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CLINICAL HETEROGENEITY IN SENILE DEMENTIA
OF THE ALZHEIMER TYPE

BY

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Thesis submitted for the Degree of Doctor of Medicine,
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Research carried out at the Institute of Psychiatry, London
1986-1990
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SUMMARY

The aim of this project was to assess clinical heterogeneity in senile dementia of the Alzheimer type, relating clinical features of the disorder to structural brain changes as assessed by Computed Tomography (CT) scan and to cognitive function. The study was based on 178 elderly psychiatric patients who satisfied criteria for Alzheimer's disease suggested by the National Institute for Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS/ADRDA).

The mean age of the sample was 80.4 years and the mean duration of illness 63 months. Each patient underwent a number of standardised assessments. The history and course of illness, before the commencement of the study, were documented with the CAMDEX; cognitive function was measured by the CAMCOG, the Mini Mental State Examination and the Abbreviated Mental Test score; physical examination was performed using a standardised schedule; psychiatric symptoms were rated by the CAMDEX and by the Geriatric Mental State Schedule; behaviour was assessed by the Stockton Geriatric Rating scale; questions were also asked regarding behaviour associated with the Kluver-Bucy syndrome; a global rating of severity of dementia was allocated to each subject (the Clinical Dementia Rating) and a CT scan of head was performed. The assessments were repeated after twelve months and the mortality of the sample was recorded for 36 months from the start of the study.

The main results can be summarised under the following headings:
Psychiatric symptoms

Since the onset of the illness, 17% of the sample had experienced hallucinations (10% auditory and 13% visual) and 30% demonstrated misidentification syndromes (12% failing to recognise other people, 4% failing to recognise their own image, 17% believing that other people were in the house and 6% believing that events on the television were real). 16% of the group were deluded, the most common themes being delusions of suspicion and of theft. A higher proportion of males than females were deluded. In addition, 20% had paranoid ideation not held with delusional intensity. Affective disturbances were common - 24% of the sample appeared depressed, 39% had symptoms suggestive of depression and 43% were rated by their relatives as being depressed. In comparison, symptoms of mania were rare - only one subject experienced manic symptomatology and only 4% appeared elated and over-active.

Patients with or without hallucinations had similar cognitive function at entry to the study but the former group had greater cognitive decline over the twelve month follow-up period. Subjects with misidentification syndromes were younger, the illness had started at a younger age and they had a lower mortality rate than those without these syndromes. Patients with systematised delusions had smaller lateral ventricles and were more likely to have basal ganglia calcification than those without these delusions. Depressive symptoms complained of by the patient correlated with ventricular size and subjects whose relatives felt they were depressed had smaller third and lateral ventricles. Manic symptoms were significantly
associated with enlargement of the interhemispheric fissure, while those with depressive symptoms had smaller fissures. The patients who appeared depressed had a higher mortality rate than those who did not.

**Behavioural disturbance**

Aggression was found in 20% of the group, excessive wandering behaviour in 19%, incontinence in 48% and excessive eating behaviour in 10%. Seven elements of the Kluver-Bucy syndrome were identified (binge eating, hyperorality, sexual disinhibition, misrecognition of others, rage behaviour, hypermetamorphosis and apathy). Aggression was more common in men and in hospitalised subjects. All behaviours except binge eating, rage behaviour and hypermetamorphosis were associated with increasing severity of dementia, both as assessed by the cognitive tests and on the CDR. The presence of incontinence was associated with an increased mortality at follow up. Individual items of the Kluver-Bucy syndrome were common, with 72% of the group having at least one symptom. Only one subject had all seven features. A factor analysis showed three factors in the Kluver-Bucy syndrome - one factor consisted of rage behaviour and hyperorality, another consisted solely of binge eating and the third of the remaining behaviours. Aggression was associated with temporal lobe atrophy, wandering with sylvian fissure atrophy and hyperorality with increased third ventricular size.

**Neurological signs**

These were assessed by a standard physical examination. A snout reflex was found in 41%, a palmomental reflex in 3% and a
grasp reflex in 7%. Myoclonus was observed in 5% and a history of epileptic fits (since the onset of the dementia) was obtained in 3%. 15% of subjects had extrapyramidal signs, 3% of which were considered neuroleptic induced. The grasp reflex, extrapyramidal signs and myoclonus were associated with a younger age of onset, longer duration of illness and more severe dementia. Non drug-induced extrapyramidal signs were associated with calcification in the globus pallidus and a grasp reflex was associated with increased frontal lobe atrophy. Patients developing a grasp reflex in the twelve month follow up period had larger ventricles while the development of a snout reflex or extrapyramidal signs was associated with increased mortality.

Longitudinal change in cognition

An attempt was made to assess heterogeneity in the pattern of cognitive decline over twelve months. Data were available on 105 subjects. There was a highly statistically significant decline in cognition over the follow up period and patients with a family history of dementia in their parents (but not siblings or second degree relatives) had a greater decline. A cluster analysis revealed three patterns of decline (mild, moderate and severe) but none of the clusters were related to other characteristics of the disease or to subsequent mortality. Thus, the decline in cognitive function was not supportive of clinical subtypes.

Longitudinal change in CT scans

Sixty-three subjects had two CT scans twelve months apart. Statistically significant deterioration occurred in all the CT measures but there was a wide variation in the size of the
changes - 14 of the 63 showed virtually no change in ventricular size whereas six showed a marked increase. These subgroups were not associated with any other disease characteristic or with subsequent mortality. An increase in ventricular size was associated with deterioration in cognitive function. Thus, there was some evidence that deterioration in CT variables was heterogeneous but not sufficient evidence to suggest significant clinical subtypes.

Factors affecting survival

Factors influencing survival were analysed using univariate and multivariate proportional hazards modelling. The mortality of the sample was 3.5 times that expected and the following features were predictive of decreased survival: male sex, advanced age, longer duration of illness, presence of physical illness, poor cognitive function, absence of misidentification syndromes and presence of observed depression. Apraxia was a stronger predictor of early death than either aphasia or amnesia.

Neuropathological findings

The ability of the NINCDS/ADRDA criteria to predict Alzheimer pathology at post mortem was assessed. 63% of the patients who died were submitted to post-mortem on whom detailed post mortem information is available on 48 subjects. Of these 48 patients, 85% had sufficient Alzheimer pathology to merit that diagnosis. Two patients had pure vascular disease, three had cortical Lewy body disease and three had no identifiable neuropathological features. Therefore, the clinical criteria were satisfactory in predicting Alzheimer
pathology at post mortem.

This work has shown that there is considerable clinical heterogeneity in senile dementia of the Alzheimer type and that certain disease characteristics are related to the natural history of the condition (cognitive decline and mortality) and to structural brain changes (as assessed by CT scan). The evidence does not prove unambiguously that there are absolute qualitative subtypes of the disorder but does suggest that features of the disease are helpful in predicting decline and death. More research is needed and the ultimate test for qualitative heterogeneity depends on the discovery of the aetiology of Alzheimer's disease and how that relates to neuropathological changes.
ACKNOWLEDGEMENTS

A research project of the size and scope described in this thesis cannot be undertaken in isolation by a solitary investigator and it is my privilege to acknowledge the contribution of others. I must pay tribute to the patients who allowed me to interview, examine and investigate them. Also, to their relatives and carers who gave permission to the study and from whom I have learned so much about dementia. The medical, nursing and care staff of the various homes and hospitals I visited were unfailingly co-operative and the staff of the Radiology Department at the Maudsley Hospital were ever helpful in performing the computed tomography scans. Drs Michael Philpot, Shon Lewis and Ian Harvey contributed to the reliability studies of the scans.

Dr Graham Dunn and Professor Brian Everitt provided useful statistical advice and Dr Glyn Lewis helped with the survival analysis statistics. The personal computer on which most of the analyses were performed was provided by a generous grant from "Research into Ageing". Dr Philip Luthert and Professor Peter Lantos of the Neuropathology Department at the Institute of Psychiatry performed the neuropathological examinations. Professor Martin Roth and Dr Felicia Huppert from the University of Cambridge generously provided a copy of the CAMDEX prior to its publication date. Mrs Margaret Reith aided the transportation of patients to and from the Maudsley Hospital and liaised skilfully with some of the relatives. Excellent and professional secretarial help was provided by Mrs Mae Wise and Mrs Margaret Derrick. Dr. Klaus Bergmann and Mrs. Janet Burns
kindly read the manuscript.

Special thanks are due to Professor Raymond Levy and to Dr Robin Jacoby who were in receipt of a Medical Research Council Special Project grant which funded the work. Both spent many hours guiding me through the labyrinth of the scientific method.

Finally, most special thanks are due to my wife, Alison, whose patience and understanding has made the project bearable and to our daughter, Hannah, whose own gestation period coincided with the gestation of this thesis.
THE EXTENT OF MY PERSONAL CONTRIBUTION

To comply with the regulations for presentation of theses in Glasgow University, I hereby state my personal contribution to the work presented in this thesis.

During the period in which the research was carried out, I was employed as a research worker to Professor Raymond Levy and Dr Robin Jacoby of the Section of Old Age Psychiatry at the Institute of Psychiatry in London. I recruited all the patients to the study, performed all the neuropsychological, psychiatric and physical evaluations and personally interviewed all the relatives. I completed all the behaviour rating scales with the help of the care staff involved and requested post mortems on every possible case.

Areas in which I have received help are the following: Mrs Margaret Reith, a part-time research nurse employed on the project, helped transport some of the patients to and from their own homes to the X-ray department of the Maudsley Hospital. The staff of the X-ray department performed the computed tomography scans on my behalf (I was present at all the scans except when on holiday). As I have no experience in neuropathology the pathologists in the Department of Neuropathology at the Institute of Psychiatry prepared and interpreted the brain sections. However, I have seen all the relevant brain sections for each person in the study.

I submit that my personal contribution to this work justifies its presentation for an MD thesis under my name.
The following terms will be used in this thesis -

Alzheimer’s Disease (AD) - this term will be used when neuropathological features of Alzheimer’s Disease have been found at post mortem in patients suffering from a clinical syndrome of dementia during life.

Senile Dementia of the Alzheimer Type (SDAT) - this will refer to the most common clinical situation viz where a patient, over the age of 65, is suffering from a clinical dementia syndrome and other causes of dementia have been excluded. The presumption is made that Alzheimer changes will be found at post mortem but has not yet been confirmed.

Dementia of the Alzheimer Type (DAT) - is analogous to SDAT but refers to patients under the age of 65. This age-based dichotomy is purely arbitrary.

Senile Dementia and Pre-Senile Dementia - this refers to the clinical syndrome of dementia occurring after the age of 65 (senile) or before 65 (pre-senile). No statement can be made as to the possible aetiology.

Multi-infarct Dementia (MID) - will refer to dementia (either presumed or proven) to be secondary to cerebrovascular damage resulting on one or more cerebral infarcts.

Primary Degenerative Dementia (PDD) - an American term used clinically to describe patients in whom other secondary causes of dementia have been excluded but where there is not sufficient confidence to predict that Alzheimer changes will be found at post mortem. In practical terms, this is synonymous with, and has been replaced by, SDAT and DAT.
Different studies apply a variety of terms to their patients. When referring to other studies, for the sake of consistency and to ensure standardisation, I use the above terminology irrespective of the terms employed in the paper. In doing so, I make no comment on the appropriateness or otherwise of terminology used by others.

Standard abbreviations are used in this thesis. The first time an abbreviation appears in the text it will be written in full followed by the abbreviation. A full list of the abbreviations appears below.

AD - Alzheimer's Disease
AMTS - Abbreviated Mental Test Score
BDS - Blessed Dementia Scale
CAMDEX - The Cambridge Battery (Roth et al, 1986)
CAMCOG - The Cognitive Section of the CAMDEX
CAPE - Clifton Assessment Procedures in the Elderly
Chat - Choline acetyl transferase
CSF - Cerebrospinal Fluid
CT - Computed Tomography
DAT - Dementia of the Alzheimer type
DCT - Digit Copying Test (Kendrick, 1972)
EEG - Electroencephalogram
GMSS - Geriatric Mental State Schedule (Copeland et al, 1976)
IHF - Interhemispheric Fissure
IMC - Information, Memory and Concentration Scale of Blessed
MTS - Mental Test Score
MID - Multi-infarct Dementia

MMSE - Mini Mental State Examination (Folstein et al, 1975)

NINCDS/ADRDA - National Institute for Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

NFT - Neurofibrillary tangle

OLT - Object Learning Test (Kendrick, 1972)

PALT - Paired Associate Learning Test (Inglis, 1958)

PDD - Primary Degenerative Dementia

SDAT - Senile Dementia of the Alzheimer Type

SP - Senile (Neuritic) Plaque

VBR - ventricular-brain Ratio

WAIS - Weschler Adult Intelligence Scale (Wechsler, 1955)
INTRODUCTION

In 1907, Alois Alzheimer published a description of the case of a 51-year old woman who presented with delusions of jealousy towards her husband. Subsequently, her memory deteriorated rapidly; she got lost around her flat and had fears that someone was going to kill her. In hospital, she exhibited abnormal behaviour - loud shrieking and dragging her bedding around the ward. She was disorientated, had a poor short term memory, demonstrated paraphasias and showed signs of apraxia. There were no abnormal physical signs in the central nervous system. She died four and a half years after the onset of her illness. A post mortem examination was performed with these results: 1) macroscopically, the brain showed clear evidence of cerebral atrophy and 2) microscopically, neurofibrillary tangles and senile plaques were seen.

