, Stern Y, Cote L, Williams BW. (1984a) "Altered serotonin metabolism in depressed patients with Parkinson's disease." Neurology. 34: 642-646.

Mayeaux R, Stern Y, Cote L, Williams BW. (1984b) "Depression and Parkinson's disease." in Advances in Neurology. 40: 241-250. Eds. Hassler RG, Christ JF. Raven Press, New York.

Mayeaux R, Stern Y, Rosen J, Leventhal J. (1981) "Depression, intellectual impairment and Parkinson's disease." Neurology. 31: 645-650.

Mayeaux R, Stern Y, Williams BW, Cote L, Franntz A, Dyrenfurth I. (1986) "Clinical and biochemical correlates of depression in Parkinson's disease." American Journal of Psychiatry. 143: 756-759.

McGarvey B, Gallagher D, Thompson LW, Zelinski E. (1979) "Reliability and factor structure of the Zung self rating depression scale in three age groups." Essence. 141-152.

McKenna P, Warrington EK. (1983) Graded naming test manual. NFER-Nelson. Windsor.

Menza MA, Sage J, Marshall E, Cody R, Duvoisin R. (1990) "Mood changes and 'on-off' phenomena in Parkinson's disease." Movement Disorders. 5: 148-151.

Mindham RHS. (1970) "Psychiatric symptoms in parkinsonism." Journal of Neurology, Neurosurgery and Psychiatry. 33: 188-191.

Mindham RHS, Marsden CD, Parkes JD. (1976) "Psychiatric symptoms during L-DOPA therapy for Parkinson's disease and their relationship to physical disability." Psychological Medicine. 6: 23-33.

Mjones H. (1949) "Paralysis agitans: a clinical and genetic study." Acta Psychiatrica et Neurologica, Supp. 54: 60-75.

Moffic HS and Paykel ES. (1975) "Depression in medical in-patients." British Journal of Psychiatry. 126: 346-353.

Montgomery SA, Asberg M. (1979) "A new depression scale designed to be sensitive to change." British Journal of Psychiatry. 134: 382-389.

Morley S, Snaith RP. (1989) "Principles of psychological assessment." In Research Methods in Psychiatry. Eds Freeman C, Tyrer P. Gaskell, London.

Morris JN, Wolf RS, Klerman LV. (1975) "Common themes among morale and depression scales." Journal of Gerontology. 30: 200-215.

Murphy E. (1986) "The concept of affective disorders in the elderly." In Affective Disorders in the Elderly. 1-12. Ed Murphy E. Churchill Livingstone.

Nelson HE. (1982) National Adult Reading Test Manual. NFER-Nelson: Windsor.

Nissenbaum H, Quinn NP, Brown RG, Toone B, Gotham A-M, Marsden CD. (1987) "Mood swings associated with the "on-off" phenomenon on Parkinson's disease." Psychological Medicine. 17: 899-904.

Parkinson J. (1817) An essay on the shaking palsy. Sherwood, Neely and Jones. London.

Parmalee PA, Katz IR, Lawton MP. (1989) "Depression among institutionalized aged: assessment and prevalence estimation." Journal of Gerontology: Medical Sciences. 44: M22-29.

Patrick HT, Levy DM. (1922) "Parkinson's disease- a clinical study of one hundred and forty six cases." Archives of Neurology and Psychiatry. 7: 712-720.

Pfeiffer RF, Hsieh HH, Diercks MJ, Glaeske C, Jefferson A, Cheng S-C. (1986) "Dexamethasone suppression test in Parkinson's disease." Advances in Neurology. Eds Yahr MD, Bergmann KJ. Raven Press, New York. 45: 439-442.

Pichot P. (1972) "The problems of quantifying the symptomatology of depression." In Depressive Illness. Ed Kielholz P. Hans Huber Publishers.

Pitt B. (1986) "Characteristics of depression in the elderly." In Affective Disorders in the Elderly. 40-51. Ed Murphy E. Churchill Livingstone.

Przuntek H, Kuhn W. (1987) The effect of R-(-)-deprenyl in de novo Parkinson patients on combination therapy with levodopa and decarboxylase inhibitor. Journal of Neural Transmission. [Suppl] 25:97-104.

Rabins PV. (1982) "Psychopathology of Parkinson's disease." Comprehensive Psychiatry. 23: 421-429.

Ring HA, Bench CJ, Trimble MR, Brooks DJ, Frackowiak RSJ, Dolan RJ. (1994) Depression in Parkinson's disease: a positron emission study. British Journal of Psychiatry. 165: 333-339.

Ring HA, Trimble MR. (1991) "Affective disturbance in Parkinson's disease." International Journal of Geriatric Psychiatry. 6: 385-393.

Robins AH. (1976) "Depression in patients with parkinsonism." British Journal of Psychiatry. 128: 141-145.

Rondot P, de Recondot J, Coignet A, Ziegler M. (1984) "Mental disorders in Parkinson's disease after treatment with L-DOPA." in Advances in Neurology. 40: 259-269. Eds. Hassler RG, Christ JF. Raven Press, New York.

Sano M, Stern Y, Williams J, Cote L, Rosenstein R, Mayeux R. (1989) "Coexisting dementia and depression in Parkinson's disease." Archives of Neurology. 46: 1284-1286.

Santamaria J, Tolosa E, Valles A. (1986a) "Parkinson's disease with depression: a possible subgroup of idiopathic parkinsonism." Neurology. 36: 1130-1133.

Santamaria J, Tolosa E, Valles A, Bayes A, Blesa R, Masana J. (1986b) "Mental depression in untreated Parkinson's disease of recent onset." Advances in Neurology. Eds Yahr MD, Bergmann KJ. Raven Press, New York. 45: 443-446.

Schiffer RB, Kurlan R, Rubin A, Boer S. (1988) "Evidence for atypical depression in Parkinson's disease." American Journal of Psychiatry. 145: 1020-1022.

Schwab RS, England AC. (1958) "Parkinson's disease." Journal of Chronic Disease. 8: 488-509.

Schwab RS, Fabing HD, Pritchard JS. (1951) "Psychiatric symptoms and syndromes in Parkinson's disease." American Journal of Psychiatry. 107: 901-907.

Siegel S, Castellan NJ. (1988) Nonparametric statistics. McGraw Hill. New York.

Singer E. (1976) "Sociopsychological factors influencing response to levodopa therapy for Parkinson's disease." Archives of Physical and Medical Rehabilitation. 57: 328-334.

Snaith RP. (1987) "The concepts of mild depression." British Journal of Psychiatry. 150: 387-393.

Snaith RP, Taylor CM. (1985) "Rating scales for depression and anxiety: a current perspective." British journal of Clinical Pharmacology. 19: 178-208.

Snaith RP. (1991) "Measurement in psychiatry." British Journal of Psychiatry. 159: 78-82.

Starkstein SE, Bolduc PL, Mayberg HS, Preziosi TJ, Robinson RG. (1990b) "Cognitive impairments and depression in Parkinson's disease: a follow up study." Journal of Neurology, Neurosurgery and Psychiatry. 53: 597-602.

Starkstein SE, Berthier ML, Bolduc PL, Preziosi TJ, Robinson RG. (1989b) "Depression in patients with early versus late onset of Parkinson's disease." Neurology. 39: 1441-1445.

Starkstein SE, Preziosi TJ, Bolduc PL, Robinson RG. (1990a) "Depression in Parkinson's disease." Journal of Nervous and Mental Disease. 178: 27-31.

Starkstein SE, Preziosi TJ, Berthier ML, Bolduc PL, Mayberg HS, Robinson RG. (1989a) "Depression and cognitive impairment in Parkinson's disease." Brain. 112: 1141-1153.

Starkstein SE, Preziosi TJ, Forrester AW, Robinson RG. (1990c) "Specificity of affective and autonomic symptoms of depression in Parkinson's disease." Journal of Neurology, Neurosurgery and Psychiatry. 53: 869-873.

Strang DD. (1965) "Imipramine in treatment of parkinsonism: a double blind placebo study." British Medical Journal. 2: 33-34.

Szekely BC, Kosanovich N, Sheppard W. (1982) "Adjunctive treatment in Parkinson's disease: physical therapy and comprehensive group therapy." Rehabilitation Literature. 43 (3-4): 72-76.

Taylor AE, Saint-Cyr JA, Lang AE, Kenny FT. (1986) "Parkinson's disease and depression: a critical re-evaluation." Brain. 109. 279-292.

Veith RC, Raskind MA. (1988) "The neurobiology of ageing: does it predispose to depression?" Neurobiology of Ageing. 9: 101-117.

Vogel HP. (1982) "Symptoms of depression in Parkinson's disease." Pharmacopsychiatry. 15: 192-196.

Warburton JW. (1967) "Depressed symptoms in parkinson patients referred for thalamotomy." Journal of Neurology, Neurosurgery and Psychiatry. 30: 368-370.

Webster DD (1968) "Critical analysis of the disability in Parkinson's disease." Medical Treatments. 5: 257-282.

Wechsler D. (1945) "A standardised memory scale for clinical use." Journal of Psychology. 19: 87-95.

Wechsler D. (1958) Manual for the Wechsler Adult Intelligence Scale. Psychological Corporation. New York.

Williams JBW. (1988) "A structured interview guide for the Hamilton depression rating scale." Archives of General Psychiatry. 45: 742-747.

Wing JK. (1983) "Use and misuse of the PSE." British Journal of Psychiatry. 143: 111-117.

Wing JK, Cooper JE, Sartorius N. (1974) The Measurement and Classification of Psychiatric Symptoms. Cambridge University Press: Cambridge.

Yesavage JA, Brink TL. (1983) "Development and validation of a geriatric depression screening scale: a preliminary report." Journal of Psychiatric Research. 17: 37-49.

Zigmond AS, Snaith RP. (1983) "The hospital anxiety and depression scale." Acta Psychiatrica Scandinavica. 67: 361-370.

Zung WWK. (1967) "Depression in the normal aged." Psychosomatics. 8: 287-292.

TABLE 1:

Showing the relationship between scores and their frequencies achieved on a test and classification by an independent criterion.

	Criterion	
TEST	1	0
1	True positive *a*	False positive *b*
0	False negative *c*	True negative *d*

Sensitivity (%) = $\frac{a}{a + c}$ x 100%

Specificity (%) = $\frac{d}{b + d}$ x 100%

Scores can be assigned to two categories: 1, when the subject exceeds the cut-off score of the test or the criterion; and 0, when the subject fails to meet the cut-off score or the criterion. The frequencies in four cells are shown as *a*, *b*, *c* and *d*. They can be used to determine the specificity and sensitivity of the test as shown.

(Taken from Morley and Snaith 1992)

TABLE 2:

Showing Hoehn and Yahr's staging for Parkinson's disease (1967)

Stage I

Unilateral involvement, usually minimal or no functional impairment.

Stage II

Bilateral or midline involvement, without impairment of balance

Stage III

First signs of impaired righting reflexes: evident in unsteadiness as the patient turns or demonstrated when he is pushed from standing equilibrium with feet together and eyes closed. Functionally somewhat restricted, but may be able to work, depending on nature of employment. Capable of independent living, with mild or moderate overall disability.

Stage IV

Fully developed, severely disabling disease. Can stand and walk unaided, but is markedly incapacitated.

Stage V

Confined to wheel-chair or bed without assistance.

TABLE 3:

Showing the number of subjects in the Parkinson's disease, healthy control and depressed control groups, with their sex and mean ages.

	Parkinson's disease	Healthy controls	Depressed controls
Number	52	32	30
Mean Age	66.0	65.4	66.2
Age range	39 - 81	39 - 80	36 - 89
Male/Female	24/28	19/13	13/17
Proportion male subjects	0.46	0.59	0.43
95% confidence intervals	0.32 to 0.61	0.41 to 0.76	0.26 to 0.63

TABLE 4:

Showing a comparison of the first test scores upon entering the Leeds PD project for PD subjects who had dropped out of the ongoing study compared to PD subjects who were tested for the current cross-sectional analysis.