There are two threads to the subsequent story. First, the relationship of the neuropathological findings in dementia to the clinical picture of dementia and normal ageing. Second, the search for heterogeneity within the primary dementias.

Kraepelin (1910) introduced the eponym "Alzheimer's disease" (AD) and suggested that the neuropathology was pathognomonic of the clinical picture of AD. Subsequently, Gellerstedt (1933), Rothschild (1941) and Tomlinson et al (1968) found that these histopathological changes were not specific to AD as they were also found in mentally unimpaired elderly people. Thus, neuropathology perpetuated the belief that observed morphological changes were not specific to dementia. In the early 1950's, Roth validated a descriptive clinical
classification (Roth and Hopkins, 1953, Roth, 1955) which showed, using mortality rates, that disease classification was justified in the elderly. This served as the blueprint for the clinical classification of psychiatric disorders of later life. In the 1960's, two developments occurred which emphasised the relationship between clinical and neuropathological findings. First, the ultra-structure of neurofibrillary tangles and senile plaques was defined (Terry, 1963, Kidd, 1963, Terry et al, 1964) and were found not to be the relatively formless structures previously considered. Second, correlations between quantitative psychological tests and quantitative neuropathological changes were found (Blessed et al, 1968). It is now generally accepted that Alzheimer type changes in the brain are responsible for the clinical features of both presenile and senile dementia.

The second thread concerns the search for heterogeneity in Dementia of the Alzheimer type (DAT). Lauter and Meyer (1968) noted differing symptoms in patients with early and late onset disease and found that parietal lobe signs and neurological disturbances decreased in frequency with increasing age but that delusions and hallucinations increased. McDonald (1969) suggested a division based on age and the presence or absence of apraxia. Subsequent clinical studies have supported this (Hare, 1978, Seltzer and Sherwin, 1983, Mayeux et al, 1985b) and neurochemical studies (Rossor et al, 1984, Perry et al, 1968) have revealed heterogeneity based on age at death.

Currently, scientific interest in Alzheimer's disease and related conditions is high, probably for three main reasons.
First, the vast numbers of elderly people suffering from dementia (6% of the over 65's rising to 18% of the over 85's, Bergmann, 1985) cannot be ignored. Second, neurochemical and molecular biology techniques have been applied with some success to the condition offering the real hope of discovering the aetiology and pathogenesis. Third, drug trials have met with moderate success and there is genuine optimism that an agent may be found which ameliorates the symptoms (Levy, 1990).

The purpose of this thesis is to examine the evidence for clinical heterogeneity in Senile Dementia of the Alzheimer Type (SDAT). It will start with three chapters reviewing the relevant literature. The first chapter will outline current concepts of Alzheimer's disease (AD), dementia of the Alzheimer Type (DAT, which includes the condition specifically relating to those patients over 65, Senile Dementia of the Alzheimer's Type, SDAT). The second chapter will assess different features of SDAT which have been implicated in clinical heterogeneity while the third will discuss the longitudinal changes which occur.

The study itself will then be presented (Chapters 4-10). Each chapter will deal with a specific topic and will include its own results, discussion and summary. Clinical features of SDAT will be described in detail (psychiatric symptoms, behavioural disturbance and neurological abnormalities) and will be related, not only to one another, but to the natural history of the disorder as assessed by survival and longitudinal changes in both cognitive function and CT scans.

Because clinical features of the disease are to be interrelated, a choice had to made at the outset as to which
variables to examine primarily. For example, the relationship between age of onset and misidentification syndromes could be assessed either by dealing with age of onset primarily and including a discussion of misidentification syndromes or vice versa. I have chosen to describe primarily features of the disorder which are apparent on examination (psychiatric symptoms, behaviour disturbances and neurological signs) and to relate them to other features such as age of onset, family history of dementia and neuropsychological function. This order has been determined both by the way in which the study evolved and by the presence of certain features which struck me as being most important in the clinical setting.

The reason that age of onset has not been used as a primary variable is that all the patients in the study (except one) were over the age of 65 when first seen which reflected the population from which the sample was drawn (elderly patients in contact with a psychiatric hospital). Thus, the traditional dichotomy of onset above and below the age of 65 was felt to be largely irrelevant to the current work. Neuropsychological heterogeneity has been discussed in relation to dementia and the relationship between the differing functions of memory, language and visuospatial ability noted. These aspects have not been emphasized in the present thesis for two reasons. First, the majority of patients were moderately demented and so detailed and sophisticated psychological tests were not possible. Second, the neuropsychological assessment instruments used in this study are relatively simple and have been developed primarily for use by
psychiatrists as screening tests to assess cognitive function globally and to indicate where more complex tests are necessary. Therefore, they provide a detailed global assessment of cognitive function and the relationship of individual scales to each other and to specific neuropsychological functions is uncertain. As such, I felt it inappropriate to place excessive weight on the results of these tests applied in a cross-sectional manner. However, using the results to indicate a change in cognitive function seemed more appropriate and so this measure has been used in an attempt to assess quantitative subtypes (Jorm, 1985).

Data on neuropathological findings will be presented, not because of a direct bearing on the heterogeneity issue, but to justify use of the clinical criteria used in the diagnosis (neuropathological heterogeneity is a separate subject and will not be tackled by this thesis).

The hypotheses at the start of the study were:
1) there is considerable clinical heterogeneity in SDAT and features of the disease will be related to cognitive decline and survival;
2) specifically, apraxia will be related to a poorer outcome, depression will carry a relatively good prognosis and Computed Tomography (CT) scan changes of ventricular enlargement will reduce survival;
3) the proportion of patients with specific psychiatric symptoms will be lower than in other studies because of the representative nature of the population examined;
4) specific psychiatric symptoms, behaviour disturbances and neurological signs will be associated with structural abnormalities as assessed by CT scan;

5) longitudinal changes in cognitive function and CT scan appearances will identify subgroups and

6) the strict application of appropriate clinical criteria will ensure that the majority of subjects will have histopathological changes of Alzheimer's disease.
CHAPTER 1

CURRENT CONCEPTS OF ALZHEIMER'S DISEASE AND SENILE DEMENTIA OF THE ALZHEIMER TYPE

1.1. INTRODUCTION

The purpose of this chapter is to review current diagnostic criteria for dementia in general and Dementia of the Alzheimer Type (DAT) in particular and to examine the proportion of cases in which a clinical diagnosis of DAT is accompanied by the neuropathological findings of Alzheimer’s disease. (For the sake of clarity in this and the following two chapters, DAT will refer to the clinical situation where Alzheimer’s disease is presumed to be responsible for the clinical picture, regardless of the age of the patient. In this sense, Senile Dementia of the Alzheimer Type (SDAT) is a subset of DAT). The clinical process involved in making a diagnosis of DAT comprises two parts. The first part is to make the diagnosis of a dementia syndrome, the second is to identify those patients who are likely to have the histopathological changes of AD. The first is essentially a diagnosis of inclusion while the second, until recently, was essentially a diagnosis of exclusion whereby other causes of dementia were excluded. If none were found, DAT was diagnosed. The most recently developed criteria, which will be discussed below, have made the diagnosis of DAT one of both inclusion and exclusion.

1.2 CRITERIA FOR THE DIAGNOSIS OF DEMENTIA

The two major diagnostic schemata for the classification of psychiatric disorders in use at present are the International
Classification of Diseases, revision 10 (ICD 10) and the North American Diagnostic and Statistical Manual, revision of the third edition (DSM IIIR, APA, 1987). ICD 10 gives a simple definition of dementia as "a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is impairment of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity language and judgement". It states that dementia must occur in the presence of clear consciousness, must be of such a degree as to "impair functioning in daily living" and that symptoms should be present for at least six months.

DSM IIIR defines dementia more fully and suggests specific criteria essential to the diagnosis. In summary these criteria are:

A. Evidence of short and long term memory impairment

B. At least one of the following:
   1) impairment of abstract thinking;
   2) impaired judgement;
   3) evidence of higher cortical dysfunction (eg aphasia, apraxia or agnosia;
   4) personality change.

C. That the disturbance in A and B significantly interferes with work or usual social activities

D. The absence of delirium.

E. The absence of an non-organic mental disorder which can mimic dementia.

Criteria are also provided which enable the severity of dementia to be rated - mild dementia (independent living is
possible although work and social functioning are impaired); moderate dementia (supervision needed for independent living) and severe dementia (continual supervision required).

The criteria presented in DSM IIIR represent an improvement on those in the previous edition (DSM III). They appear largely to have resulted from a paper by Jorm and Henderson (1985). These authors questioned the classification of dementia as a categorical entity and suggested that defined cut-offs be laid down so that the disorder was diagnosed as part of a continuum. They also criticised use of the term "loss of intellectual abilities" indicating that it was very difficult to evaluate "loss" unless the previous level of functioning was known. One further criticism, which still holds true for DSM IIIR, was that in criterion B, ".... at least one of the following must be present...". If only one of the four subcriteria was required, then it was apparent that any single criterion was not essential to the diagnosis but simply increased diagnostic certainty. Therefore, it was theoretically possible that a case of dementia could exist where none of the four subcriteria was present.

Thus, DSM IIIR is a significant improvement on DSM III, emphasising how current concepts of dementia are continually being refined. It is superior to its European counterpart (ICD 10) which remains essentially a descriptive paragraph lacking defined guidelines. The two advantages of ICD 10 are first, that it suggests a time period over which symptoms should be present (six months) and second, that it attempts to introduce the notion of heterogeneity by dividing dementia associated with Alzheimer's
disease into early onset (Type 2) and late onset (Type 1).

1.3 CRITERIA FOR THE DIAGNOSIS OF ALZHEIMER'S DISEASE

It is important to understand that dementia, as defined above, indicates the presence or absence of a particular clinical picture (ie a dementia syndrome). The aetiology of the syndrome is a separate consideration. Both ICD10 and DSM IIIR offer additional guidelines as to how DAT may be diagnosed. The former states that, in addition to the presence of dementia, the diagnosis of DAT requires that the condition have an insidious onset and that other causes of such a syndrome be excluded. It divides DAT into two types - early onset (beginning prior to age 65, Type 2, presenile onset) and late onset (beginning after the age of 65, Type 1, senile onset).

DSM IIIR has essentially the same criteria but, in addition, has subcategories under the senile and presenile headings for dementia associated with delusions, depression, delirium and "uncomplicated" categories. This recognition of phenomenological subtypes of DAT is of importance and will be discussed at length later in this thesis (Chapters 2 and 6).

In DAT, there exists a yardstick against which clinical criteria may be measured - neuropathological examination. This situation does not obtain in the other major psychiatric conditions such as schizophrenia and depression. Whilst being an obvious advantage to the scientific study of the disorder, it also has the disadvantage in that a clinical diagnosis can be disproven, an opportunity not generally present in other branches of psychiatry.
In an attempt to refine diagnostic criteria for DAT, a work group was set up by the National Institute for Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (referred to hereafter as the NINCDS/ADRDA). Their remit was to establish a set of criteria, to be adopted by researchers studying the disorder, which would ensure a degree of homogeneity for the diagnosis amongst researchers from different centres. The published criteria (McKhann et al, 1984) represented a consensus from participants drawn from a variety of disciplines. The criteria are reproduced in Table 1.1. Three main subsets are defined - possible AD, probable AD and definite AD. Briefly, definite AD requires the presence of possible or probable AD with neuropathological confirmation of the diagnosis. Probable AD is diagnosed when a dementia syndrome of gradual onset is present and other causes excluded ie essentially the same as the definition in DSM IIIR and ICD10. The criteria are an improvement in that much greater detail is given as to how the condition should be diagnosed and various psychological tests and investigations are mentioned. Possible AD is diagnosed when a dementia syndrome is present but probable AD cannot be diagnosed confidently - either due to the presence of a coexisting physical illness or of an atypical clinical picture. The criteria state that they are to be used for "the clinical diagnosis of Alzheimer's disease". In other words, they are clinical criteria which, if applied, will predict which patients will have the histopathological changes of Alzheimer's disease. Thus, they can be regarded as synonymous with clinical criteria for DAT and SDAT.
Table 1.1 NINCDS/ADRDA CRITERIA FOR THE DIAGNOSIS OF ALZHEIMER'S DISEASE

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:
- dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests;
- deficits in two or more areas of cognition;
- progressive worsening of memory and other cognitive functions;
- no disturbance of consciousness;
- onset between ages 40 and 80; and
- absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:
- progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);
- impaired activities of daily living and altered patterns of behavior;
- family history of similar disorders, particularly if confirmed neuropathologically; and
- laboratory results of:
  - normal lumbar puncture as evaluated by standard techniques;
  - normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and
  - evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:
- plateaus in the course of progression of the illness;
- associated symptoms of depression, insomnia, incontinence, delusions, hallucinations, cachexia, or physical outbursts, sexual disorders, and weight loss.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:
- sudden, apoplectic onset;
- focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and
- seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:
- may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;
- may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia; and
- should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are:
- the clinical criteria for probable Alzheimer’s disease and
- histopathologic evidence obtained from a biopsy or autopsy.

VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:
- familial occurrence;
- onset before age of 65;
- presence of trisomy-21; and
- coexistence of other relevant conditions such as Parkinson's disease.

1.4 CLINICO-PATHOLOGICAL CORRELATIONS

The NINCDS/ADRDA criteria appear at face value to be the most sophisticated in the clinical diagnosis of AD (ie DAT). However, it is essential to examine those studies in which clinical criteria are validated against neuropathological findings. These studies are summarised in Table 1.2.