VARIABLE	U	p
Age	518.5	0.0004
HY	728.5	0.063
Webs	721.0	0.079
NUDS	607.0	0.012
IDD	510.0	0.95
MÅDRS	879.5	0.69
WAIS	627.5	0.42
NART	547.0	0.25
GNT	592.0	0.14

U: Mann-Whitney "U" score
p=probability value (two tailed)
HY=Hoehn and Yahr Staging for PD
Webs=Webster's rating scale for PD
NUDS=North Western Universities Disability Scale for PD
IDD=Leeds Irritability, Depression and Anxiety scale, depression score
MÅDRS=Montgomery Åsberg depression rating scale score
WAIS=Weschler Adult Intelligence Scale score
NART=National Adult Reading Test score
GNT=Graded Naming Test score

TABLE 5:

Showing a comparison of the first test scores upon entering the Leeds PD project for control subjects who had dropped out of the ongoing study compared to control subjects who were tested for the current cross-sectional analysis.

VARIABLE	U	p
Age	532.5	0.0036
IDD	688.0	0.082
MÅDRS	572.5	0.73
WAIS	734.5	0.10
NART	629.5	0.093
GNT	592.5	0.77

U: Mann-Whitney "U" score
p=probability value (two tailed)
IDD=Leeds Irritability, Depression and Anxiety scale, depression score
MÅDRS=Montgomery Åsberg depression rating scale score
WAIS=Weschler Adult Intelligence Scale score
NART=National Adult Reading Test score
GNT=Graded Naming Test score

TABLE 6:

Showing the median and range of scores for the Parkinson's disease, control and depressed groups on the ordinal rating scales for depression.

SCALE	PD GROUP	CONTROL GROUP	DEPRESSED GROUP
	(n=52)	(n=32)	(n=30)
HADD	4 (0 to 16)	2 (0 to 7)	14 (7 to 21)
HADA	6 (0 to 17)	3.5 (1 to 10)	13 (3 to 20)
BDI	8 (0 to 31)	3.5 (0 to 19)	30.5 (8 to 40)
MÅDRS	5 (0 to 24)	0.5 (0 to 15)	28.5 (14 to 45)
HDRS	3 (0 to 18)	0 (0 to 14)	17.5 (4 to 29)

HADD: Hospital Anxiety and Depression Scale; depression subscale.
HADA: Hospital Anxiety and Depression Scale; anxiety subscale.
BDI: Beck Depression Inventory.
MÅDRS: Montgomery Åsberg Depression Rating Scale.
HDRS: Hamilton Depression Rating Scale.

TABLE 7:

a) Showing Spearman's rank correlation coefficients between the rating scales for depression in the Parkinson's disease group.

	HADD	HADA	BDI	MÅDRS
HADA	0.64**			
BDI	0.55**	0.65**		
MÅDRS	0.34**	0.67**	0.66**	
HDRS	0.33**	0.62**	0.69**	0.82**

b) Showing Spearman's rank correlation coefficients between the rating scales for depression in the control group.

	HADD	HADA	BDI	MÅDRS
HADA	0.39*			
BDI	0.38*	0.37*		
MÅDRS	-0.09	0.17	0.42**	
HDRS	-0.05	0.16	0.41**	0.92**

c) Showing Spearman's rank correlation coefficients between the rating scales for depression in the depressed group.

	HADD	HADA	BDI	MÅDRS
HADA	0.34*			
BDI	0.55**	0.30		
MÅDRS	0.48**	0.46**	0.64**	
HDRS	0.34*	0.44**	0.60**	0.86**

* = value significant at p=0.05
** = value significant at p=0.01
All other values are not statistically significant

HADD: Hospital Anxiety and Depression Scale; depression subscale.
HADA: Hospital Anxiety and Depression Scale; anxiety subscale.
BDI: Beck Depression Inventory.
MÅDRS: Montgomery Åsberg Depression Rating Scale.
HDRS: Hamilton Depression Rating Scale.

TABLE 8:

Showing Spearman's rank correlation coefficients between the rating scales for depression and the measures of disease severity and disability in the Parkinson's disease group.

	NUDS	HY	WEBS
HADD	-0.32*	0.35**	0.15
HADA	-0.38**	0.40**	0.25*
BDI	-0.47**	0.41**	0.26*
MÅDRS	-0.47**	0.54**	0.28*
HDRS	-0.31*	0.39**	0.10

* = value significant at p=0.05
** = value significant at p=0.01
All other values are not statistically significant

HADD: Hospital Anxiety and Depression Scale; depression subscale.
HADA: Hospital Anxiety and Depression Scale; anxiety subscale.
BDI: Beck Depression Inventory.
MÅDRS: Montgomery Åsberg Depression Rating Scale.
HDRS: Hamilton Depression Rating Scale.
NUDS: North Western Universities Disability Scale.
HY: Hoehn and Yahr's Staging for Parkinson's disease.
WEBS: Webster's rating scale for Parkinson's disease.

TABLE 9:

showing values of Cronbach's alpha in rating scales for depression when administered to the Parkinson's disease, control and depressed groups, and for the three groups combined.

RATING SCALE	PD GROUP	CONTROL GROUP	DEPRESSED GROUP	ALL GROUPS
BDI	0.85	0.78	0.77	0.93
HDRS	0.74	0.77	0.69	0.87
MÅDRS	0.74	0.64	0.68	0.91
HADD	0.78	0.65	0.74	0.90
HADA	0.82	0.73	0.79	0.87

HADD: Hospital Anxiety and Depression Scale; depression subscale.
HADA: Hospital Anxiety and Depression Scale; anxiety subscale.
BDI: Beck Depression Inventory.
MÅDRS: Montgomery Åsberg Depression Rating Scale.
HDRS: Hamilton Depression Rating Scale.

TABLE 10:

Showing survivorship tables for Parkinson's disease patients and control subjects. The terminal event occurs when a subject scores 17 or greater on the Montgomery Åsberg depression rating scale, and survivorship, therefore, is failure to reach this score.

	Time from initial assessment (months)	Number of subjects entering interval	Number of subjects withdrawn in interval[7]	Number of terminal events	Proportion terminating	Cumulative proportion surviving at end
Parkinson's disease patients	0	92	11	5	0.058	0.942
	9	76	10	2	0.028	0.916
	18	64	7	5	0.083	0.840
	27	52	6	2	0.041	0.806
	36	44	6	0	0.000	0.806
	45	38	10	1	0.030	0.781
	54	27	16	0	0.000	0.781
	63	11	11	0	0.000	0.781
control subjects	0	50	7	1	0.022	0.979
	9	42	1	0	0.000	0.979
	18	41	3	0	0.000	0.979
	27	37	4	0	0.000	0.979
	36	34	10	0	0.000	0.979
	45	24	5	0	0.000	0.979
	54+	19	12	1	0.077	0.903

[7]Includes not only subjects dropping out of the study, but also subjects who have not been in the study long enough to reach the next interval.

FIGURE 1:

Showing the frequency of PSE syndromes in the Parkinson's disease group.

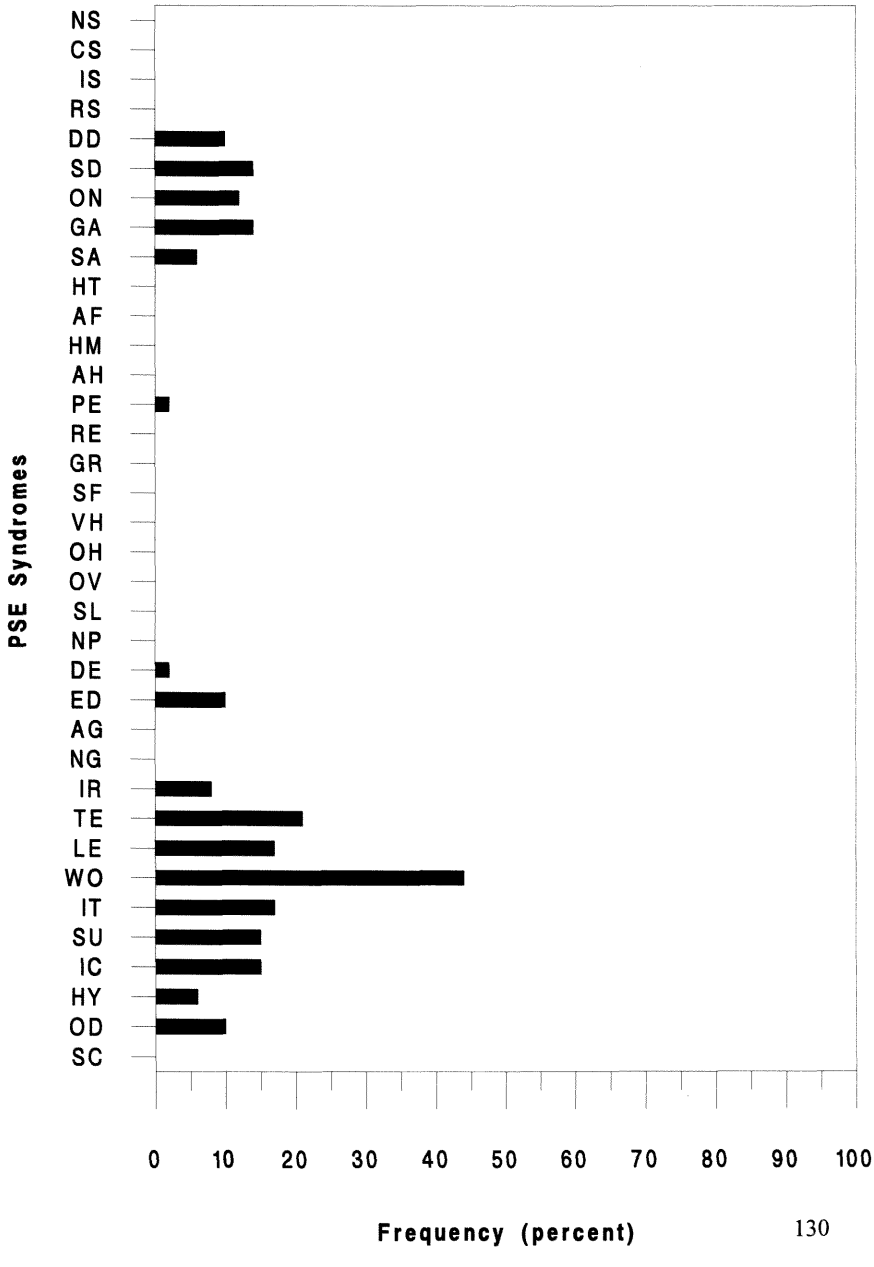


FIGURE 2:

Showing the frequency of PSE syndromes in the healthy control group.