Todorov et al (1975) in a large study reported the results of 776 autopsies, performed over a 10 year period in Geneva (the same work was published, without reference to the previous publication, by Constantinidis, 1978). The clinical classification was based on nosology developed at the University of Geneva. Clinically, 273 cases could be allocated to three main categories:

1) senile dementia - onset around age 70, with amnesia as the prominent feature and little or no aphasia/apraxia;
2) "Alzheimerised" senile dementia - similar to (1) but with apraxia and aphasia and
3) Alzheimer presenile dementia - similar to (2) but with onset before age 65.

The authors also defined neuropathological criteria. Senile dementia was characterised by brain atrophy, numerous senile plaques (SP) in the neocortex and neurofibrillary tangles (NFT) in the hippocampus (but not in the neocortex).

"Alzheimerised" senile dementia and Alzheimer's presenile dementia were indistinguishable by their neuropathology - widespread brain atrophy with NFT in the hippocampus and neocortex.

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**Key:**
- N/S - not stated in the paper
- AD - Alzheimer's disease
- HC - no change in Huntington's disease
- NINCDS/ADRDA - National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association
- CT - computed tomography
- MRI - magnetic resonance imaging
- Pathologist - pathologist
- Autopsy - autopsy
- BC - brain computer
- NC - no change
"Alzheimerised" senile dementia corresponded to a diagnosis of SDAT then, of 237 patients with senile dementia, only 121 (48%) had Alzheimer pathology at post mortem. In the younger patients, 28 out of 36 had Alzheimer pathology (78%). It is possible that the clinical criteria, which did not mention ancillary investigations or the presence or absence of physical disease, were incorrectly classifying elderly patients with confusional states, mild memory disorders or physical illness as demented. Also, it is possible that younger patients were more rigorously investigated to exclude secondary dementias resulting in a higher "success rate" of correct diagnoses in this population.

Muller and Schwartz (1978) examined EEG and post-mortem findings in 100 elderly psychiatric patients. The patients had been diagnosed according to the contemporary European classification of the time, ICD 8, and 37 were given the diagnosis of SDAT. Of these, 32 had Alzheimer neuropathology (not operationally defined, but representing the diagnosis given by the pathologist on the basis of plaque and tangle formation). Despite the drawbacks of the study (observations made by a number of clinicians and pathologists over a number of years, the retrospective nature of the study and the relatively crude clinical criteria employed), the success rate of correct diagnoses was 86%. The main criticism which can be directed against the study is the lack of standardisation of the neuropathology examinations. There was no mention of vascular lesions. It is possible that AD was diagnosed in the presence of small numbers of SP's or NFT's or in the presence of vascular
damage. Such cases would not meet current neuropathological definitions.

Sulkava et al (1983) reported the autopsy results of 27 subjects suffering from primary degenerative dementia who formed part of a prospective series of 71 patients. The clinical criteria employed in the study were based on those of Roth (1955). Twenty-two of the 27 patients had typical Alzheimer changes at post mortem (defined as "abundant" NFT and SP in the hippocampus and "moderate to large numbers" in the neocortex). Of the five patients without these features, one had Parkinson's Disease (neuronal loss and Lewy body formation in the substantia nigra), two had hippocampal cell loss and gliosis and two a non-specific encephalopathy. Thus, Roth's (1955) criteria were validated neuropathologically. It is noteworthy that these criteria successfully excluded all cases of vascular dementia.

Perl et al (1984) reported clinico-pathological findings in 26 patients referred with a physician's diagnosis of DAT. Twenty-one had Alzheimer features but only nine had pure AD. Of the others, two had evidence of cerebral infarction, two had evidence of cortical anoxia, one an infarct in the temporo-parietal region and seven had the additional pathological features of Parkinson's disease. Excluding those with evidence of infarction, 18 of the 26 had features of AD. It seems likely that these cases represented a biased sample in that they were referred to a brain bank. In this case, physicians might have referred a larger proportion of cases in whom a diagnosis of AD was more likely.

Molsa et al (1985) presented the results of a prospective study of 58 autopsies of patients with dementia, three of whom
were under 65 years of age. They were drawn from a previously identified community sample. Three groups were defined clinically:

1) patients with a SDAT (defined as the absence of secondary causes of dementia and a Hachinski score (Hachinski et al, 1975) of less than four);

2) MID (defined as present when the Hachinski score was greater than seven) and

3) combined MID and SDAT (defined as a Hachinski score of between four and seven).

Results were presented of a group described as having "other" dementias but these dementias were not defined clinically. Neuropathological criteria were specified - for a diagnosis of AD at least three NFT in "any neocortical field", or at least one NFT in more than one section, were required. SP counts were not quantified separately but it was stated that moderate or high counts "invariably" were accompanied by significant NFT counts. MID was diagnosed pathologically as the presence of "any ischaemic lesions" and in the absence of AD criteria being satisfied. Of 28 cases defined clinically as DAT, 20 satisfied neuropathological criteria for AD. However, of 19 patients diagnosed clinically as MID, six had AD at post-mortem. The authors concluded that the Hachinski score produced a moderately reliable instrument to distinguish between AD and MID during life.

The results of cerebral biopsies were analysed in 24 patients by Neary et al (1986). The patients were young (mean
age 58 years, range 43 to 69 years) and performing a cerebral biopsy was obviously regarded as ethically justifiable. Normal control material was obtained from non-demented subjects undergoing other neurosurgical procedures. Many neuropsychological tests were performed on the group, all of whom had:

1) progressive deterioration of mental function of at least one year's duration;
2) an absence of other causes of dementia and
3) evidence of non-focal cerebral atrophy and ventricular enlargement on CT scan.

AD was diagnosed neuropathologically if any SP or NFTs were present. 18 of the 24 patients had these features at biopsy. They were divided into 4 different groups on clinical grounds:

1) 11 patients who conformed to the typical picture of AD with amnesia, aphasia and apraxia;
2) three patients with no aphasia but with constructional loss and amnesia;
3) two patients with prominent loss of motor skills, dysarthria and some signs of Parkinson's Disease and
4) two patients with pure amnesia.

The authors argued that this study confirmed the heterogeneity of pre-senile dementia. However, several points should be made in relation to the diagnosis of AD. First, the sample was a highly unusual one. The patients were all very young, they had very "neurological" illnesses, many of them had neurological signs and all were considered to be sufficient.
diagnostic "puzzles" to merit a brain biopsy. Second, the heterogeneity was based purely on anecdotal clinical descriptions and not subjected to proper statistical analysis. Third, the criteria for the neuropathological diagnosis of AD were rather unusual in that any NFTs or SPs were sufficient. Fourth, the drawbacks of a solitary cerebral biopsy in the diagnosis of AD are obvious - an area of unaffected cortex could easily have been biopsied. Thus, general comparisons cannot be drawn from this study.

Kokmen et al (1987) studied all the autopsies of patients within Olmsted County in Minnesota who died in 1980 and 1981. Autopsies had been carried out on 350 subjects (out of a total of 1,042 who had died). Of the 350, 32 were clinically demented and sufficiently detailed post-mortems had been undertaken to allow a re-evaluation of the cerebral sections to be made. The pathological diagnosis of AD was made on the basis of "abundant" NFTs and SPs in the hippocampus and neocortex. Of the 32 patients, 23 had these features (72%). The remainder had evidence of vascular disease, subdural haematomata and hydrocephalus. The high proportion with AD at post mortem was surprising as the criteria for inclusion in the study were not those of DAT but of dementia in general. Twenty-six of the 32 were in chronic care facilities which may have acted as a source of bias in that patients with dementia of the Alzheimer type may have been over represented by being more often referred for post mortem by their families. Also, cerebral sections were more likely to have been made when a diagnosis of AD was suspected.
clinically and where other causes of dementia had been ruled out at general macroscopic examination of the brain.

Roth's (1955) criteria (to be discussed in detail in Chapter 3.1) were employed by Wade et al (1987) who studied 65 patients of whom 39 had a clinical diagnosis of DAT. Additional information was obtained from a Computed Tomography (CT) scan and the Hachinski score. The other patients consisted of those with diagnoses of multi infarct dementia (MID), mixed dementia and "other types" of dementia. The ischaemic score was found to be less than four in 35 of 38 cases of neuropathologically confirmed AD.

Alafuzoff et al (1987) employed multivariate data analysis and principal component modelling to categorise histopathological and clinical variables in 55 demented patients. A neuropathological score was computed to assess NFT and SP counts in the frontal lobe and anterior hippocampus. Combining these with measures of infarcts and perivascular protein deposits, specific histological criteria were applied. Of 32 patients with a clinical diagnosis of SDAT, 17 had neuropathological evidence of AD. Another finding of the paper was a non-linear relationship between the neuropathological features of mixed SDAT/MID and SDAT or MID. Thus, combined dementia was postulated to represent a distinct entity and not merely as part of a continuum between AD and MID. Of course, this may well have been an artefact of the complicated statistical analysis employed.

Homer et al (1988) reported on the results of 27 autopsies on a series of 400 patients with dementia admitted for investigation to St. George’s Hospital, London. The patients were
older than in other studies (range 70 to 94 years, mean 82 years). The reasons for admission were not specified and it was not therefore clear whether the cases were atypical ie if there was sufficient doubt about the diagnosis the cases might not merit further investigation. Other possible sources of bias were not mentioned. A detailed list of investigations performed was presented in the paper. However, no criteria were given as to how the clinical diagnosis was reached. Of the 27 patients, 13 were clinically diagnosed at DAT, ten as MID and four as "other" types of dementia. Only six of the 13 DAT patients had their diagnoses confirmed at post mortem. The Hachinski score was successful in discriminating between AD and MID in only 64% of cases. Likewise, the CT scan was, likewise, disappointing at discriminating between the two groups.

The study, because of its publication in a journal aimed at a general medical readership (The British Medical Journal), was an influential one. However, several methodological flaws must be discussed and have been outlined elsewhere (Burns et al, 1988). First, no clinical criteria were given. It was stated simply that, at a weekly multidisciplinary meeting, a consensus view was reached as to the diagnosis. From that information it is impossible to ascertain how a particular diagnosis was reached. Second, the patients represented only a tiny proportion of the total number of cases seen and so general conclusions cannot validly be drawn. Third, many of the patients had coexisting physical disease - some apparent clinically but some discovered only at post mortem. These patients would certainly not have
satisfied the NINCDS/ADRDA criteria. Finally, an over-reliance on the Hachinski score and an idiosyncratic definition of some terms (such as preservation of personality defined as retention of insight) may have contributed to the diagnostic inaccuracy.

In a large retrospective study of 150 autopsies, Joachim et al (1988) examined the brains in a standardised way according to the pathological criteria suggested by Khachaturian (1985). The autopsies were referred from many sources, the only common links being 1) that the relatives had requested a post mortem and 2) that the clinical diagnosis in each case was DAT. Over 100 physicians were responsible for the referrals. Remarkably, 87% of cases satisfied the neuropathological criteria for AD. In common with other studies reporting a relatively large number of patients, neuropathological findings other than those of AD were present. For example, patients with plaques only were included as AD, Lewy bodies in the substantia nigra were seen in 18% (in just over half of whom a separate diagnosis of Parkinson's disease was justified) and amyloid angiopathy was seen in all cases of AD. Only 2% of the 150 cases had evidence of significant vascular disease, none of whom in addition fulfilled the AD criteria. In keeping with Homer et al (1988) and other studies, a small number of cases had insufficient neuropathological findings to account for the clinical syndrome of dementia. The authors concluded that:

1) physicians diagnosed AD with a high degree of accuracy;
2) degenerative changes in the substantia nigra and amyloid angiopathy were common accompaniments of AD and
3) vascular dementia was rare.
The method of obtaining the material was not made clear in the paper. A comment in the discussion section suggested that brains were referred by other pathologists. Consequently, the centre must have acted as a specialist advisor for brains in which AD was suspected. Thus, a strong bias in favour of AD cases (where for example other causes of dementia had been ruled out at general post mortem) must have been present. Another significant source of bias was that relatives had specifically asked for post mortems in order to substantiate a clinical diagnosis of AD. Also the type of stain used (the Bielschowsky Silver Stain), was said to be more sensitive than other stains in common use. These sources of bias are not discussed.

Some studies have employed the same current strict clinical criteria for the diagnosis of DAT employed in the present study (McKhann et al, 1984). Morris et al (1987) reported the cerebral biopsy results on 11 patients who had undergone intraventricular bethanacol infusions. Biopsies were taken from the frontal lobe at the time of insertion of the canula. All patients satisfied the pathological criteria for AD while none of the nine control patients had any evidence of AD. The mean SP count correlated with dementia in the expected direction, with tests of language and on the Mini Mental State Examination (ie more severe impairment, more SPs). NFT counts were not included in the correlations as they were rated on a four point scale of severity rather than on actual counts. The authors concluded that aphasia had been confirmed as a bad prognostic feature in DAT, whether it was measured against histopathological severity.
or diminished survival (the latter as in the studies by Kaszniak et al, 1978, Berg et al, 1984). The lack of correlation between memory scores and neuropathology was explained by the universality of amnesia in DAT. Thus, a suitable range of scores would not be obtained. On the other hand, language disorder was more preserved and so a sufficient range of scores could be obtained. One possible conclusion to be drawn from the results was that the only point they had demonstrated was a relationship between language and pathology in the left frontal cortex. The paper gives three reasons against acceptance of this conclusion:

1) that a relationship between global severity as measured by the MMSE and SP count, was noted;
2) although cross region plaque counts did vary, they did so only in early disease and therefore would not be expected in the patients seen and
3) language deficits are traditionally associated with posterior cortical pathology.

Martin et al (1986, 1987) studied 26 patients, all of whom satisfied the NINCDS/ADRDA criteria. The study was particularly interesting in that 17 of the 26 cases had been diagnosed early in the course of their illness. Although all cases satisfied neuropathological criteria for AD, additional features were found. Four patients had no NFTs in the neocortex, features of Parkinson's Disease (Lewy bodies) were seen in 38% and some degree of infarction was present in the brains of over one-third of the cases.

Boller et al (1989) used a different method to assess the accuracy of predicting AD neuropathology. The case notes of 54
patients in whom autopsies had been performed were subjected to an independent analysis by two neurologists. They used a check list derived from the NINCDS/ADRDA criteria to categorise patients as probable or possible DAT. Three groups were studied—the first group consisted of 12 patients assessed in an Alzheimer’s Disease research centre, the second of 28 patients seen in a geriatric or psychogeriatric setting and the third group of 14 patients in other institutions, not all of whom had been assessed by a neurologist. In each of the three groups the percentage of cases in which both neurologists successfully predicted AD neuropathology were 75%, 57% and 57% respectively. When at least one neurologist was correct, the "success rate" increased to 83%, 61% and 71%. Total agreement on the diagnosis of DAT was reached only in 63% of cases and partial agreement in 80%. The authors concluded from these findings that the aetiology of dementia could not be predicted accurately during life. However, for each observer, the "success rate" was 85% and 95% respectively, tending to validate the NINCDS/ADRDA criteria.

The authors pointed out that, although the group followed most intensively during life (group 1) had the lowest percentage of misdiagnoses (16%), the group about which least was known (group 3) were misdiagnosed in 21%—statistically, not a significant difference. This conclusion is in keeping with Muller and Schwartz (1978), Kokmen et al (1987) and Joachim et al (1987), who showed that physicians were generally accurate at predicting AD during life. Boller et al (1989) suggested, rather contentiously, that detailed clinical and radiological
investigations were not necessary for the improvement of routine clinical diagnosis.

Tierney et al (1988) specifically tested the NINCDS/ADRDA guidelines in a clinical pathological study. 57 cases, 22 with a clinical diagnosis of DAT and 35 suffering either from another type of dementia or with no dementia, were analysed using nine different neuropathological criteria. The analyses consisted of any combination of three inclusion criteria and three exclusion criteria. The inclusion criteria were:

1) one or more NFTs and SPs in the hippocampus, regardless of neocortical findings;
2) one or more NFTs and SPs in both the hippocampus and neocortex and
3) one or more NFTs or SPs in the neocortex, regardless of the findings in the hippocampus.

Exclusion criteria were:

1) ischaemic lesions of greater than 50 mls;
2) any ischaemic lesion anywhere in the brain and
3) any ischaemic lesion in the neocortex, white matter or hippocampus.

Combinations of the inclusion and exclusion criteria were tested, against the clinical diagnoses, for accuracy, sensitivity and specificity. Accuracy varied between 81% and 88%. Sensitivity (ie the number of clinical AD cases classified pathologically as AD) varied between 64% and 86%. The best classification occurred with inclusion criterion 1 (NFTs and SPs in the hippocampus only) and exclusion criterion 1 (ischaemic lesions of greater than 50 mls). The specificity of the criteria
(ie the percentage with neither a clinical diagnosis of AD nor a neuropathological one) was high and showed little variability across combinations of criteria (89% to 91%).

There was no difference in the classifications using inclusion criterion 2 (requiring both hippocampal and neocortical lesions) and inclusion criterion 3 (requiring neocortical lesions only) as in all cases where neocortical lesions were found, hippocampal lesions were also present. However, hippocampal lesions occurred without neocortical ones. The main conclusion of the paper was that the NINCDS/ADRDA criteria had been validated against a wide range of neuropathological features.

Jellinger et al (1989) reported on a large series of 440 consecutive autopsies of patients clinically diagnosed as demented, drawn from subjects in a psychiatric hospital, a geriatric hospital and a general hospital. The aim of the study was to "validate the clinical diagnosis" made by DSM IIIR, ICD 10 and the NINCDS/ADRDA criteria but no further information was given as to how this was done. Of 382 patients in whom DAT was diagnosed, 315 (82.6%) satisfied neuropathological criteria for AD. As the report was presented as an abstract, the lack of detail makes interpretation of the results difficult.

Ettlin et al (1989) assessed the accuracy with which SDAT and MID could be diagnosed during life. Thirty-two cases with autopsy proven AD, MID or a combination of the two were included in the sample. A retrospective analysis of clinical features during life revealed that AD was correctly predicted in 80% of cases — the clinical features, CT and EEG all being equally
useful in the diagnostic process. In MID, clinical features were the most successful at correctly predicting neuropathological findings - the CT and EEG were unhelpful. Mixed cases were diagnosed most successfully in the same way as MID - it was not possible to differentiate the two ante mortem. The study can be criticised on two counts - (1) the sample consisted of only 32 cases (which represented only a sample of 50 cases which came to post mortem) and (2) the study was dependent on the retrospective analysis of case notes.

Finally, Blessed (1989), reviewed the experience of the Newcastle group from 1963 to 1977 with regard to clinico-pathological correlations. A total of 50 cases in whom a clinical diagnosis of senile dementia, SDAT or AD was given had post mortem examinations. All but seven were diagnosed as AD at post mortem. Blessed noted that when patients with parietal lobe signs (apraxia, aphasia or agnosia) were assessed at post mortem, every case had AD. The report was not primarily concerned with clinico-pathological correlations but its main purpose was to put all the clinico-pathological studies into perspective. The main achievement of the work was to confirm that correlations existed between the clinical features of psychiatric disorders and neuropathological and neurochemical changes. Although correct prediction of subsequent pathology by the application of certain clinical criteria was not the main function of the studies, they clearly showed that Roth's (1955) definition of SDAT was valid.

It should be noted that the neuropathological diagnosis of Alzheimer's disease varies slightly from study to study. The basic requirements of NFT and SP in the cortex and hippocampus
are always met but differences occur in relation to the numbers involved and the stains used to assess their presence. As can be seen from Table 1.2, the numbers of NFT and SP required for the diagnosis varies from "any" (Neary et al, 1986) to "extensive" (Perl et al, 1984). All studies mention histological changes in the neocortex as being a prerequisite for the diagnosis (although one report confined this to the frontal lobe, Alafuzoff et al, 1987) but not all include changes in the hippocampus as being essential.

Some authors have attempted to formalise neuropathological criteria eg Khachaturian (1985), Ball et al (1987). Others have simply described their methodology which has later been taken up by others eg Blessed et al (1968), Tierney et al (1988). Wisniewski et al (1989) surveyed the diagnostic practices of neuropathologists in the USA and Canada. The majority reported that they used quantitative (or semi-quantitative) methods of analysis. However, wide variation occurred in relation to the stains used with half using Bielschowsky or thioflavin S staining while the others concentrated on amyloid or silver stains. As the former are generally more sensitive to the presence of lesions, any quantitative judgement of neuropathology must take into account the stain employed. (A detailed description of the neuropathology of Alzheimer's disease is outwith the scope of this thesis but is mentioned here for the sake of completeness and to add a note of caution to the interpretation of clinico-pathological studies.)
1.5 SUMMARY

The correct diagnosis of Alzheimer's disease is a two stage process - first, the diagnosis of a dementia syndrome and second, the selection of cases in whom Alzheimer's disease is likely to be histologically proven. Strictly speaking, Alzheimer's disease is a neuropathological diagnosis, the clinical equivalent of which is Dementia of the Alzheimer type or, when dealing specifically with an elderly population, Senile Dementia of the Alzheimer type. The most rigorous clinical criteria for the clinical diagnosis of Alzheimer's disease are those of the National Institute for Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA). They have evolved from other clinical criteria and have been consistently shown to be highly accurate. Non-adherence to such criteria leads to considerable diagnostic inaccuracy.
CHAPTER 2

HETEROGENEITY IN SENILE DEMENTIA OF THE ALZHEIMER TYPE

2.1 INTRODUCTION

The purpose of this chapter is to present evidence (clinical, genetic and neuropathological) to support the hypothesis that DAT is a heterogeneous disorder. Amongst patients suffering from DAT, there appear to exist distinct subtypes of the disease, each with a different clinical presentation and natural history despite sharing a common pathology. That subtypes of DAT exist has been known for some time and the neuropathological differences between senile and presenile dementia were noted by Alzheimer (1911). Merritt (1955) recognised that the disease duration varied enormously - ".....the duration of the disease is usually between four and 10 years, with extremes varying from less than one year to more than 20 years". Different clinical presentations have been observed, each with its own symptom complex. Karnosh and Zucker (1945) in their "Handbook of Psychiatry" describe the following presentations: "Simple deterioration, depressed/agitated, delirious/confused, paranoid and presbyophrenia" (excited and over-active). More recently, phenomenological subtypes have been recognised by DSM IIIR (see Chapter 1). This chapter will deal predominantly with results from cross sectional studies. Chapter 3 will address longitudinal changes and will examine survival in more detail. (Some cross referencing across the two chapters and within individual sections is inevitable because of the diverse
nature of the material with which some papers deal.)

Whether or not there are subtypes of a number of psychiatric disorders has been debated for some time with regard to depression and schizophrenia. The problem cannot be resolved completely because, as yet, no criteria exist which define unambiguously where a subtype of a particular disorder may be regarded as present. Theoretically, two forms of subtype may be defined - qualitative and quantitative (Jorm, 1985).

Qualitative subtypes can be said to exist when an aetiological factor acts independently on the core disorder to produce a subtype characterised by additional symptoms (eg aphasia occurring as an additional cognitive deficit in a dementia syndrome characterised primarily by amnesia).

Qualitative subtypes can be difficult to evaluate for three reasons. First, the aetiological factor must be strongly related to the subtype or it would have few implications for treatment or prevention. Second, if the primary symptom of the subtype is a continuous variable (and represented by, for example, a shift on a test for aphasia) and the aetiological factor is dichotomous (eg the presence or absence of a particular gene) then bimodality in the distribution of a test score for aphasia may be present. Bimodality may indicate the presence of subtypes but if two normal distributions (each representing a subtype) are not widely separated or if the sample sizes are different, then bimodality would not appear. Alternatively, bimodality may be present if another dichotomous variable (not aetiologically related to the subtype) such as gender bears an influence on the aphasia score.
Third, in a progressive disorder such as DAT, cross sectional studies may include patients with both early and late stages of the disease. Thus, the aphasia may not indicate the presence of a true subtype.

Quantitative subtypes are present if two aetiological factors (such as a gene and head injury) have an additive influence on the disorder. Thus, if both factors were present the disorder would be more severe.

These subtypes are theoretical and as Jorm (1985) points out, no studies have been done which prove conclusively the existence of either category of subtype. Only when definite biological markers of the disease have been elucidated can this be done, as in the case of Duchenne and Becker Muscular Dystrophy. However, clinical studies are able to indicate whether subtypes may be present.

2.2 AGE OF ONSET

Seltzer and Sherwin (1983) examined the distinction between early and late onset DAT. Of their 65 male patients, all of whom satisfied DSM III criteria for Primary Degenerative Dementia (PDD, equivalent to a diagnosis of DAT), 34 were deemed to have a age of onset less than 65 years of age and 31 an onset older than 65 years. They examined the prevalence of a number of clinical features in the two groups. The younger onset group had significantly poorer scores on tests of language, a higher number of left-handers and a shorter survival time compared to the older onset group. They had a tendency to be more apraxic but this did not reach statistical significance. No significant differences
between the two groups were found for the proportion with seizures, personality change or the neurological signs of increased tone and primitive reflexes. The authors postulated that this heterogeneity was due to a genetic predisposition leading to an early age of onset and left hemisphere dysfunction - the latter resulting in language disturbance. The higher proportion of left handers in the younger group was regarded as an indication of right hemisphere damage. The authors argued that this did not confound their hypothesis because first, 50% of them would have left hemisphere dominance despite being left handed, and second, the higher than expected number of left handers suggested prior damage to the left hemisphere favouring development of the right hemisphere and so left handedness. This genetic theory, although plausible, is not supported by any information on family history of dementia.

Heyman et al (1987) further investigated the early/late onset dichotomy when reporting the results of a longitudinal study on 92 patients with early onset DAT (mean age 62.4 years). Almost all were seen for at least two years and 13 were followed for six years. Clinical features were examined which were predictive of two predetermined 'end points' - institutionalisation and death. The five year mortality rate was 2.5 times greater than would have been expected in the normal population. Complex statistical models were applied to estimate the relative contribution of cognitive impairment to institutionalisation and death. It was found, not surprisingly, that greater impairment was a significant factor in predicting both institutionalisation and
death. Age had a significant modifying effect - younger patients were at greater risk of institutionalisation and death than older patients with the same degree of cognitive impairment. That many factors influence admission to nursing homes was recognised by the authors (indeed ten of the 54 patients were admitted because of death or serious illness in the responsible caregiver). Also, the young age of the sample may also have influenced reasons for admission. Thus, unmeasured factors may have resulted in institutionalisation. Death was obviously less likely to be influenced by social factors and represents a more robust biological measure of the severity of the disorder (although patients die from causes other than the direct effect of their DAT).

Mayeux et al (1985b) examined the case records of 121 patients satisfying DSM III criteria for PDD to determine whether clinical subgroups existed. Age of onset showed a bimodal distribution with a point of rarity at age 70 years. The young group was characterised by severe cognitive impairment and a greater proportion exhibiting myoclonus. The authors noted that, although they had demonstrated bimodality in age of onset, this factor was not definitive evidence for subgroups.