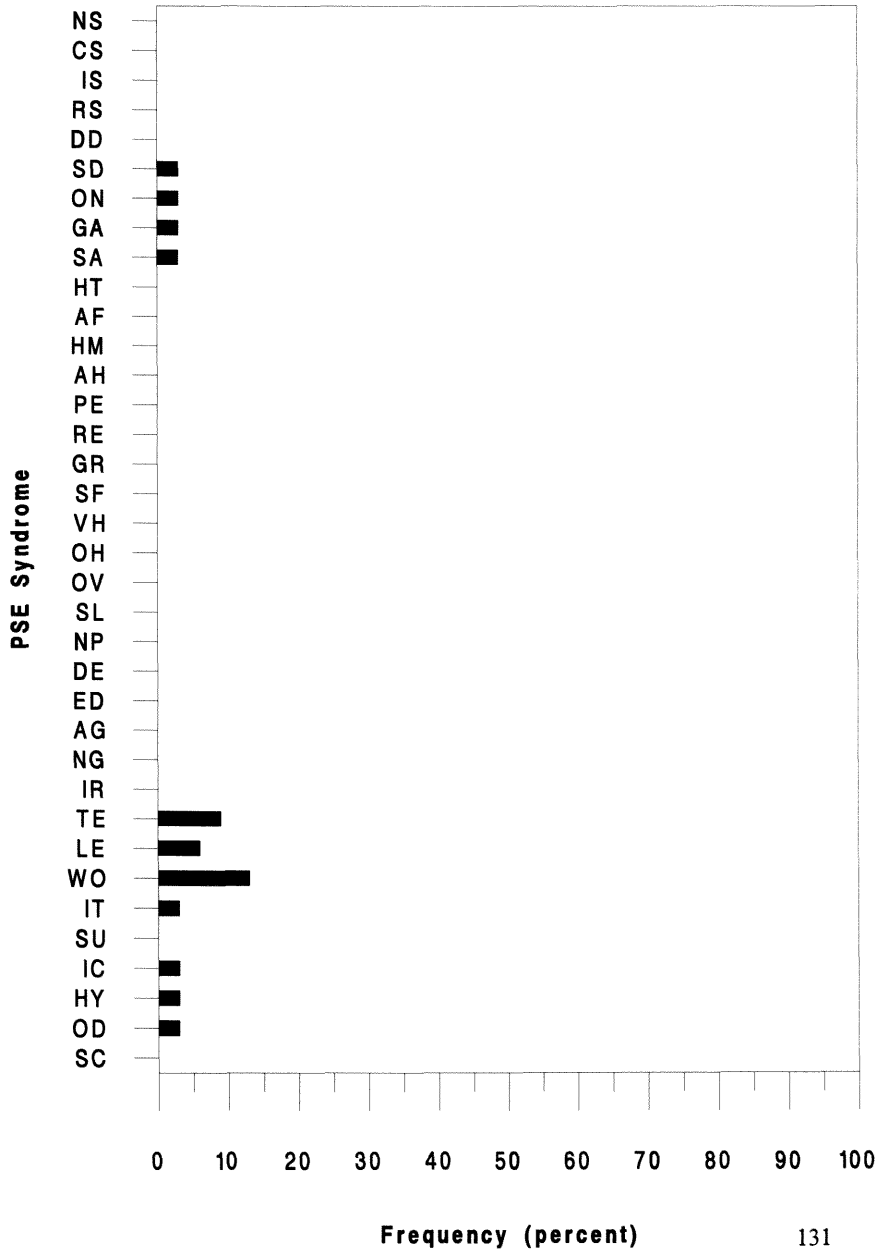
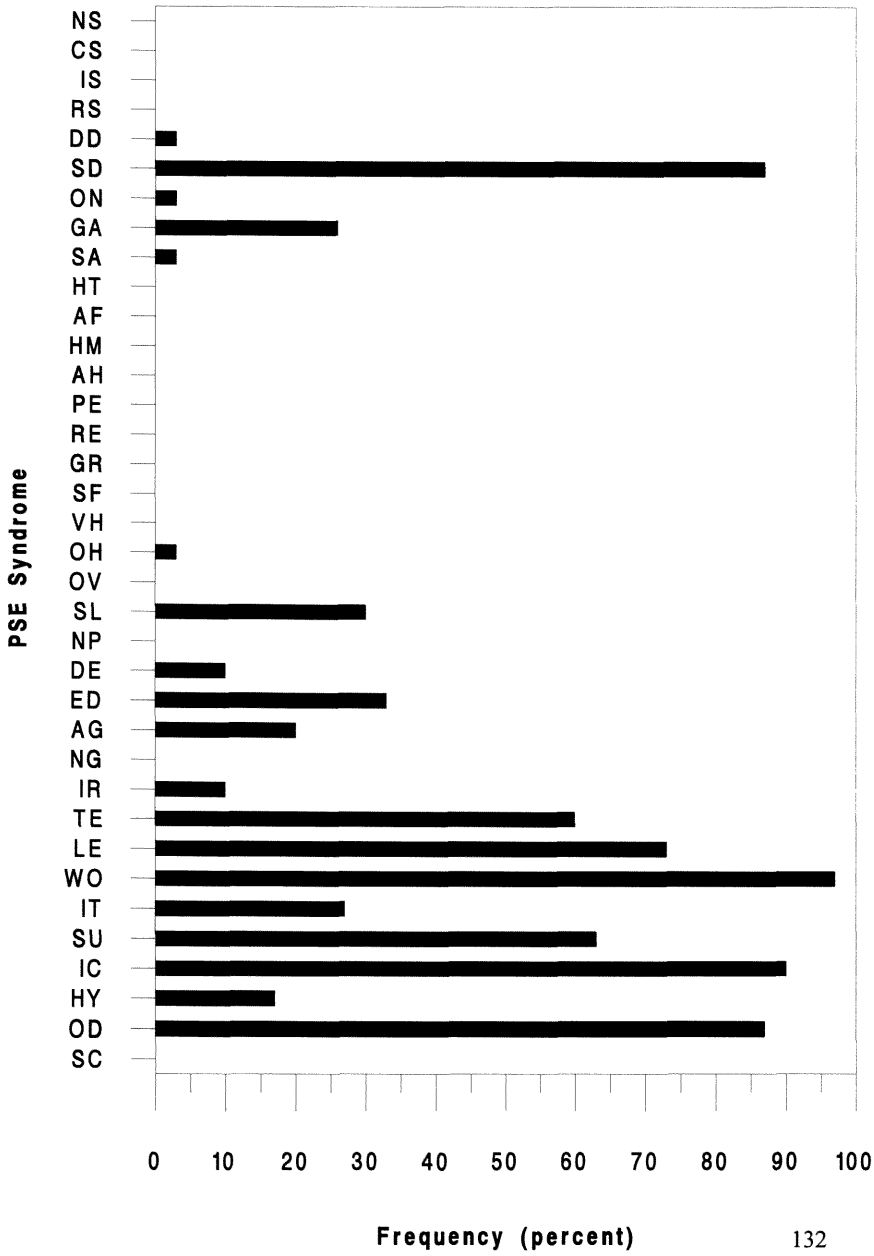


FIGURE 3:

Showing the frequency of PSE syndromes in the depressed group.



KEY TO FIGURES 1,2,3 & 15

NS: Nuclear syndrome
CS: Catatonic syndrome
IS: Incoherent speech
RS: Residual syndrome
DD: Depressive delusions and hallucinations
SD: Simple depression
ON: Obsessional neurosis
GA: General anxiety
SA: Situational anxiety
HT: Hysteria
AF: Affective flattening
HM: Hypomania
AH: Auditory hallucinations
PE: Delusions of persecution
RE: Delusions of reference
GR: Grandiose and religious delusions
SF: Sexual and fantastic delusions
VH: Visual hallucinations
OH: Olfactory halluicinations
OV: Overactivity
SL: Slowness
NP: Non-specific psychosis
DE: Depersonalisation
ED: Special features of depression
AG: Agitation
NG: Self-neglect
IR: Ideas of reference
TE: Tension
LE: Lack of energy
WO: Worrying
IT: Irritability
SU: Social unease
IC: Loss of interest and concentration
HY: Hypochondriasis
OD: Other symptoms of depression
SC: Subcultural delusions or hallucinations

FIGURE 4:

Showing the distribution of the total scores obtained on the BDI by PD subjects.

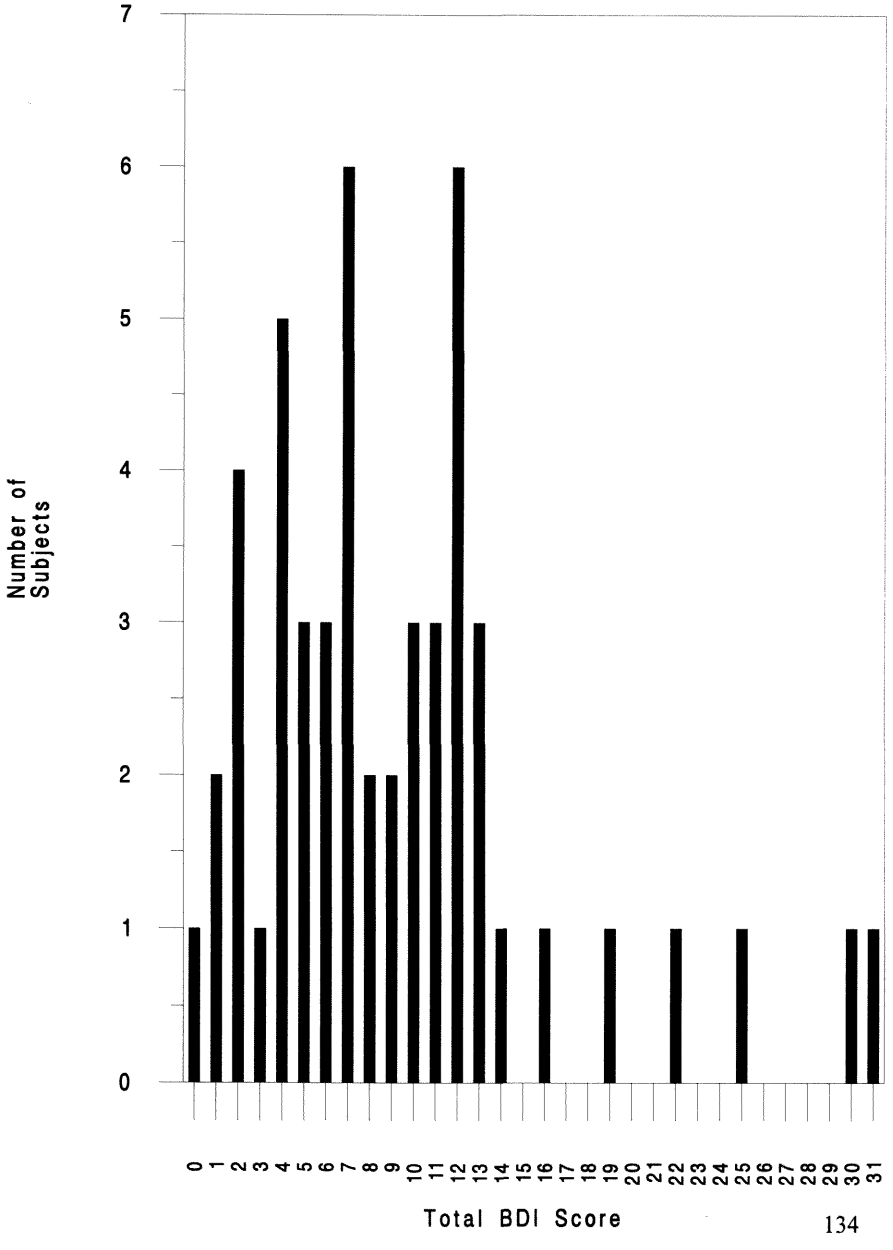


FIGURE 5:

Showing the distribution of the total scores obtained on the HDRS by PD subjects.