Chui et al (1985) performed a cross-sectional analysis of 146 patients satisfying DSM III criteria for DAT in an attempt to define clinical subtypes. In addition to the information sought by Mayeux et al (1985b), they noted whether or not a family history of dementia was present or not and examined aphasia in more detail. The mean age of their sample was slightly older than that of Mayeux et al (1985b) - 73 years compared to 69 years. A
family history was present in 45% of the total (families with inadequate information or where first degree relatives failed to survive to an age comparable to the patient’s age of onset were excluded). Aphasia was present in 60% of patients. Patients in whom symptoms started before age 65 had a longer duration of illness and more had aphasia than the late onset group. The authors recognised that the increased proportion with aphasia in the younger group may have been due to their longer duration of illness. However, when subsamples of young and old patients with comparable duration of illness were compared, aphasia remained more common in the younger group.

Patients with a family history of dementia did not differ from those without on all variables, with two important exceptions. First, agraphic subjects were more likely to have a family history of dementia (confirming earlier work by Breitner and Folstein, 1984). Second, there was a trend showing a positive relationship between the presence of aphasia and family history (in keeping with the work of Selzer and Sherwin, 1983). However, no increased prevalence of left handers in the early onset group was observed. Patients with extrapyramidal signs and myoclonus were more severely demented. This finding concurred with earlier work by Mayeux et al (1985). Chui et al (1985) tentatively concluded that there were subtypes of DAT in view of the association between early age of onset and aphasia. However, the lack of longitudinal data detracts from their conclusions.

Filley et al (1986) examined neuropsychological test results on 23 patients with early onset DAT (mean age 57
years) and 18 patients with late onset DAT (mean age 70 years), all of whom satisfied DSM III criteria for DAT. The tests were divided broadly into those assessing memory, language function and visuo-constructional ability. Although the two groups were similar for overall impairment of cognitive function and memory, significant differences existed in the other tests. Language impairment was significantly greater in the early onset group, confirming the earlier work by Chui et al (1985) and also Seltzer and Sherwin (1983). Visuo-constructional performance was worse in the late onset group. By extracting standardised scores and comparing relative impairments on language and visuo-constructional performance, the differences between the two groups were even greater. The authors concluded that left hemisphere damage characterised early onset DAT and that right hemisphere damage was responsible for the impairments seen in late onset DAT. Only one patient in each group was left handed and, when they were excluded from the analyses, the results were unchanged. The authors argued that their results suggested clinical variability in early and late onset DAT but showed no evidence of distinct disease entities. A follow-up study would be required to explore the possibility that subjects progressed to develop additional neuropsychological deficits.

Grady et al (1987) assessed both neuropsychological function and regional cerebral metabolism in subjects with early and late onset DAT. The 34 patients (early onset N=21, late onset, N=13) were diagnosed according to NINCDS/ADRDA criteria and both "probable" and "possible" cases were included. Each subject underwent an extensive neuropsychological battery including the
Welscher Adult Intelligence Scale (with additional assessments of aphasia and visuo-perceptual function) and an 18F Deoxyglucose Positron Emission Tomography scan. In addition, 21 were assessed longitudinally for an average of 19 months. There were no significant differences in the neuropsychological profiles between the early and late onset groups at entry to the study, the rate of decline in each being almost identical. The authors concluded that they did not find heterogeneity based on age of onset. They argued that the findings of Mayeux et al (1985b) could be explained in terms of differing disease severity, not subtypes, and that their own results were more persuasive as they had the benefit of longitudinal data. Although the study of Grady et al (1987) was well executed and the neuropsychological battery impressive, the numbers involved were small (N=26 for the follow up) and should be regarded as preliminary findings requiring replication.

2.3 NEUROPSYCHOLOGICAL FUNCTION

McDonald (1969) was among the first to address specifically the question of heterogeneity in SDAT based on neuropsychological tests. The study was in two parts. In the first, 51 patients completed five scales as a measure of cognitive function - memory, parietal, abstract thinking, aphasia and colour/shape sorting (Weigl). When the distribution of error scores was examined, the parietal and Weigl scores had a bimodal distribution. The former scale was chosen for further examination because the distribution was more evenly weighted between success
and failure. The group was divided into low error scorers (up to one error, group B) and high error scorers (two or more errors, group A). The mean ages of the groups was 81 and 79 years respectively. The author argued that the results indicated the low error scorers did not simply precede high error scorers in the natural history of the condition.

In the second part of the study a different sample of 57 patients was divided into two groups according to their scores on the same five cognitive tests. Their six month mortality was compared. Twenty-six percent of the high error group (mean age 76 years) had died compared to 4% of the less impaired group (mean age 83 years). Thus, the group who were less impaired on the parietal test were older and survived longer than those more impaired. McDonald (1969) postulated that there were two different types of senile dementia, a younger group with a poor prognosis and an older group with a better prognosis. He argued that this latter group may be related to the the concept of "benign senescence" as described by Kral (1962). Although McDonald (1969) presents some evidence to support qualitative subtypes in SDAT, the absence of longitudinal data on cognitive decline makes it impossible to draw definite conclusions. If, for example, the less impaired group developed high error scores on the parietal scale over time, this would suggest the subtypes were quantitative rather than qualitative. The fact that those who were less impaired were older does not necessarily mean that they were qualitatively different. A differential age of onset could explain the differences in terms of quantitative subtypes.

Further evidence for neuropsychological heterogeneity was
presented by Martin et al (1986). They analysed the results of six neuropsychological tests (three assessing non-verbal abilities and three assessing verbal abilities) in 42 patients satisfying the NINCDS/ADRDA criteria (McKhann et al, 1984). A principal components analysis revealed two separate cognitive profiles - one with high loadings on non-verbal tests (visual perception and construction) and another with high loadings on verbal tests (mainly word finding ability). There was no significant correlation between the verbal and non-verbal tests which confirmed that they represented discrete categories. A cluster analysis revealed five subgroups. Three were defined as showing global impairment (mild, moderate and severe, N=25) with similar degrees of deficits between the two factors. The fourth group (N=9) showed word finding difficulty with relative preservation of visuo-constructive performance while the fifth (N=8) had a test profile the mirror image of the fourth group with more pronounced visuo-constructive deficits. There was no difference in the five subgroups with regard to age of onset or symptom duration. The graphical display of the results was very impressive and showed clear differences in the groups. The conclusion was made that qualitatively different profiles of cognitive impairment and cortical metabolism existed in DAT and thus subgroups had been demonstrated.

The authors cautioned that the evidence for subgroups was strong enough to cast doubt on the common practice of averaging data across groups of DAT or SDAT patients on the assumption that they shared a common diagnosis (inferred from a presumed common
neuropathology). They warned that this was erroneous and could serve to hinder neuropsychological research in the field.

Freed et al (1989) investigated picture recognition in 20 patients with DAT and assessed delayed recognition (72 hours after initial testing) and attentional focusing (the difference in reaction time between a cued and uncued stimulus). A subgroup of patients (N=10) was found to show impaired 72 hour recognition and to have impaired visual selective attention. Based on animal models, the authors associated this finding with lesions in the ascending noradrenergic system of the locus coeruleus. While the results of this study were interesting and provided evidence that cognitive subtypes exist, it should be noted that the cognitive tests used were complicated and, to a certain extent experimental, all of which raises questions both about their validity and usefulness in clinical practice.

2.4 PSYCHIATRIC SYMPTOMS

Psychiatric symptoms have received very little attention compared to the cognitive changes which occur in DAT. Alzheimer's first case in which delusions of jealousy and hallucinations were prominent (Alzheimer, 1907) has already been described (Chapter 1.1). Psychiatric symptoms are of importance in the study of DAT for two main reasons. First, the strain on carers is directly related to their presence (Rabins et al, 1982). Second, and most germane to the present study, is that their presence may indicate subtypes of the disorder.

Descriptions of psychiatric symptomatology in DAT can be divided into two temporal categories - those before and those
after the mid-1970's. Early studies relied on substantially anecdotal reports from clinical observers, usually in small and unrepresentative samples of patients (eg young patients referred to hospital for assessment). Later, instruments of proven validity and reliability were used to assess symptoms in more representative groups of patients.

Henderson and MacLachlan (1930) reported four female patients (mean age 57), only one of whom was without psychotic features. Of the other three, one had hallucinations (type unspecified), one paranoid delusions and the third had both. Goodman (1953) noted that in his 23 autopsy proven AD cases that "...hallucinations frequently occurred", visual being the most common type. Paranoid delusions "were fairly common early in the disease" and most were of a simple, unsystematised type.

Ziegler (1954) found in his sample of 40 psychiatric patients with idiopathic atrophy on pneumoencephalography, that 15% were "paranoid", 15% were "depressed" and the sample proportion had "neurotic" symptoms. However, although quoted in many articles as indicative of the prevalence of psychiatric symptoms in DAT (eg Liston, 1979), it is uncertain how many of these patients were suffering from primary dementia. Sim and Sussman (1962) reported on 46 patients referred to a department of psychological medicine, 22 of whom had AD diagnosed by cerebral biopsy. They reported that in this group, depressive symptoms occurred early in the disease and tended to disappear as the dementia became more severe; also that "psychotic" features (not further defined) were a late manifestation. "Agitation" was present in 29% . Coblentz (1973) examined ten subjects with
histologically confirmed AD and described five as "agitated" and two with psychotic features.

Gustafsson and Hagberg (1975) studied 57 patients with pre-senile dementia. Extensive psychiatric assessments were performed on the patients and 50 had cerebral blood flow assessed by Xenon-133. Seven factors were described based on a factor analysis of a standardised psychiatric interview - ixophrenia (an emotionally charged "clinging" attitude), depression, explosive temper, hypochondriasis, paranoia, psychomotor overactivity (euphoria and affective liability). Associations were described between the presence of these symptoms, regional cerebral blood flow and severity of dementia. Ixophrenia, depression and hypochondriasis were all found in subjects with mild dementia and relatively normal cerebral blood flow, although the first two were associated with slightly reduced flow. As such, these three symptoms were considered as "compensatory" (both psychologically and physiologically) for mild impairment of cerebral function, but also possibly related to pre-morbid personality characteristics. Affective lability, explosive temper and overactivity were associated with severe cognitive impairment and were designated as signs of disinhibition related to low frontal blood flow. Paranoia was said to be present at all levels of cognitive impairment - in mild dementia it was considered a psychological reaction to diminished comprehension of the environment and in the later stages, the result of direct brain damage. The authors stated that blood flow studies appeared to confirm this with high
frontal flow in the early stages, reducing in the later stages. Gustafsson and Hagberg (1975) were the first to describe an association between blood flow and particular symptoms which went some way towards the elucidation of subtypes ie different clinical manifestations (with different symptom complexes) were associated with pathophysiological markers (alterations in regional cerebral blood flow).

More recent work has used standardised and reproducible measures of assessing phenomenology. Three main types of psychiatric phenomena have been defined (Lancet, 1989) - disorders of thought content (delusions and paranoid ideation), disorders of perception (hallucinations and misidentifications) and disorders of affect (depression and elevated mood).

The importance of non-cognitive symptoms in dementia from a heuristic point of view has been discussed by Berrios (1989). He cites four possible explanations for the occurrence of such symptoms - the presence of an intercurrent delirium, cortical disinhibition, the pathoplastic effects of personality and the coexistence of two mental disorders. Berrios (1989) states that patients with prominent non-cognitive symptoms represent a subgroup of DAT subjects but he did not go as far (as would have seemed logical to do) as to suggest that they were representative of clinical subtypes of DAT.

Disorders of Thought Content

It is recognised that delusions occur in association with DAT. DSM IIIR has a separate category, subsumed under the main heading "Primary Degenerative Dementia of the Alzheimer Type", for patients with delusions but no such subheading occurs in ICD
10. Delusions are known to occur in patients with organic brain disease such as Huntington's Disease (Dewhurst, 1969) and post-encephalitic Parkinsonism (Fairweather, 1947). Regional localisation has suggested an association between delusions and temporal lobe damage as in temporal lobe epilepsy (Toone, 1981) and Herpes Encephalitis (which preferentially affects temporal structures, Rennick et al, 1973). Schneiderian first rank symptoms of schizophrenia have also been related to temporal lobe atrophy (Trimble 1990). Idiopathic basal ganglia calcification has been implicated in the genesis of delusions (Cummings and Benson, 1983).

Attempts have been made to subclassify delusions associated with organic brain damage. Cummings (1985) suggested that they be divided into four types - simple persecutory delusions, complex persecutory delusions, grandiose delusions and those delusions associated with specific neurological deficits. He identified delusion ideation in a prospective study of 20 male patients with organic disorders, four of whom had DAT (representing 15% of all DAT subjects seen in the service). Patients with mood congruent delusions were excluded. Simple delusions were confined to subjects with DAT or vascular dementia while the other delusions occurred in patients with a variety of neurological disorders such as tumours and encephalopathies. It was found that those with simple delusions were more cognitively impaired than those with any of the other three types. Cummings (1985) also made the practical observation that simple delusions were more responsive to neuroleptic medication than complex
Cutting (1987) followed Cummings' (1985) scheme in an attempt to classify delusions in 74 patients with acute organic psychoses, 35 of whom were deluded. He was able to classify only seventeen patients according to the Cummings (1985) classification - eight with simple persecutory delusions and nine with mood congruent delusions (this category replacing that of grandiose delusions as described by Cummings, 1985). Seventeen of the remaining 18 were afforded a separate category described as "complex, bizarre or multiple". This category was similar to the "complex persecutory" delusions described by Cummings (1985). In addition, one patient had a delusion "based on a specific neuropsychology deficit" (a phrase employed by Cutting to describe the concept suggested by Cummings).

There have been some studies specifically assessing the frequency with which delusions occur in DAT. Cummings et al (1987) defined both delusions and DAT using DSM III criteria. They found that delusions had occurred, since the onset of illness, in 14 out of 30 DAT subjects (average age 70.4 years) and that there was a trend (not statistically significant) for these patients to be less cognitively impaired. Although well characterised, the sample had only 30 subjects who were referred from a variety of sources (out-patients or inpatients, geriatric, psychiatric or neurological) and thus cannot be considered to be a representative population of DAT subjects. Rubin et al (1988) found 31% of their sample to be deluded, the commonest type of delusion being that of stealing (which would have been in the "simple persecutory" category of Cummings, 1985). Although, in
comparison to the sample of Cummings et al (1987), the number studied was large (N=110), there was no definition of delusions. It can be inferred from the paper that the patients were diagnosed by a number of investigators, thus reducing the reliability of the results.

Berrios and Brook (1985) reported delusions in 37% of 100 demented patients referred to an out patient clinic. Twenty three of 68 patients with DAT were diagnosed as deluded. These subjects scored less than the non-deluded patients on the information, but not on the memory subscale of the Blessed Dementia Scale (BDS, Blessed et al, 1968). Patients with both vascular dementia and DAT were included and it seems likely that some of the subjects had an intercurrent delirium at the time of examination. Also, 14 of the 37 deluded subjects had an additional diagnosis of a functional illness. This factor raises the suspicion that they had a previous psychiatric disorder, thereby casting doubt on the diagnosis of DAT.

Common delusional themes include delusions of abandonment and impostering (Reisberg et al, 1987), suspicion and stealing (Rubin et al, 1988; Berrios and Brook, 1985; Cummings et al, 1987). None of these studies divided delusions in DAT into the subtypes described by Cummings (1985) and Cutting (1987).

Clues to the pathological substrate of delusions come from two lines of evidence. First, delusional ideation seems to require relatively intact cerebral function. Jacoby and Levy (1980,a) and Gustafsson and Risberg (1974) found delusions to be inversely related to the cerebral atrophy and to cortical
perfusion respectively. Second, delusions have been associated with basal ganglia calcification (Cummings, 1985). There appears to be no difference in the prevalence of delusions in patients with vascular or degenerative dementia (Berrios and Brook, 1985; Cummings et al., 1987) suggesting that they are not specific to a particular pathological process but that they result from brain damage of diverse aetiology, perhaps localised to particular brain regions.

Paranoid ideation, held without delusional intensity, has not been examined specifically in DAT although Reisberg et al (1987) described 21% of his sample as exhibiting "paranoia" (not further defined). Merriam et al (1988) found 42% to have paranoid ideation "of a relatively minor nature" and 56% to have "more severe paranoid symptoms". It may be that the former finding represented paranoid ideation and the latter delusions, but this conclusion cannot be made with certainty. The relatively high rates suggest that some difference in definition is present or that a very biased sample has been studied. No definitions of the symptoms were given and the sample was drawn from patients referred to a neurology clinic and, as stated in the paper, not a clinic dealing particularly with psychiatric or behavioural problems. These factors make the high proportion of patients with psychopathology even more surprising. Most studies lack a precise definition of delusions (with the exception of Cummings et al., 1987) so it is possible that some patients have paranoid ideation which has been wrongly equated with ideas held with delusional intensity and vice versa. The absence of operational criteria for the diagnosis should be borne in mind when comparing
Disorders of Perception

Perceptual disturbances can be divided into two types (Fish, 1985) - sensory distortions (changes in the intensity, quality or spatial form of perception) and sensory deceptions (illusions and hallucinations). Hallucinations occur in many psychiatric conditions such as schizophrenia, depression and acute organic psychoses (Cutting, 1987). Their presence in senile dementia was partly responsible for the condition being classified as a senile psychosis. There is a considerable French literature on hallucinations. Lhermitte (1951) noted that hallucinations (in particular visual hallucinations) occurred in elderly patients with atherosclerosis and cerebral atrophy. Henri Ey (Ey, 1973) observed that clinicians had long been familiar with the tendency for the aged to experience hallucinations especially those suffering from DAT though rarely in patients with Pick's disease. Both authors mention the "Charles Bonnet syndrome" as an example of visual hallucinosis in the elderly. This syndrome has been well documented (Berrios and Brook, 1984; Damas-Mora et al, 1982). Characteristically, the sufferers have insight into their experiences, generally have poor vision, are not worried by the hallucinosis and remain cognitively intact which makes a misdiagnosis of dementia unlikely.

Several studies have reported the prevalence of hallucinations in DAT. For example, Sjogren et al (1952) reported a prevalence of 15%. More recently, Cummings et al (1987), in addition to diagnosing delusions, assessed
hallucinations in their 30 DAT patients (average age 70.4 years) and 15 with MID. Of the DAT patients, only one had auditory and none had visual hallucinations; in MID, three experienced visual and one auditory hallucinations. The authors required that only those subjects reporting "a sensory perception" would be regarded as suffering from hallucinations. The patients were interviewed directly to ascertain whether hallucinations were present but information was also sought from the casenotes. Three of the four patients with these experiences had visual defects. The association between this type of hallucinatory experience and ocular pathology has been described previously (Berrios and Brook, 1984). Clinical subtypes of DAT based on visual hallucinations, which do not take ocular pathology into consideration, cannot therefore be posited.

Reisberg et al (1987), in describing a new behavioural rating scale, found that 12% of their sample of 57 out-patients (mean age 75.0 years) had suffered visual hallucinations. Auditory hallucinations were not mentioned. Merriam et al (1988) examined 175 subjects with DAT using the Schedule for Affective Disorders to assess depression and reported, incidentally, that 28% had experienced either visual or auditory hallucinations. Similarly, Teri et al (1988) reported that in 127 out-patients, 21% of subjects had hallucinations (type unspecified). There was a tendency (not statistically significant) for the proportion of subjects with these perceptual phenomena to be greater as severity of cognitive impairment increased.

The difference in frequency rates in various studies may be explained in three ways. First, the sample studied. Most
reports from North America describe populations of patients referred to outpatient clinics or to AD research facilities. There may be differences in referral procedure to each centre and the patient group may be biased in favour of subjects suffering from psychiatric problems. No reports have yet described the rates of psychiatric symptoms for an epidemiologically representative population. Second, the definition and method of ascertainment of symptoms. For example, Cummings et al (1987) used a very stringent definition of hallucinations and relied mainly on direct interview with the patient. By contrast, Reisberg et al (1987) relied solely on review of medical casenotes. Third, the periods of time to which the given rates refer. In the majority of studies, it is unclear whether the prevalence rates refer to symptoms occurring at any time since the onset of the illness or if they are reserved for symptoms present at the time of the examination.

The other main types of perceptual disturbance seen are misrecognitions and misidentifications which have been virtually ignored as symptoms of DAT. There have been a number of case reports in the literature of misidentification of relatives in dementia (some manifesting as the Capgras Syndrome, eg Burns and Philpot, 1987). Misidentification of mirror image has also been described and "Signe du miroir" is the term used to refer to patients conversing with their own image (Mayer Gross et al, 1960). Rubin et al (1988) described three types of misidentification - imagining that other people were in the same house, the inability of a subject to recognise his or her own
image in a mirror and treating events or people on the television as if in real three-dimensional space. Rubin et al (1988) reported that 23% of their 110 patients had experienced at least one type of misidentification (the belief that others were in the house being the most common). Merriam et al (1988) described these as "perceptual" symptoms and found that 49% of the patients misidentified other people and 41% misidentified places. The study by Merriam et al (1988) is, again, unusual in the very high rates of symptomatology described (eg major depression was found in 86% of cases, vide infra) and so the number of patients experiencing these disorders of perception may be falsely high.

Delusions, misidentifications and hallucinations have been reported as being associated with an accelerated cognitive decline (Drevets and Rubin, 1989) and with a decreased death rate. Mayeux et al (1985a) reviewed the records of 62 patients in a longitudinal study and found that those with "psychosis" (inadequately defined as persistent or recurrent thought disorder) deteriorated more rapidly in both cognitive and functional abilities over time. Stern et al (1987) reported on the follow up of 55 patients in the study. They reported that the sudden onset of psychosis was associated with a rapid decline in one of the "benign" group (an intermittent delirium may have been present but there was no mention of it). Very little has been recorded as to the pathological substrate of perceptual symptoms. However, one recent preliminary report has suggested that in cortical Lewy body disease, cholineacetyltransferase activity is lower in patients who have experienced hallucinations than in those who have not (Perry et al, 1990).
Disorders of Affect

The relationship between depression and DAT is particularly interesting in view of the occurrence of cognitive impairment in depression embodied in the concept of "pseudodementia" (Kiloh, 1961; Rabins et al, 1984; Pearlson et al, 1989). The documentation of mood disorders in DAT and their relationship to cognitive impairment is another way in which to assess this complex relationship.

Follow-up studies from the 1960's suggested that there was no increased incidence of primary dementia in subjects with affective disorder (Post, 1962; Kay 1962). However, more recent studies have cast doubt on this finding. Kral (1983) followed 22 patients (for an average of eight years) diagnosed as having depressive pseudodementia and found that 20 of them had developed SDAT at follow up. Reding et al (1985) reported that, of 28 patients with depression, 16 developed dementia over a three year follow up. Cerebrovascular, extrapyramidal or spinocerebellar disease and a Hachinski score of greater than four were found to be particularly associated with progression to dementia. It can be argued that the association between depression and the later occurrence of primary dementia has not been proven convincingly by these two papers. The patients described by Kral (1983) obviously had some cognitive impairment initially (they were diagnosed as having pseudodementia) and only five of the 16 patients described by Reding et al (1985) developed SDAT - the others developed Parkinson's dementia, cerebrovascular dementia or other types of dementia. Thus, the contention that
uncomplicated depression gives rise to SDAT later in life is unproven. Retrospectively, a history of depression in DAT is described in 10% of patients (Agbayewa, 1986). This observation has recently been extended by Henderson et al (1989) who, in a case control study, found an increased number of episodes of depression in the previous ten years (but not before then) in patients with DAT. Whether this represents a risk factor for DAT or prodromal symptoms is not yet clear. No studies have yet assessed non-cognitive symptoms as the possible prodromata of dementia (Berrios, 1989).

Cross-sectional studies of the prevalence of depression in DAT are common but inevitably the results differ widely because of variations in the population under study and in the assessment instruments employed. In a recent comprehensive review, Wragg and Jeste (1989) reviewed 14 studies. These 14 studies plus an additional six papers (published after the literature search commissioned by Wragg and Jeste) are presented in Table 2.1. Wragg and Jeste (1989) concluded that depression was more prevalent in DAT patients drawn from acute care facilities (compared to research clinics) and that depressive "symptoms" were more common than depressive "disorders".

The prevalence of depression in DAT varies from between 0% (Knesevich et al, 1983; Cummings et al, 1987) and 86% (Merriam et al, 1988). The majority of studies have described a prevalence rate of between 20% and 40% (Liston 1979, Ron et al 1979; Ballinger et al, 1982; Burke et al, 1988). The method by which DAT was diagnosed was either by clinical impression (eg Bucht and Adolfsson, 1983) or adherence to standardised criteria
<table>
<thead>
<tr>
<th>DSM III Criteria</th>
<th>Clinical Population</th>
<th>References</th>
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<tbody>
<tr>
<td>17%</td>
<td>Hamilton, 1985</td>
<td>30</td>
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<td>9%</td>
<td>Clinical</td>
<td>69</td>
</tr>
<tr>
<td>0%</td>
<td>Zung</td>
<td>0</td>
</tr>
<tr>
<td>11%</td>
<td>New Scale</td>
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<td>23%</td>
<td>Cognitive Outpatients</td>
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<table>
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<tr>
<th>Admission Interview</th>
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<tr>
<td>42%</td>
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<tr>
<td>7%</td>
<td>Psychogeriatric Inpatients Clinical</td>
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<td>30%</td>
<td>Psychogeriatric Inpatients Clinical</td>
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<tr>
<td>33%</td>
<td>Psychogeriatric Inpatients Clinical</td>
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<tr>
<td>47%</td>
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<tr>
<td>10%</td>
<td>State Psychiatric Psychiatric Inpatients</td>
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<tr>
<td>10%</td>
<td>Hospital Psychiatric Psychiatric Inpatients</td>
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<tr>
<td>52%</td>
<td>Neurology Psychiatric Hospital Psychiatric</td>
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<td>Alzheimer's Population</td>
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<td>(1962)</td>
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</table>