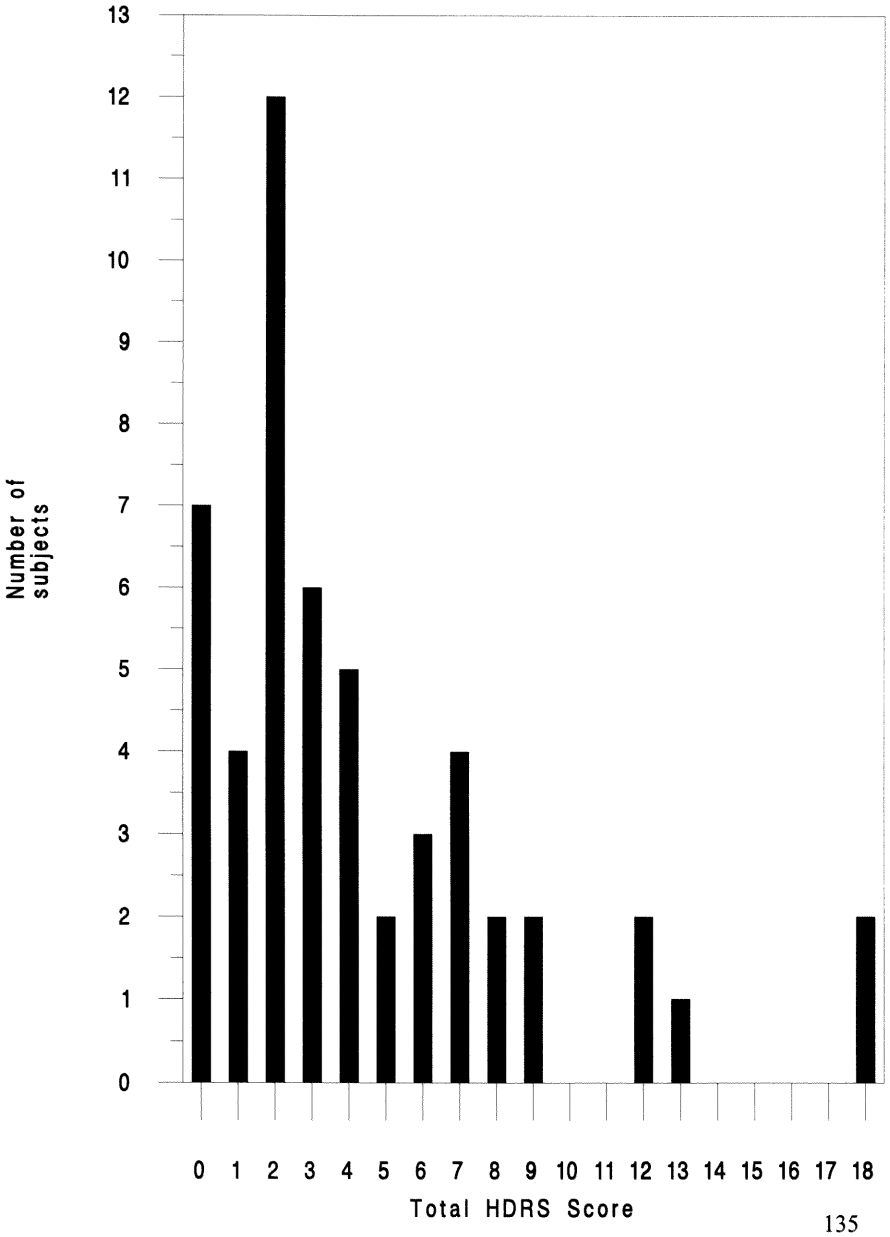


FIGURE 6:

Showing the distribution of the total scores obtained on the MÅDRS by PD subjects.

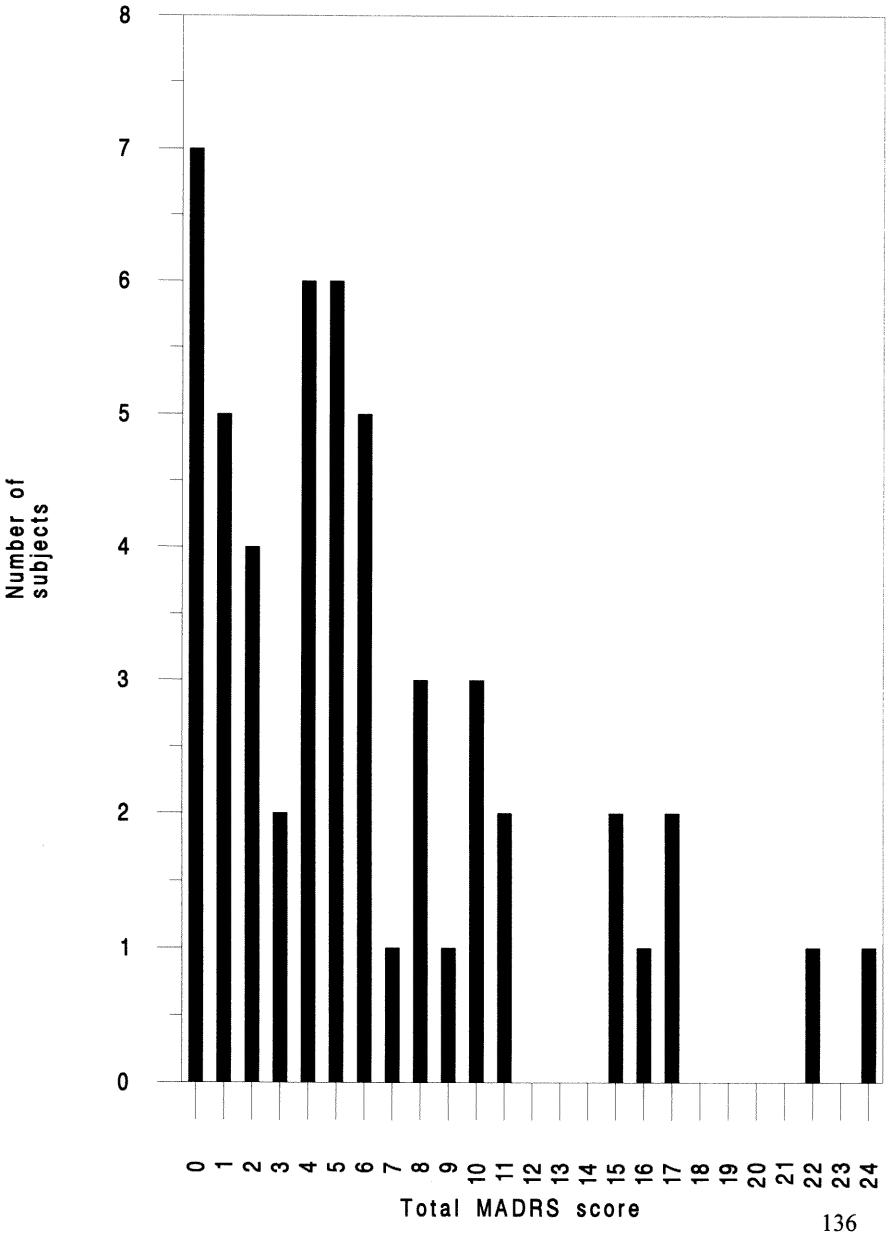


FIGURE 7:

Showing the distribution of the total scores obtained on the HAD(D) by PD subjects.

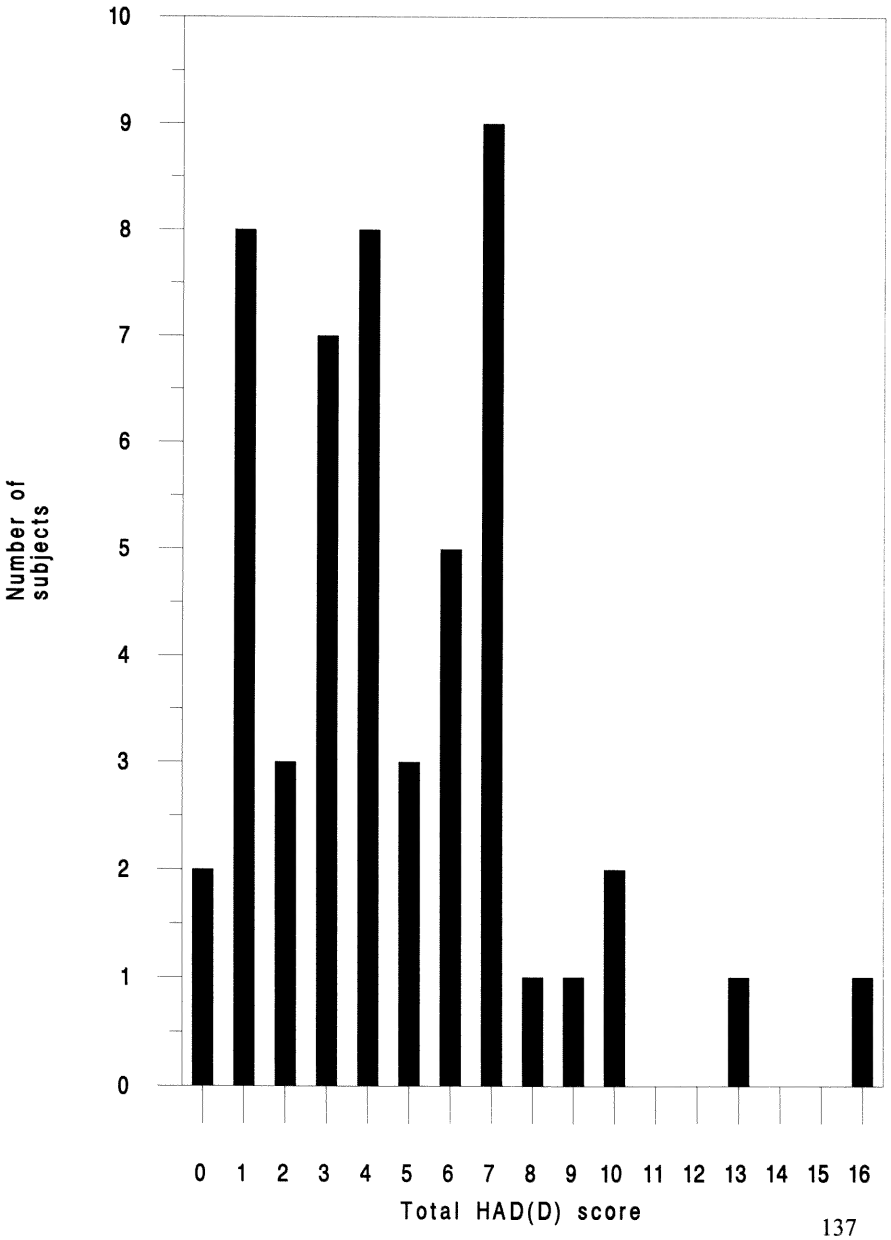


FIGURE 8:

Showing the effect of various cut-off scores on the sensitivity of the BDI in PD.