Depression Symptomatology in Alzheimer's Disease

Table 2.1 (continued overleaf)
<table>
<thead>
<tr>
<th>% REPORTED:14%</th>
<th>% REPORTED:26%</th>
<th>% REPORTED:50%</th>
<th>% REPORTED:22% C</th>
<th>% REPORTED:41%</th>
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<td>DSM III</td>
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<td>Geriatric Depression Criteria</td>
<td>Geriatric Depression Criteria</td>
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<td>DSM III</td>
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<tr>
<td>NINDS/ADRA</td>
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<td>NINDS/ADRA</td>
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<tr>
<td>86%</td>
<td>75%</td>
<td>50%</td>
<td>22% C</td>
<td>41%</td>
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<tr>
<td>232</td>
<td>72</td>
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<td>36</td>
<td>75</td>
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<table>
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<th>Diagnosis Population</th>
<th>% Depressed</th>
<th>Disease</th>
<th>Author(s)</th>
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</thead>
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<td>Greenwald et al. (1989)</td>
<td>232</td>
<td>DSM III</td>
<td>11%</td>
<td>Geriatric Depression</td>
<td>Burke et al. (1989)</td>
</tr>
<tr>
<td>Ruben and Kinscherf (1989)</td>
<td>72</td>
<td>DSM III</td>
<td>14%</td>
<td>Geriatric Depression</td>
<td>Burke et al. (1989)</td>
</tr>
<tr>
<td>Mackenzie et al. (1989)</td>
<td>68</td>
<td>DSM III</td>
<td>14%</td>
<td>Geriatric Depression</td>
<td>Burke et al. (1989)</td>
</tr>
<tr>
<td>Merritt et al. (1989)</td>
<td>36</td>
<td>DSM III</td>
<td>14%</td>
<td>Geriatric Depression</td>
<td>Burke et al. (1989)</td>
</tr>
<tr>
<td>Kumar et al. (1989)</td>
<td>75</td>
<td>DSM III</td>
<td>14%</td>
<td>Geriatric Depression</td>
<td>Burke et al. (1989)</td>
</tr>
<tr>
<td>Lazarus et al. (1987)</td>
<td>44</td>
<td>DSM III</td>
<td>22% C</td>
<td>Geriatric Depression</td>
<td>Burke et al. (1989)</td>
</tr>
</tbody>
</table>

**Note:** The majority were considered to have Alzheimer's Disease.

**Key:**
- C - Average figures for 9 individual symptoms assessed.
- F - The majority were considered to have Alzheimer's Disease.
- N - Average figures for prevalence at different stages of disease.
(eg those of the NINCDS/ADRDA, McKhann et al, 1984, utilised by Rubin and Kinscherf, 1989 and McKenzie et al, 1989). In two studies, there was neuropathological confirmation of the diagnosis (Sim and Sussman 1962; Birkett 1972). Similarly, the diagnosis of depression was often clinically based (eg Nott and Fleminger, 1975) or adhered to one of the recognised diagnostic schemata (eg DSM III or Feighner criteria - employed by Reding et al, 1985 and Burke et al, 1988, respectively). Standardised depression rating skills were commonly used (eg the Hamilton and Zung Rating Scales - Knesevich et al, 1983 and Lazarus et al, 1987). Two recent studies have compared depressive symptomatology complained of by the patient to that observed by a relative or interviewer (McKenzie et al, 1989; Rubin and Kinscherf, 1989). Both found that observed depression was greater than reported depression.

Reifler et al (1982) noted that depression was more common in women and became less apparent as cognitive impairment increased. Cummings et al (1987) reported that major depression occurred in patients with an Mini Mental State Examination (MMSE, Folstein et al, 1975) score of 17 or above but not below this level. These authors suggested that although behavioural manifestations of depression (appetite loss, sleeplessness, crying) could be discerned in advanced dementia, symptoms such as anxiety and guilt could not be assessed so easily. This factor may explain the low rates of depression found in patients with advanced disease. However, Knesevich et al (1983) confined their studies to patients with early DAT and found no cases of
depression. Lazarus et al (1987) assessed individual items on the Hamilton Depression Rating Scale. They found that patients with primary dementia scored higher on items assessing intrapsychic as opposed to vegetative symptoms. At first sight, this finding appears to contradict the view of Cummings et al (1987) but may be explained in terms of the sample studied by Lazarus et al (1987). The latter authors compared the depressive phenomenology of demented patients with normal (ie non-depressed, non-demented) controls. Hence, no statement could be made regarding depressive symptomatology at different stages of DAT. In agreement with Reifler et al (1982), Lazarus et al (1987) found depression to be more common in women but reported no correlation between cognitive impairment and degree of depression.

The significance which individual authors place on particular symptom complexes is also variable. For example, Merriam et al (1988) reported the frequency of depression in 175 community residents with DAT. They employed DSM III criteria to diagnose both depression and dementia and found that 87% of demented patients satisfied either criterion A (dysphoria) or criterion B (four out of eight symptoms which include biological features of depression, agitation, worthlessness and suicidal ideation) for major depressive disorder. 86% satisfied both criteria A and B (the unusually high proportion of patients affected with symptoms in this study has already been mentioned). Cummings et al (1987) applied these same criteria to diagnose depression but found no cases in their DAT sample. Thus, although some differences in prevalence of depression may be due to the population studied and assessment instruments employed, it is
possible that individual interpretation by the authors of criteria (such as those in DSM III) is responsible for some of the differences seen.

A point which has never been discussed in the literature is that in DSM III (and DSM IIIR), a diagnosis of primary degenerative dementia of the Alzheimer type and major depressive disorder are mutually exclusive. In DSM IIIR, criterion E2 for primary dementia states that one can only assume that an organic factor is present in dementia if the disorder "...cannot be accounted for by any non-organic mental disorder, eg major depression". In the criteria for major depressive episode, criterion B1 states that the diagnosis of major depressive episode may be made if "...it cannot be established that an organic factor initiated and maintained the disturbance". Alternatively, "major depressive syndrome" may be diagnosed instead of major depressive episode (the former involves the presence of defined depressive symptomatology and makes no inference as to their origin). The point may seem like hair splitting but is an important one in that it perpetuates the confusion surrounding the association between depression and dementia. DSM IIIR does not allow the diagnoses of major depressive episode and of primary dementia of the Alzheimer type to be made together and yet it concedes that depressive symptoms occur in DAT by having a sub-category under the latter for patients with depression. However, no guidance is given as to how depression should be diagnosed in DAT.

Two recent studies have assessed neuropathological changes
in depressed and non-depressed AD patients. Zweig et al (1988) found that subjects with AD and major depression had more neuronal cell loss at the mid-level of the locus coeruleus than the non-depressed. There was a tendency towards greater loss of neurones at all levels of the locus coeruleus and dorsal raphe nucleus in depressed patients. Zubenko and Moossy (1988) found that patients with major depression and primary dementia had more degenerative features in the locus coeruleus and substantia nigra than non-depressives with dementia. These findings are intriguing and represent one of the definitive tests for the possible existence of subgroups of AD - that based on neuropathology. In addition, they may shed light on the organic substrate of functional illnesses such as depression.

In contrast to depression, elevated mood has been reported less often as an accompaniment to DAT. Rothschild (1941) reported that one out of 31 cases of DAT presented "a manic like picture". Sim and Sussman (1952) described one out of 22 patients with histologically proven AD as being euphoric and Bucht and Adolfsson (1982) found three out of 20 patients with "elated mood". Berrios (1985) reviewed the concept presbyophrenia which was used at the beginning of the century to categorise a subtype of dementia with features of elevated mood and hyperactivity. He described 15 cases and found elevated mood to be present in nine arguing that presbyophrenia may represent a true subtype of dementia. As with depression, definite cerebral organic changes have been demonstrated in patients presenting with manic illnesses in old age (Shulman and Post, 1980; Broadhead and Jacoby, 1990).
Behavioural disturbances, like psychiatric symptoms, have received very little attention when compared to the large literature on cognitive changes in DAT. Abnormal behaviours are, however, very important as they impose a significant burden on carers (Rabins et al, 1982) and because their presence or absence may indicate clinical heterogeneity in DAT. While behavioural problems may be related to previous personality traits, they may also be a manifestation of underlying structural brain damage (Fairburn and Hope, 1988a). Behaviours are considered separate to psychiatric symptoms and can be defined as acts observed by and which affect others. Aggression, incontinence, binge eating and wandering are examples. I believe that it is necessary to make this distinction from psychiatric symptoms although I recognise that the two may often be associated (eg a hallucinating patient responding to his or her experiences by becoming aggressive). Many authors do not make such a distinction with the result that some studies assess aggression and hallucinations in the same way, seemingly unaware of such an important potential distinction (eg Swearer et al, 1988; Teri et al, 1989).

Sanford (1975) was among the first to highlight the difficulties experienced by carers because of behavioural disturbance. Fifty carers of elderly subjects admitted to a geriatric ward for "social reasons" were interviewed. Behaviours particularly disruptive and a cause for admission to hospital were nocturnal wandering, incontinence of urine or faeces and
physical aggression. Although no detailed information regarding
diagnosis was given, it was stated that these behaviours were
specifically related to senile dementia.

Rabins et al (1982) highlighted the difficulties which were
experienced by caregivers. The families of 55 demented patients
were interviewed and behaviours regarded by them as a "problem"
were recorded. Of the seven items of behaviour cited as causing
serious problems, only one (memory disturbance) could be related
to cognitive function. The others (physical violence, hitting,
incontinence, catastrophic reactions, suspiciousness and
accusatory behaviour) appeared to be unrelated to cognitive
deficits.

Greene et al (1982) extended simple behavioural observation
by administering two scales to the relatives of 38 patients with
senile dementia who were attending a day hospital. One assessed
the patients' behaviour and the other measured relatives'
distress. Using factor analysis, it was found that relatives'
personal distress was related to patients' apathy and withdrawal
while negative feelings towards to the patient were associated
with disturbances in the patients' mood. This well conducted
study also showed that relatives' distress was unrelated to the
degree of cognitive impairment.

Several recent studies have highlighted behavioural
demented patients (56 with DAT) who attended an AD Research
Centre. "Angry outbursts" occurred in over 50% of the sample and
"violent behaviour" was present in 21%. "Dietary change" (not
further specified) was present in 46% of subjects and violent or
bizarre behaviour and incontinence became proportionally more common as the severity of the dementia increased. Teri et al (1988), in 127 out-patients with DAT, found wandering behaviour in 26%, agitation in 24% and restlessness in 45%. The lack of definition of terms and the conversational tone of the study detract a great deal from the scientific validity of the study. In a subsequent publication, the same group (Teri et al, 1989) presented more detailed results on 56 subjects. They stated categorically in the Methods section that they did not refer to the same group described by the authors previously (Teri et al, 1988), but were drawn from the same clinical source. There were differences in the proportion of patients exhibiting certain behaviours, eg in the 1988 sample, 26% demonstrated wandering compared to 5% in the 1989 sample; 21% in the earlier study had hallucinations but only 6% in the later study. Such differences in the proportion of individuals with a particular behaviour requires explanation but none is given. One of the main reasons was probably that the 1989 study involved the presentation of a new scale for assessing behaviour. This new scale may have been more rigorous in its assessment of behaviours rather than relying on the individual assumptions of various clinicians, which may have been the case in the previous sample.

In a community study of aggression (Ryden et al 1988) found 65% of the 183 subjects to be aggressive. However, dementias of any aetiology were included in this sample and some of the definitions of aggression appeared idiosyncratic (eg sexual aggression included the behaviours of kissing, hugging and
sexual intercourse).

A particular syndrome encompassing behavioural changes in dementia is of interest - the "Kluver-Bucy Syndrome". This syndrome was originally described following bitemporal lobectomy in monkeys (Kluver and Bucy 1937). The following striking behavioural changes were described:

1) visual agnosia;
2) strong oral tendencies with hyperphagia;
3) hypermetamorphosis (an excessive tendency to attend to and react to every visual stimulus;
4) increased sexual behaviour and
5) emotional changes, both withdrawal and apathy but also loss of fear and "rage" reactions.

In man, the syndrome has been described following bilateral removal of the temporal lobes (Terzain and Ore, 1955), in DAT (Sourander and Sjogren, 1970) and in Pick's Disease (Cummings and Duchen, 1981).

Sourander and Sjogren (1970) reported a detailed analysis of the features of the Kluver-Bucy syndrome in 60 patients with DAT. Over 70% of cases had features of the syndrome, with the exception of hypersexuality which occurred in only ten subjects. They confirmed that temporal and plaque counts were higher in subjects who had features of the syndrome during life. However, damage to other parts of the brain appear to be required. It is unusual for all the features of the syndrome to occur in man as it seems to be specific to primates (Pilleri, 1966). Sourander and Sjogren (1970) emphasized, however, that individual symptoms were common.
Probably the most widely recognised feature of the syndrome seen in DAT is increased eating (often associated with hyperorality for other objects). Hope et al (1989) described four cases of increased food intake in DAT patients and suggested five reasons why it occurred - as a result of the patient forgetting they had eaten, release from previous dieting habits, a behavioural stereotypy, a response to malabsorption or occurring as a direct result of brain damage. The authors favoured the last explanation and backed up their contention with data from animal experiments. Their conclusions were, however, premature as no direct clinical evidence was presented to support the theory. Their material was based on four anecdotal case reports and it appeared that it was mainly a rejection of the other hypotheses that led to their conclusions.

Morris et al (1989) studied the eating habits of 33 patients with dementia. Both decreased and increased food intake were described. Twenty-six percent noted excess oral behaviour with eating of inedible and inappropriate objects. The sample consisted of elderly patients (27 with DAT, four with MID and two with mixed DAT/MID). The paper described a wide range of eating behaviours and their possible mechanisms which was helpful in drawing attention to these abnormal behaviours.

2.6 NEUROLOGICAL SIGNS

Neurological phenomena such as primitive reflexes, extrapyramidal signs and myoclonus have all been described in DAT. Traditionally, they are considered to be late manifestations of the disorder and are regarded as the
consequence of advanced cerebral damage (Lishman, 1987).