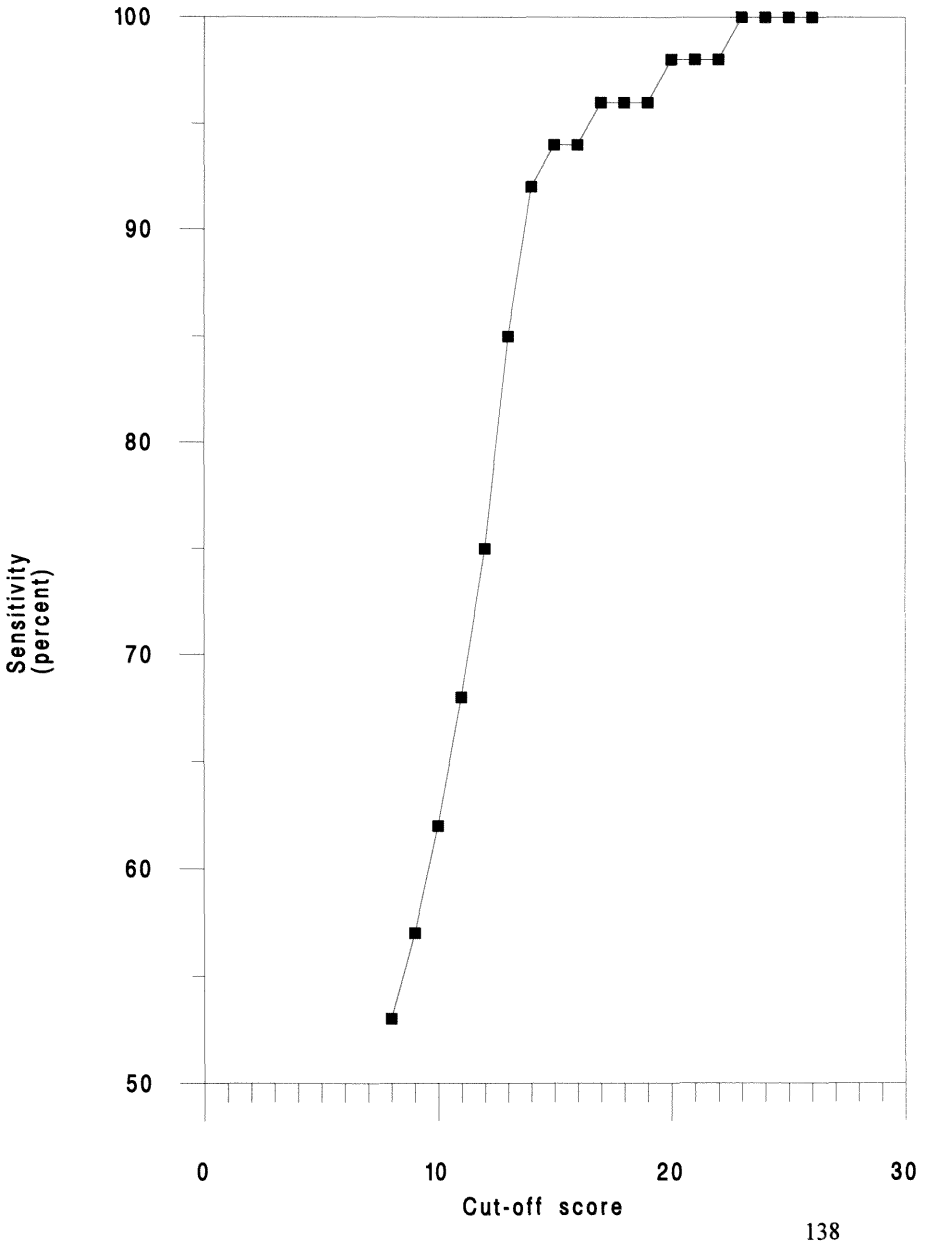


FIGURE 9:

Showing the effect of various cut-off scores on the sensitivity of the HDRS in PD.

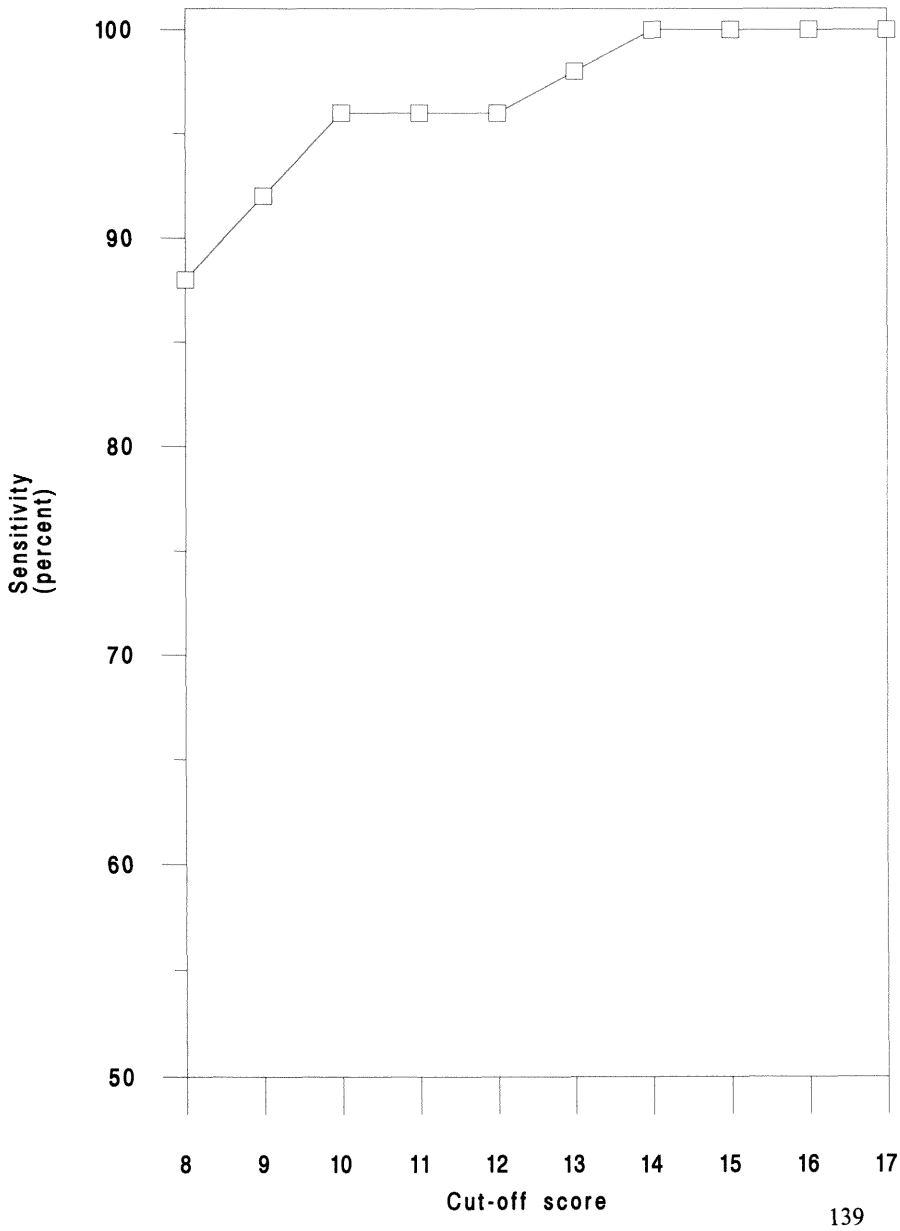


FIGURE 10:

Showing the effect of various cut-off scores on the sensitivity of the MÅDRS in PD.

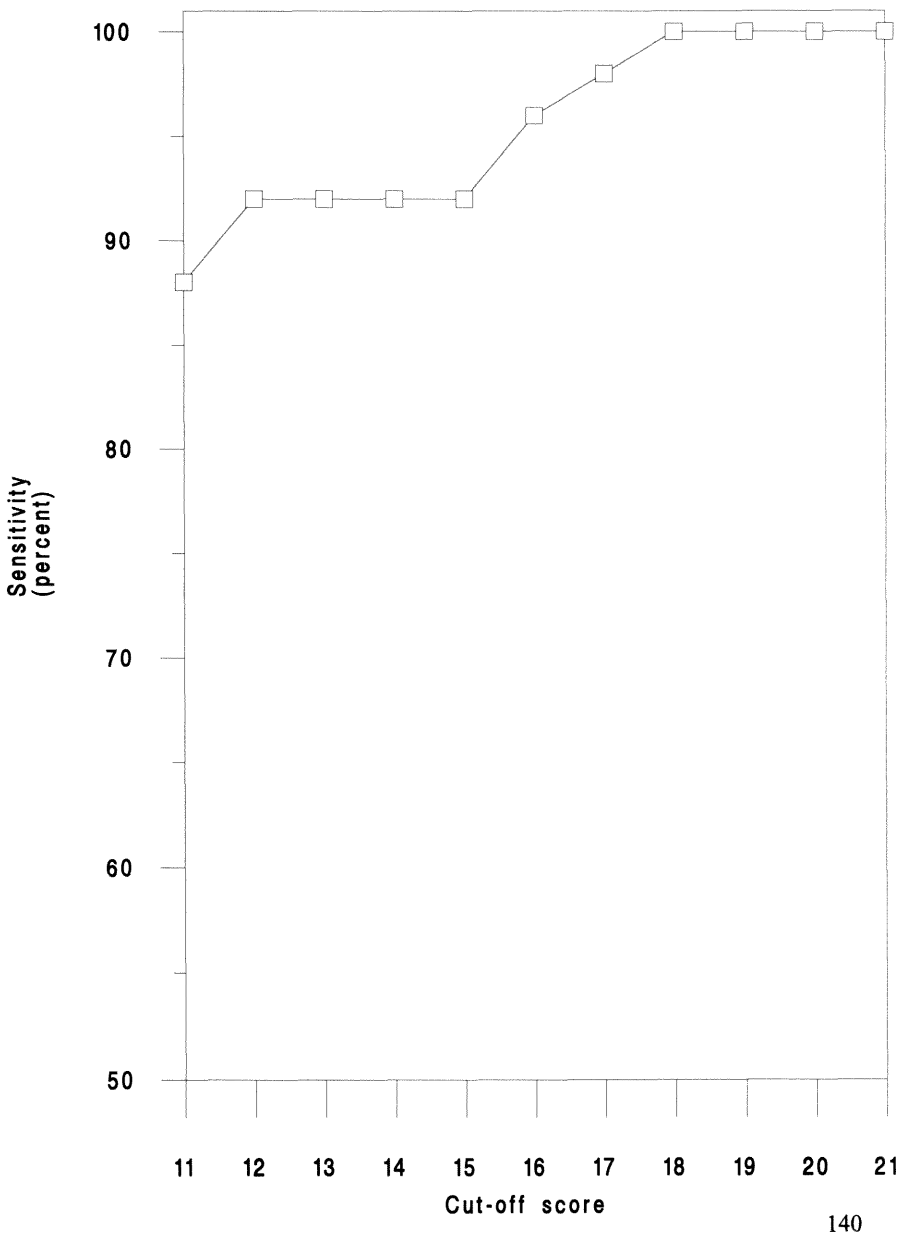


FIGURE 11:

Showing the effect of various cut-off scores on the sensitivity of the HAD(D) in PD.

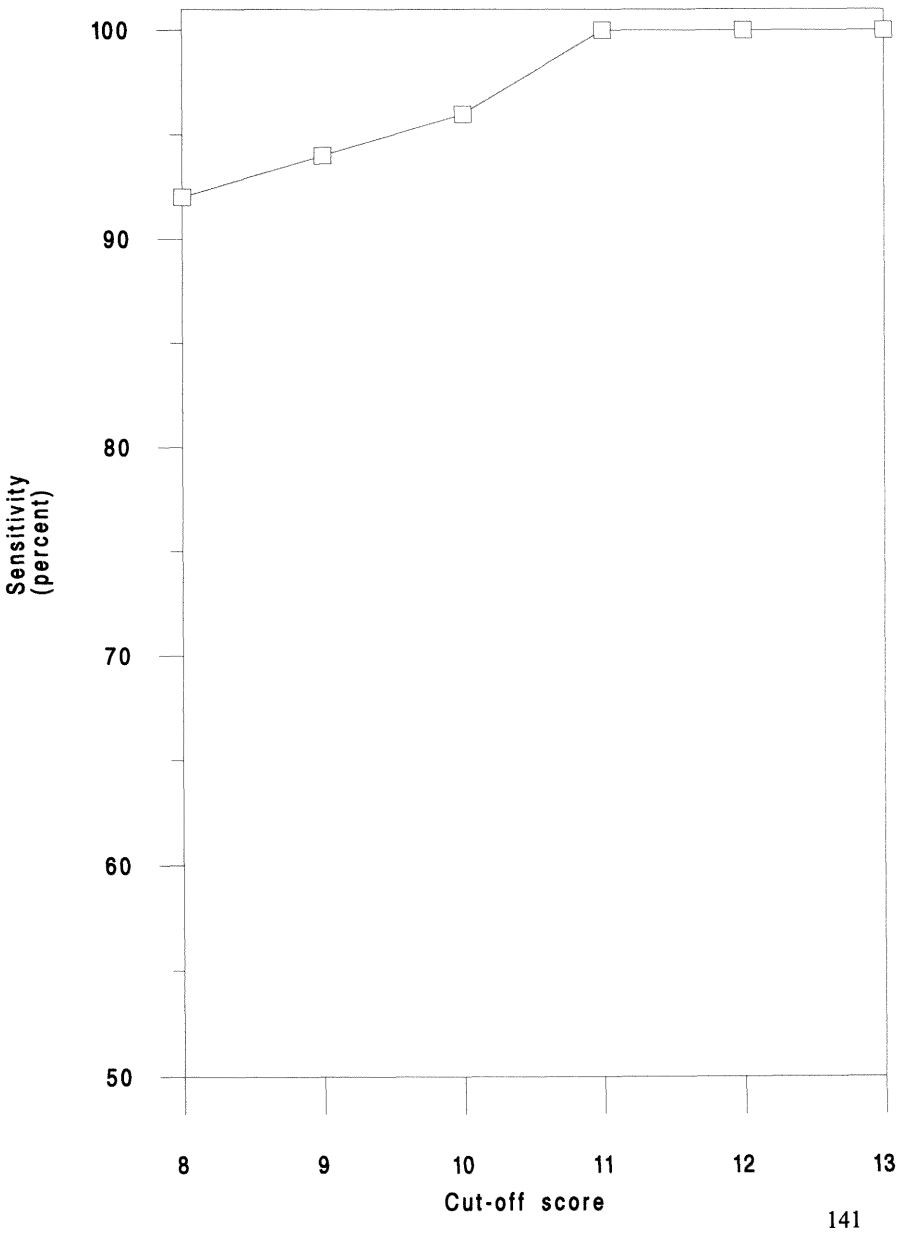


FIGURE 12:

Showing the frequency distribution of scores on the items of the BDI for PD subjects with total scores from 7 to 17 inclusive.

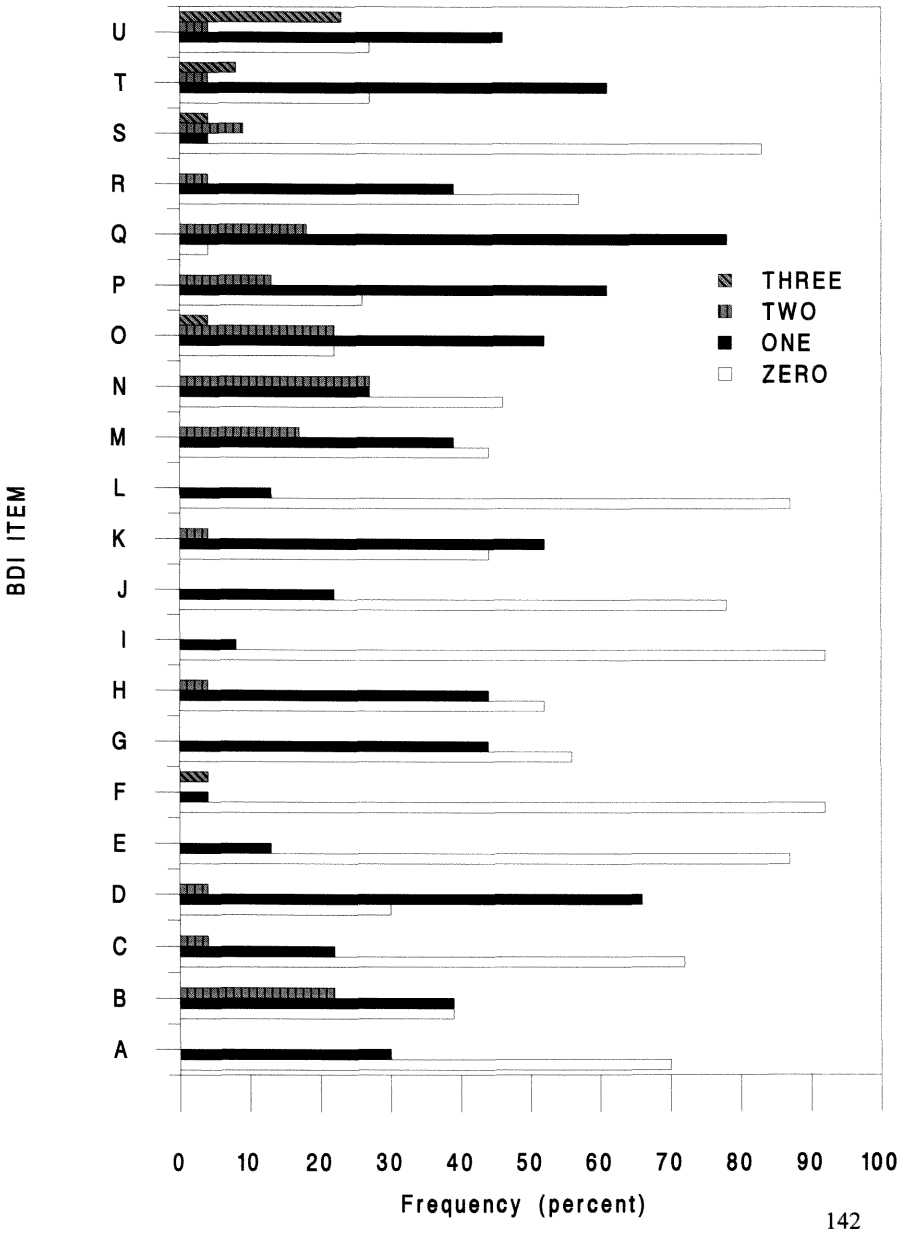


FIGURE 13:

Showing the frequency distribution of scores on the items of the HDRS for PD subjects with total scores from 7 to 17 inclusive.

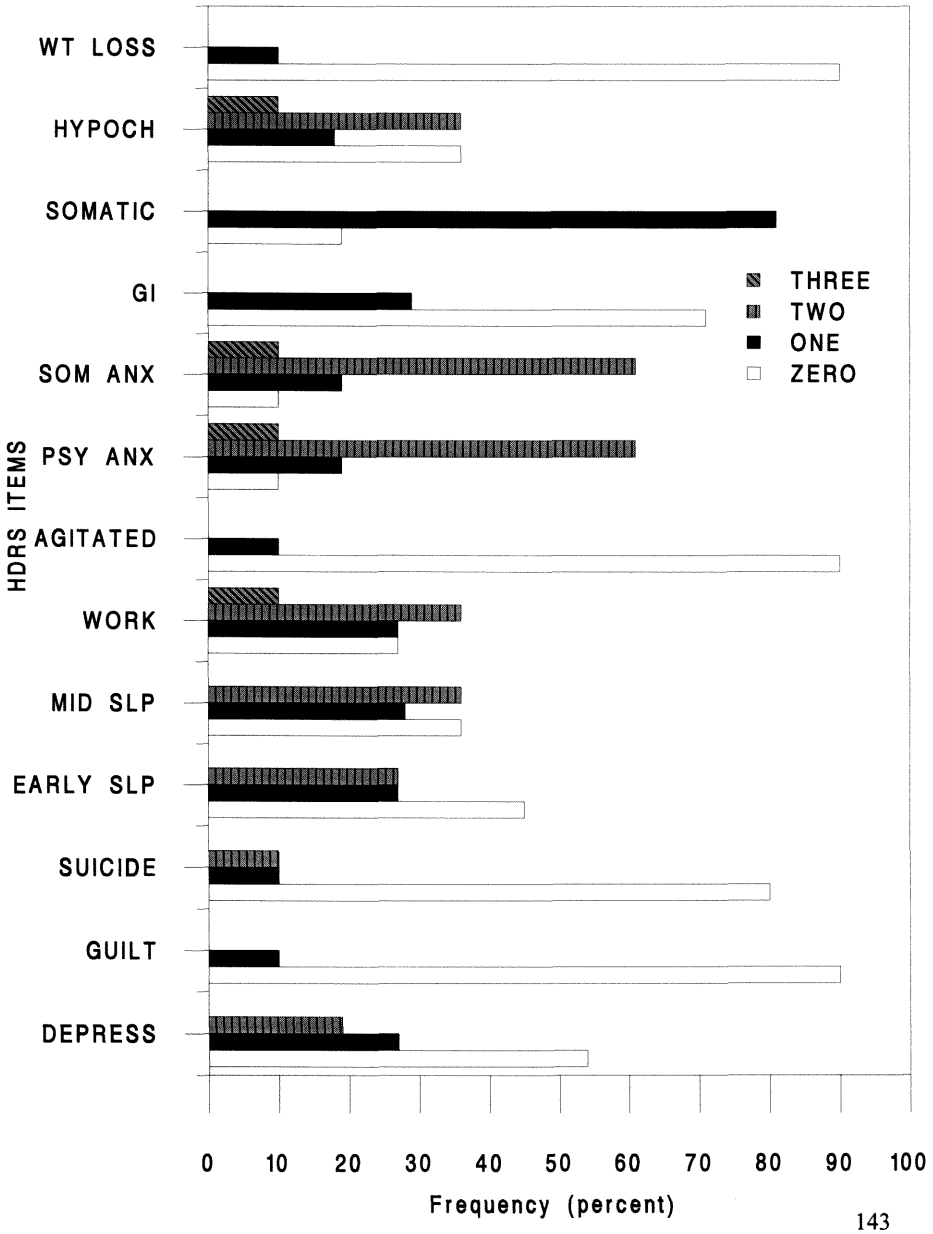


FIGURE 14:

Showing the survival curves for the Parkinson's disease and control subjects who remain not depressed (i.e. who never score 17 or greater on the MÅDRS).

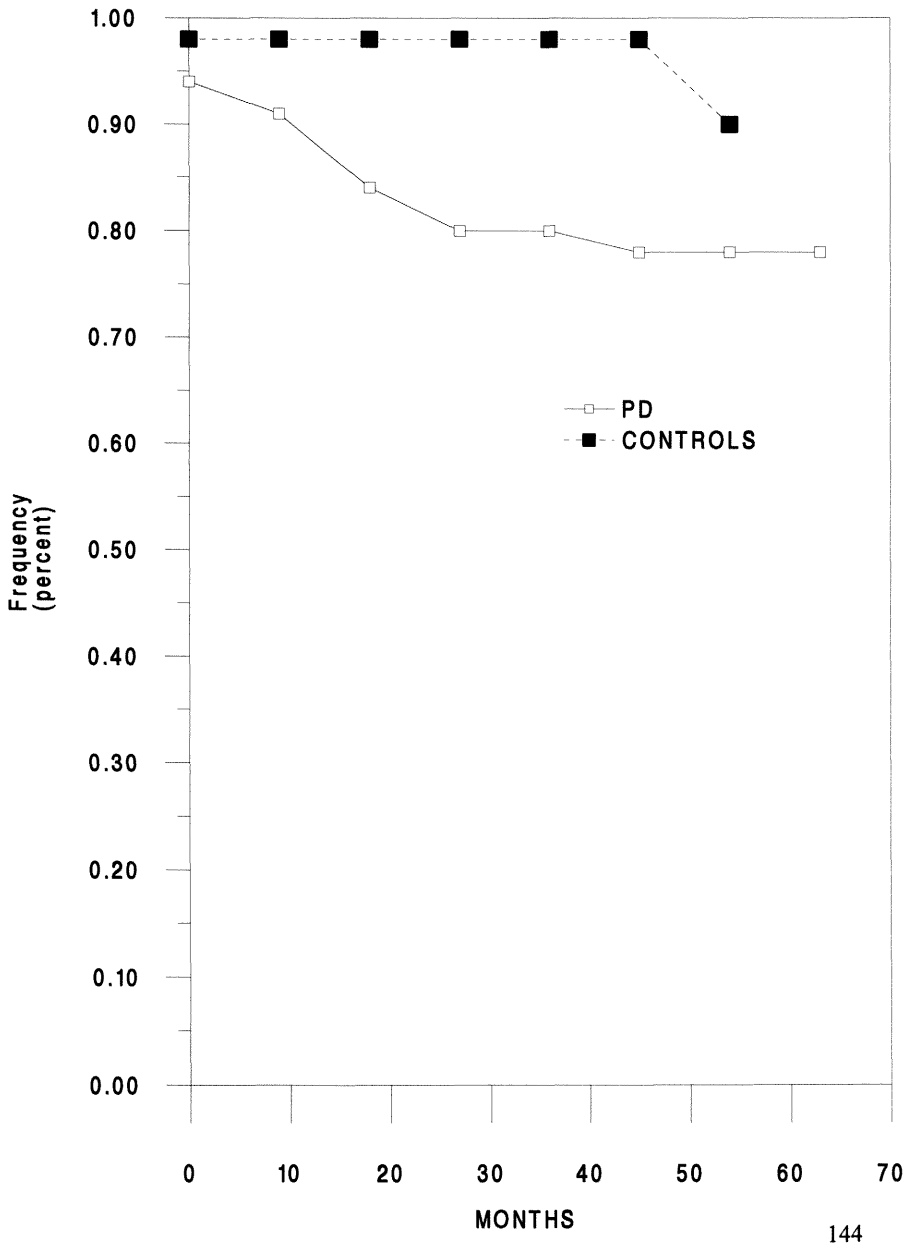


FIGURE 15:

Showing a comparison of the frequency of PSE syndromes in the PD group in this thesis with PD subjects as reported by Brown and MacCarthy (1990).

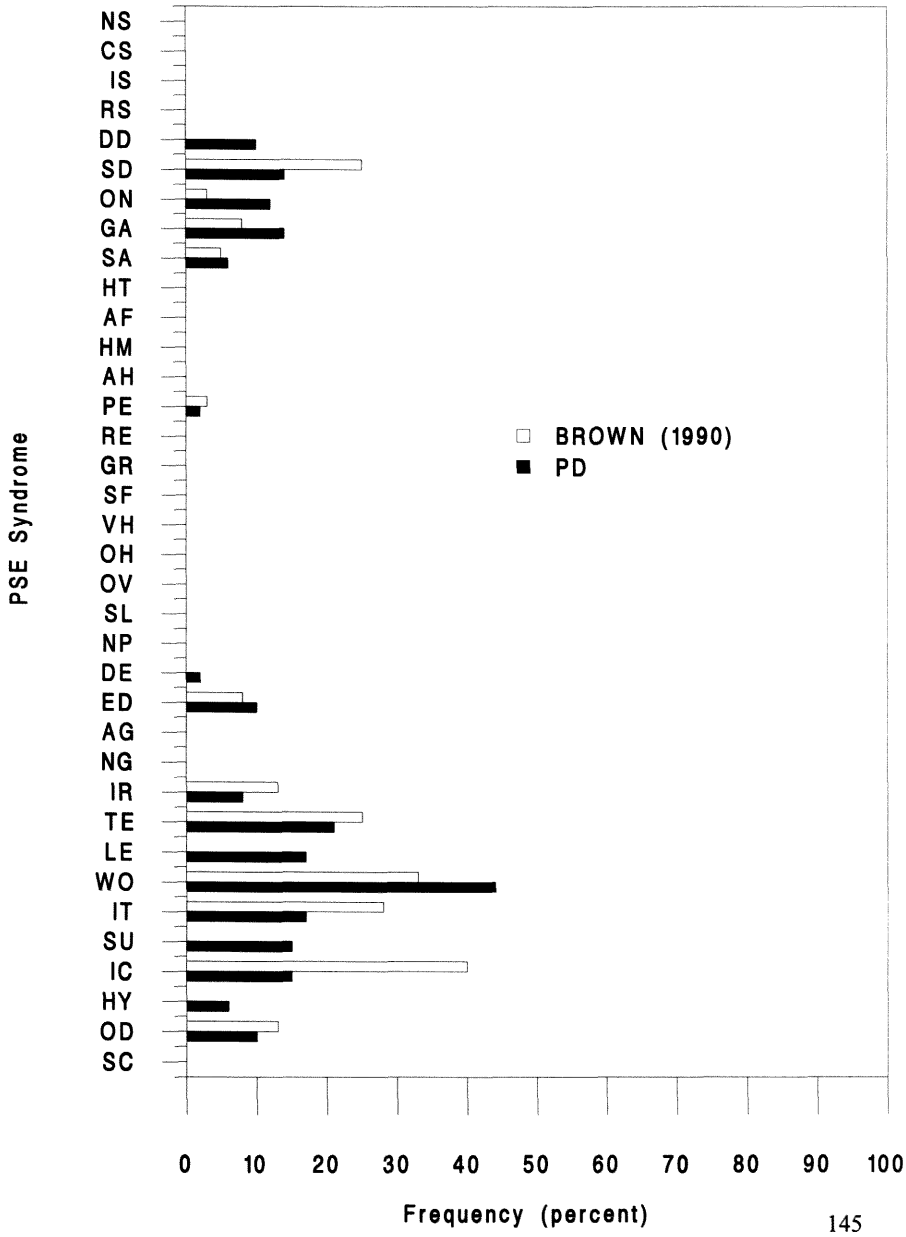
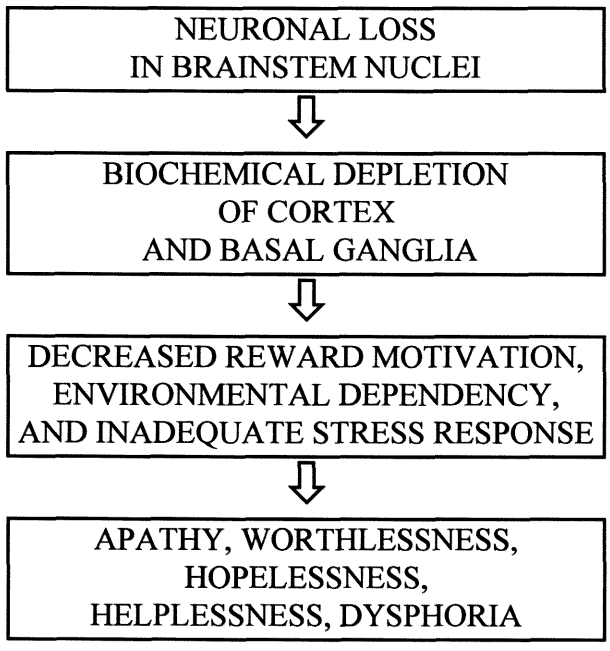


FIGURE 16:
Showing the model devised by Cummings (1992) for the pathogenesis of depression in Parkinson's disease.



APPENDIX

PRESENT STATE EXAMINATION

Score Sheet

PROJECT NUMBER | | | 1,2

SUBJECT'S IDENTIFICATION NUMBER | | | | 3,4,5

| | | | 6,7,8

CARD NUMBER | | 9,10

Rater's initials | |

Subject's initials | |

Date of completion | | || | | || | | |
day month year

Rater is Interviewer = 0
Rater not Interviewer = 1 | |

Live interview = 0
Video interview = 1
Audio interview = 2 | |

PSE Full Version
MRC Social Psychiatry Unit
London SE5 8AF

Dept. of Psychiatry
University of Leeds
September 1988
Not for publication

IMPORTANT NOTE : THIS SCORE SHEET SHOULD BE USED IN CONJUNCTION
WITH THE PSE (9th EDITION) INTERVIEW SCHEDULE.
Unless otherwise stated in the PSE schedule the
following codes should be used :

0 = Not present
1 = Moderate
2 = Severe
8 = Not applicable
9 = Not known

TIME : Past four weeks

NB The numbers to the left of the symptoms conform to the PSE (9th Edition) symptom number.

2. HEALTH, WORRYING, TENSION

1	Subject's own subjective evaluation of present physical health	[ ]	11
2	Presence of physical illness or handicap	[ ]	12
3	Psychosomatic symptoms (Special projects only)	[ ]	13
4	Worrying	[ ]	14
5	Tension pains	[ ]	15
6	Tiredness or exhaustion	[ ]	16
7	Muscular tension	[ ]	17
8	Restlessness	[ ]	18

Hypochondriasis [ ] 19

Subjective feeling of 'Nervous tension' [ ] 20

AUTONOMIC ANXIETY

Free-floating autonomic anxiety [ ] 21

Anxious foreboding with autonomic accompaniments [ ] 22

Autonomic anxiety due to delusions, etc. [ ] 23

.....cut off.....

Panic attacks with autonomic symptoms [ ] 24

Situational autonomic anxiety [ ] 25

Autonomic anxiety on meeting people [ ] 26

Specific phobias (not general situational anxiety) [ ] 27

Avoidance of anxiety provoking situations [ ] 28

HYPOCHONDRIASIS:

0 - not present
1 - self-absorption (bodily)
2 - preoccupation with health
3 - frequent complaints, requests for help, etc.
4 - hypochondriacal delusions

[ ] H15

3. Inner tension

Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish.
Rate according to intensity, frequency, duration and the extent of reassurance called for.

0 Placid. Only fleeting inner tension.
1
2 Occasional feelings of edginess and ill-defined discomfort.
3
4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
5
6 Unrelenting dread or anguish. Overwhelming panic.

[ ] MA3

ANXIETY SOMATIC (physiologic concomitants of anxiety, such as
GI - dry mouth, gas, indigestion, diarrhea, cramps, belching
C-V - heart palpitations, headaches
Resp - hyperventilating, sighing
Having to urinate frequently
Sweating):

0 - absent
1 - mild
2 - moderate
3 - severe
4 - incapacitating

[ ] H11

ANXIETY PSYCHIC:

0 - no difficulty
1 - subjective tension and irritability
2 - worrying about minor matters
3 - apprehensive attitude apparent in face or speech
4 - fears expressed without questioning

[ ] H10

DSMIII*: Hypochondriasis/unexplained pain Yes/No [ ]

4 THINKING, CONCENTRATION, ETC.

19 Subjectively inefficient thinking [ ] 29

20 Poor concentration [ ] 30

21 Neglect due to brooding [ ] 31

22 Loss of interest [ ] 32

.....cut off.....

DSMIII: Poor concentration Yes/No [ ]

DSMIII: Anhedonia Yes/No [ ]

6. Concentration difficulties

Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.

0 No difficulties in concentration.
1
2 Occasional difficulties in collecting one's thoughts.
3
4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
5
6 Unable to read or converse without great difficulty [ ] MA6

8. Inability to feel

Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

0 Normal interest in the surroundings and in other people.
1
2 Reduced ability to enjoy usual interests.
3
4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
5
6 The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends. [ ] MA8

9. Pessimistic thoughts

Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.

0 No pessimistic thoughts.
1
2 Fluctuating ideas of failure, self-reproach or self depreciation.
3
4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
5
6 Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakable. [ ] MA9

WORK AND ACTIVITIES:

0 - no difficulty

1 - thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies
2 - loss of interest in activity, hobbies or work - by direct report of the patient or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activites)
3 - decrease in actual time spent in activities or decrease in productivity. In hosp, pt. spends less than 3 hrs/day in activities (hospital job or hobbies) exclusive of ward chores
4 - stopped working bec. of present illness. In hospital, no activities except ward chores, or fails to perform ward chores unassisted [ ] H7

5. DEPRESSED MOOD

23	Depressed mood		33
24	Hopelessness (Subject's own view at present)		34
25	Suicidal plans or acts		35
	.....cut off.....		
26	Anxiety or depression primary		36
27	Morning depression		37

DSMIII: Dysphoria Yes/No ☐

DSMIII: Suicidal ideation/Recurrent thought of death Yes/No ☐

DEPRESSED MOOD (sadness, hopeless, helpless, worthless):

0 - absent
1 - indicated only on questioning
2 - spontaneously reported verbally
3 - communicated non-verbally, i.e. facial expression, posture, voice, tendency to weep
4 - VIRTUALLY ONLY this in spontaneous verbal and non-verbal communication

H1

2. Reported sadness

Representing reports of depressed moods, regardless of whether it is reflected in appearance or not. Includes low spirits, despondancy or the feeling of being beyond help and without hope.
Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

0 Occasional sadness in keeping with the circumstances.
1
2 Sad or low but brightens up without difficulty.
3
4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
5
6 Continuous or unvarying sadness, misery or despondancy.

MA2

10. Suicidal thoughts

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide.
Suicidal attempts should not in themselves influence the rating.

0 Enjoys life or takes it as it comes.
1
2 Weary of life. Only fleeting suicidal thoughts.
3
4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
5
6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

MA1C

SUICIDE:

0 - absent
1 - feels life is not worth living
2 - wishes he were dead or any thoughts of possible death to self
3 - suicidal ideas or gesture
4 - attempts at suicide

H3

0-2 | *Diurnal Variation* Symptoms worse in morning or evening. Note which it is.

H18

6. SELF AND OTHERS

28 Social withdrawal [ ] 38

29 Self-depreciation [ ] 39

30 Lack of self-confidence with other people (in social relationships) [ ] 40

31 Simple ideas of reference (not delusions) [ ] 41

.....cut off.....

2 Guilty ideas of reference [ ] 42

8 Pathological guilt [ ] 43

7. APPETITE, SLEEP, RETARDATION, LIBIDO

4 Loss of weight due to poor appetite [ ] 44

DSMIII: Worthlessness/Self reproach/Guilt Yes/No [ ]

DMSIII: Poor Appetite/Weight Loss Yes/No [ ]

FEELINGS OF GUILT:

0 - absent
1 - self-reproach, feels he has let people down
2 - ideas of guilt or rumination over past errors or sinful deeds
3 - present illness is a punishment. Delusions of guilt
4 - hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

[ ] H2

5. Reduced appetite

Representing the feeling of a loss of of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

0 Normal or increased appetite.
1
2 Slightly reduced appetite.
3
4 No appetite. Food is tasteless.
5
6 Needs persuasion to eat at all.

[ ] MA5

SOMATIC SYMPTOMS GASTROINTESTINAL:

0 - none
1 - loss of appetite but eating without encouragement
2 - difficulty eating without urging

[ ] H12

LOSS OF WEIGHT (Rate either A or B):

A. When rating by history:

0 - no weight loss
1 - probable weight loss associated with present illness
2 - definite (according to patient) weight loss
3 - not assessed

[ ] H17

B. On weekly ratings by ward staff, when actual weight changes are measured:

0 - less than 1 lb. loss in week
1 - more than 1 lb. loss in week
2 - more than 2 lb. loss in week
3 - not assessed

[ ] H17

SOMATIC SYMPTOMS GENERAL:

0 - none
1 - heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatiguability.
2 - any clear-cut symptom

[ ] H13

0-4 - *Paranoid Symptoms*
Suspicious
Ideas of reference
Delusions of reference and persecution
Hallucinations, persecutory
} Not with a depressive quality

[ ] H20

35 Delayed sleep | | 45

36 Subjective anergia and retardation | | 46

.....cut off.....

37 Early waking | | 47

38 Loss of libido (within present episode of illness and persisting during past month | | 48

Premenstrual exacerbation | | 49

DSMIII: Insomnia/Hyposomnia Yes/No [ ]

DSMIII: Loss of energy/Fatigue Yes/No [ ]

4. Reduced sleep

Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

0 Sleeps as usual.
1
2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
3
4 Sleep reduced or broken by at least two hours.
5
6 Less than two or three hours sleep.

| | MA4

INSOMNIA EARLY:

0 - no difficulty falling asleep
1 - complains of occasional difficulty falling asleep - i.e., more than 1/2 hour
2 - complains of nightly difficulty falling asleep

| | H4

INSOMNIA MIDDLE:

0 - no difficulty
1 - complains of being restless and disturbed during the night
2 - waking during the night - any getting out of bed (except to void)

| | H5

INSOMNIA LATE:

0 - no difficulty
1 - waking in early hours of morning but goes back to sleep
2 - unable to fall asleep again if gets out of bed

| | H6

7. Lassitude

Representing a difficulty getting started or slowness initiating and performing everyday activities.

0 Hardly any difficulty in getting started. No sluggishness.
1
2 Difficulties in starting activities.
3
4 Difficulties in starting simple routine activities which are carried out without effort.
5
6 Complete lassitude. Unable to do anything without help.

| | MA7

---

s GENITAL SYMPTOMS (such as loss of libido, menstrual disturbances):

0 - absent

1 - mild
2 - severe

| | H14

IRRITABILITY

Irritability [ ] 50

EXPANSIVE MOOD AND IDEATION

Expansive mood (not ordinary high spirits) [ ] 51

Subjective ideomotor pressure [ ] 52

.....cut off.....

Grandiose ideas and actions and similar rituals [ ] 53

OBSESSIONS

Obsessional checking and repeating [ ] 54

Obsessional cleanliness and similar rituals [ ] 55

Obsessional ideas and rumination [ ] 56

11. DEREALISATION AND DEPERSONALISATION

47 Derealisation [ ] 57

48 Depersonalisation [ ] 58

12. OTHER PERCEPTUAL DISORDERS (NOT HALLUCINATIONS)

49 Delusional mood [ ] 59

.....cut off.....

50 Heightened perception [ ] 60

0-4	*Depersonalization and Derealization* Feelings of unreality Nihilistic ideas Specify	[ ]	H20
0-2	*Obsessional Symptoms* Obsessive thoughts and compulsions against which the patient struggles	[ ]	H21

51 Dulled perception | | 61

52 Changed perception | | 62

53 Changed perception of time | | 63

54 Lost emotions | | 64

13. THOUGHT READING, INSERTION ECHO, BROADCAST

.....cut off.....

55 Thought insertion | | 65

56 Thought broadcast | | 66

57 Thought echo or commentary | | 67

58 Thought block or withdrawal | | 68

59 Delusions of thoughts being read | | 69

14. HALLUCINATIONS

.....cut off.....

14A. Auditory Hallucinations

60 Non-verbal auditory hallucinations | | 70

61 Verbal hallucinations based on depression or elation or voice calling subject | | 71

62 Voice(s) discussion of subject in third person or commenting on thoughts or actions (not based on depression or elation) | | 72

63 Voice(s) speaking to subject (not based on depression or elation) | | 73

64 Dissociative hallucinations (verbal and /or other) | | 74

65 Pseudo- or true hallucinations | | 75

14B. Visual Hallucinations

.....cut off.....

66 Visual hallucinations | | 76

67 Delirious visual hallucinations | | 77

14C. Other Hallucinations

.....cut off.....

68 Olfactory hallucinations [ ] 78

69 Delusion that subject smells [ ] 79

70 Other hallucinations and delusional elaboration [ ] 80

Project [ ] 1,2

Patient [ ] 3,4,5

[ ] 6,7,8

Card No. [ ] 9,10

15. DELUSIONS

.....cut off.....

15A. Delusions of Control

71 Delusions of control [ ] 11

15B. Misinterpretations, Misidentification and Delusions of Reference

72 Delusions of reference [ ] 12

73 Delusional misinterpretation and misidentification [ ] 13

15C. Delusions of Persecution

74 Delusions of persecution [ ] 14

15D. Expansive Delusions

75 Delusions of assistance [ ] 15

76 Delusions of grandiose abilities [ ] 16

77 Delusions of grandiose identity [ ] 17

15E. Delusions Concerning Various Types of Influence and Primary Delusions

78 Religious Delusions [ ] 18

79 Delusional explanations in terms of paranormal phenomena [ ] 19

80 Delusional explanations in terms of physical forces [ ] 20

81 Delusions of alien forces penetrating or controlling mind (or body) [ ] 21

82 Primary delusions [ ] 22

15F Other Delusions

83 Subculturally influenced delusions [ ] 23

84 Morbid jealousy [ ] 24

85 Delusion of pregnancy [ ] 25

86 Sexual delusions [ ] 26

87 Fantastic delusions, delusional memories, delusional confabulations [ ] 27

15G Simple Delusions Based on Guilt, Depersonalisation, Hypochondriasis, etc.

88 Delusions of guilt [ ] 28

89 Simple delusions concerning appearance [ ] 29

90 Delusions of depersonalisation [ ] 30

91 Hypochondriacal delusions [ ] 31

92 Delusions of catastrophe [ ] 32

15H General Ratings of Delusions and Hallucinations

93 Systematisation of delusions [ ] 33

94 Evasiveness [ ] 34

95 Preoccupation with delusions and hallucinations [ ] 35

96 Acting out delusions [ ] 36

15 SENSORIUM AND FACTORS AFFECTING

97 Fugues, blackouts, amnesia lasting more than one hour [ ] 37

98 Drug abuse during month [ ] 38

99 Alcohol abuse during past month [ ] 39

100 Dissociative states during past month [ ] 40

101 Conversion symptoms [ ] 41

102 Clouding or stupor at examination [ ] 42

Any suspicion of poor memory/disorientation

103 Organic impairment of memory [ ] 43

17 INSIGHT

104 If psychotic symptoms (sections 12-15) [ ] 44

105	If neurotic symptoms (sections I-II only)		45
106	Social impairment due to neurotic condition		46
107	Social impairment due to psychotic condition		47

INSIGHT:

0 - acknowledges being depressed and ill OR not currently depressed
1 - acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2 - denies being ill at all

H16

18 - 20 BEHAVIOUR, AFFECT AND SPEECH

108	Self-neglect		48
109	Bizarre appearance		49
110	Slowness and underactivity		50
111	Agitation		51
112	Gross excitement and violence		52
113	Irreverent behaviour		53
114	Distractability		54
115	Embarrassing behaviour		55
116	Mannerisms and posturing		56
117	Stereotypies etc.		57
118	Behaves as if hallucinated		58
119	Catatonic movements		59
120	Observed anxiety		60
121	Observed depression		61
22	Histrionic		62

AGITATION:

0 - none
1 - fidgetiness
2 - playing with hands, hair, etc.
3 - moving about, can't sit still
4 - hand-wringing, nail biting, hair-pulling, biting of lips

H9

1. Apparent sadness

Representing despondance, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

0 No sadness.
1
2 Looks dispirited but does brighten up without difficulty.
3
4 Appears sad and unhappy most of the time.
5
6 Looks miserable all the time, extremely despondent.

MA1

Hypomanic affect		63
Hostile irritability		64
Suspicion		65
Perplexity (puzzlement)		66
Lability of mood		67
Blunted affect		68
Incongruity of affect		69
Slow speech		70
Pressure of speech		71
Non-social speech		72
luteness		73
estricted quantity of speech		74
eologisms and idiosyncratic se of words or phrases		75
ncoherence of speech		76
light of ideas		77
overty of content of speech		78
isleading answers		79
e-rate adequacy of interview		80

RETARDATION (slowness of thought and speech; impaired ability to concentrate; decreased motor activity):

0 - normal speech and thought
1 - slight retardation at interview
2 - obvious retardation at interview
3 - interview difficult
4 - complete stupor

H8

DSMIII: Psychomotor agitation or retardation Yes/No