Koller et al (1982) found a snout reflex in 54% of 52 patients with DAT (mean age 68.3 years) and in exactly the same proportion of 48 elderly age matched non-demented controls. The proportion with this reflex increased with age. A glabellar tap was found in 23% of DAT subjects but in only 8% of controls (a difference which was statistically significant). Tweedy et al (1982) found that a glabellar tap was the most common primitive reflex (79%) in 32 subjects with DAT, a palmomental reflex was present in 47%, a snout reflex in 19% and a grasp reflex in 17%. Snout and grasp reflexes were associated with cognitive impairment while a glabellar tap and palmomental reflexes were not. Neurological signs were strongly associated with CT evidence of ventricular enlargement but not with cortical atrophy. Huff and Growdon (1986) found comparatively smaller proportions of 165 DAT subjects with primitive reflexes - a snout reflex in 18% and a grasp and palmomental reflex in 10%. The palmomental reflex was unrelated to degree of dementia but the other two were significantly more common as severity of dementia increased.

The presence of myoclonus in DAT has often led to an erroneous diagnosis of Creutzfeld-Jakob disease in which myoclonus occurs frequently (Fadden and Townsend, 1976). Cases of myoclonus in association with DAT have been reported (eg Barratt, 1913) and some are hereditary (Jacob, 1970). More recent studies have described the prevalence of myoclonus in large populations of DAT subjects (eg Mayeux et al, 1985b; Chui et al, 1985).
Mayeux et al (1985b) found that 28% of 121 patients had extrapyramidal signs - bradykinesia and rigidity most frequently observed with tremor being rare (an additional 10% were described as having extrapyramidal signs due to neuroleptic medication). Patients with extrapyramidal signs had poorer cognitive function (as assessed by a modification of the MMSE), poorer functional capacity (assessed by the BDS) and were more likely to have delusions and hallucinations. Subjects with drug-induced extrapyramidal signs were the most impaired on the cognitive and functional scales. No differences were observed between the groups with regard to age, age of onset of dementia or family history of dementia. Ten per cent of the sample had myoclonus. These patients had a younger age of onset and more cognitive impairment than subjects without myoclonus. Fifty patients were followed longitudinally from between six months and four years after initial evaluation. Extrapyramidal signs developed in 10% and these signs were accompanied by cognitive and functional impairment greater than in those patients who did not develop the signs. 18% developed myoclonus during the follow-up period. They were characterised by poorer performance on the modified MMSE but functional capacity was not diminished.

In agreement with other studies, eg Berg et al (1987), a subgroup of patients (seven out of 50) had mild impairment of intellectual function and did not deteriorate throughout the follow-up period. The authors claimed to have delineated four subgroups of DAT - extrapyramidal (sporadic and drug-induced), typical, myoclonic and benign. They had the benefit of longitudinal analyses to test the stability of their subgroups
and as such satisfy many of the criteria for the existence of subgroups as outlined by Jorm (1985). Quite correctly, they do not suggest that the bimodality seen in the age of onset is suggestive of subgroups but do not present the longitudinal data in different age groups. Most of their findings could be explained in terms of quantitative subgroups, eg the differences in modified MMSE and functional ratings at the beginning of the survey being a function of disease duration. The development of extrapyramidal signs and myoclonus in 10% and 18% of the patients respectively may also indicate a progression to a common type.

Chui et al (1985) found that 34% of 146 patients had extrapyramidal signs while 6% had myoclonus. Patients with these signs were more demented than those without, in agreement with the findings of Mayeux et al (1985b). Therefore, the presence or absence of certain neurological signs may indicate subtypes of DAT.

2.7 GENETIC HETEROGENEITY

Larsson et al (1963) were pioneers of the genetics of DAT. In a large investigation (Larsson et al, 1963), 719 subjects with SDAT were studied comprehensively and information gathered regarding familial factors. The conclusion was that there was a significant genetic component and the favoured mode of transmission was autosomal dominant. Around the same time, Constantinidis (later summarised in Constantinidis, 1968) reported, in a study of 229 probands, that presenile dementia was inherited as an autosomal dominant and senile dementia as an autosomal recessive condition.
Two papers dealing with the issue of familial DAT can be considered together (Folstein and Breitner, 1981; Breitner and Folstein, 1984). In the first of these studies, two important observations were made. Of 39 subjects with DAT, 41% had a first degree relative affected. This percentage was significantly greater than in patients with vascular dementia or other types of dementia. Within the DAT group, those who could not write a sentence (defined as being agraphic) had a significantly increased chance of having a family member affected (54% compared to 20%). The authors' conclusion was that the classic features of DAT (aphasia and agraphia) identify specifically a familial form of DAT. They quoted from existing pedigree studies which suggested that the inheritance was by an autosomal dominant gene which led them to conclude that the lifetime risk to first degree relatives of patients with aphasia and agraphia would be about 50%. Their next paper examined this in greater detail.

Breitner and Folstein (1984) drew their sample from 15 nursing homes in Baltimore, Maryland. They had strict exclusion criteria (approximating to NINCDS-ADRDA criteria) but no physical investigations were performed on the subjects. Of 3,500 subjects screened, 62 patients (all were white females) were selected for further investigation. Subjects were assigned to categories on the basis of the presence or absence of agraphia (assessed by the ability to write a sentence spontaneously) and aphasia/apraxia (assessed by an interview with caregivers). A very high association between the two categories was found and, because the cases split conveniently into two using the agraphic/non-agraphic
distinction, the analyses were based on this distinction. Using
information obtained from interviews with relatives, the
prevalence of cases of dementia in the families was estimated.
There was an increase risk of cases of dementia in both male and
female relatives of agraphic DAT subjects. 10.5% of first degree
relatives (N=181) of agraphic DAT patients were demented compared
to 3.8% (N=79) of non-agraphic subjects. The prevalence in first
degree relatives of non-demented control subjects was 2.5%
(N=157). Using the Weinberg Morbidity table, the authors
estimated that the cumulative risk to relatives of agraphic
probands was greater than 50%. Their conclusion was that agraphic
DAT was inherited by an autosomal dominant gene with age-
dependent penetrance.

Several aspects of the paper merit comment. The cases
represented a biased sample in that all the patients were in
nursing homes and therefore their dementia syndrome could be
considered severe. Language disordered subjects may have been
overrepresented in this group. Although the inclusion/exclusion
criteria were carefully specified, no physical investigations
were performed and this omission may well have led to erroneous
diagnoses. The presence or absence of aphasia/agraphia was
ascertained by historical information taken from relatives by
non-medically qualified interviewers. Despite these
reservations, the results of the paper are so significant that
they cannot be easily ignored. The authors concluded that further
studies were required to replicate their findings. Although such
investigations might be used as evidence for the existence of
qualitative subtypes of DAT, the possibility remains that the
language disorder described in familial DAT is merely a late manifestation and that it would develop in all cases with sufficient time. Breitner and Folstein (1984) recognised this and excluded eight cases who did not have aphasia, apraxia or agraphia and who had been ill for less than four years. They did so on the assumption that the patients may have developed these signs later in their illness.

Knesevich et al (1985) presented details on the longitudinal course of SDAT (discussed in detail in Chapter 3.3). In addition, they reported information on the family history of the disorder. It was found that subjects with aphasia had a more rapidly progressive form of the disorder. Calculating the risk of dementia in relatives of the probands (up to age 79) showed that the relative risk was (in aphasic and non-aphasic probands respectively) 7.5% and 26.3% for siblings and 17.7% and 34.5% for parents. The authors concluded that SDAT was a heterogeneous condition with aphasia early in the illness signifying a non-familial rapidly progressive subtype. The association between aphasia and rapid progression was predictable while the lower familial risk was not. One possible explanation for this result was that aetiological heterogeneity exists and that aphasia (independent of genetic risk) in some way lowers the threshold for the development of the clinical disorder.

The development of the techniques of molecular genetics has been useful in the genetic investigation of DAT. Recent developments began when three articles appeared in the same issue of "Science" (St. George-Hyslop et al, 1987; Goldgaber et al,
1987; Tanzi et al, 1987). The first reported genetic linkage of
the disorder to chromosome 21 (the same gene duplicated in Down's
syndrome, sufferers from which universally develop AD brain
changes). The other two articles showed that the gene coding for
B-amyloid (an integral part of the neuritic plaque) was also on
chromosome 21. Two subsequent publications (Van Broeckhoven et
al, 1987; Tanzi et al, 1987) found that, using restriction
fragment length polymorphisms, recombination events occurred
between the gene for familial DAT and that for amyloid protein,
proving that the genes were not one and the same.

The findings of St. George-Hyslop et al (1987) have been
replicated by Goate et al (1989) but refuted by Roses et al
(1988) and Schellenberg et al (1988). Analogies may be drawn
between the search for the familial DAT gene and that for
muscular dystrophy. In the latter, genetic heterogeneity has
been found (ie two loci) resulting in the description of two
types of muscular dystrophy - Becker and Duchenne. If genetic
heterogeneity were present in DAT, then at least two loci would
occur which would not even necessarily be on the same chromosome
If this was so, the task of identifying the gene for DAT
would be much more difficult. However, as Goate et al (1989)
argued, the negative results of these two studies may be
explained in terms of the populations examined - Roses et al
studied the Volga Germans, a genetically inbred and therefore
unusual sample. Even if genetic homogeneity (ie only one mutant
gene) were present, the phenotype might have variable expression
as in the case of Sickle Cell Disease.

2.8 NEUROPATHOLOGICAL AND NEUROCHEMICAL HETEROGENEITY

The main drawback to clinical studies of DAT is that the diagnosis cannot be made with absolute certainty before death. Thus, even although the most rigorous diagnostic criteria classify correctly 80-90% of cases, 10-20% will still be diagnosed wrongly. This fact would seem to cast doubt on the validity of clinical studies. The advantage of neuropathological studies is that a neuropathological diagnosis can be made at the same time as a search for subtypes. Ideally, both clinical and neuropathological information is required.

Hubbard and Anderson (1981) examined the brains of 20 severely demented patients and 18 non-demented age-matched controls. Cerebral volume was estimated in relation to cranial capacity making a correction for shrinkage of the brain during formalin fixation. The clinical diagnoses of the demented patients were all of SDAT - 15 were confirmed as AD at necropsy. None of the non-demented control group had neuropathological evidence of AD. The demented group were divided according to age at death - eight over 80 years of age, seven less than 80 years. Compared to controls, the younger patients had significantly more atrophy throughout all regions of the cerebral cortex (average 14%). In contrast, the older patients did not show this significant atrophy when compared to controls with the exception of the temporal lobes (which had on average 21% less tissue).

The cerebral cortex was primarily affected - atrophy in this region was more pronounced than in the white matter. No atrophy
was demonstrated in the hind brain. Cerebral ventricular size was significantly greater in the younger patients compared to controls while older AD patients had similar sized ventricles to controls. The authors postulated the existence of two groups of AD patients with a genetic predisposition differentially expressed in young and old. The lack of clinical information detracts from their results - details about disease duration and family history of dementia would have added to the strength of the findings. Although showing differences between young and old AD patients, the paper falls short of showing distinct subtypes. This point was made by the authors.

Neuronal counts have been described in two studies and claims for heterogeneity made on the basis of the results. Bondareff et al (1981) performed neuronal counts in the locus coeruleus of 20 patients with AD and compared them to counts in ten non-demented control subjects. A histogram of total cell counts showed a definite bimodality in distribution. Subjects with low counts (group 1) were younger at death and were more demented (as measured by the BDS) than subjects with high counts (group 2). Brain weights were the same in both samples. The control group had similar brain weights to the two demented groups and similar neuronal counts to group 2.

Bondareff et al (1982) examined adrenergic cell counts in the nucleus locus coeruleus in 20 patients (average age 78 years) diagnosed as SDAT during life. Nineteen of these patients had AD confirmed at autopsy. Neurones were counted using an image analyser in a standardised section of the nucleus. The authors
reported that this area was ideally suited to such analysis as the cells could be visualised easily as a result of their intracytoplasmic melanin. The results were quite striking, showing as clear bimodal distribution of neuronal counts with a point of rarity at between 5,000 and 7,000 neurones. They assigned the label AD-1 to that group with the lower counts and AD-2 to the group with the higher counts. A significant overlap existed between the counts in AD-2 and normal controls. AD-1 were significantly younger at death and were more demented than AD-2. The latter result became non-significant when women only were included. The authors argued that they had demonstrated subgroups of female SDAT patients and had localised one of the principal deficits to the noradrenergic system. The study can be criticised on three grounds. First, the inclusion of a patient in the analysis suffering from dementia, but without cerebral pathology, was probably a mistake. Second, the conclusions drawn are out of proportion to the number of cases involved. Third, the results could be explained entirely in terms of quantitative rather than qualitative subtypes.

Tagliavini and Pilleri (1983) produced similar results with neuronal counts in the basal nucleus of Meynert. The counts from nine patients with AD (average age 70 years) were compared with those of three patients with "simple senile dementia" (average age 93 years) and with five controls. In the AD group, a linear relationship was found between neuronal loss and age at death showing that the greatest neuronal fall-out was in the younger patients. No difference was found in the neuronal counts of the "simple senile dementia" group and the controls. Wilcock
and Esiri (1983) quote their own work to demonstrate a decrease in cell counts in the nucleus basalis in eight patients with AD but no decrease in normal ageing. They made the point that the findings in the group described by Bondareff et al (1981), of late onset with relatively intact neuronal counts, do not support the hypothesis that this type of AD is age related.

Similar criticisms can be levelled at the work of Bondareff et al (1981) and Tagliavini and Pilleri (1983). First, the numbers of subjects involved are too small to make any meaningful statements on the presence of subtypes. Bimodal distributions may result from small numbers (Everitt, 1981). Second, and more fundamental, is the danger of interpreting quantitative differences as evidence of qualitative subtypes (Jorm, 1985). Bondareff (1983) brought together evidence from a number of sources (mainly neuropathological but also clinical and neuroradiological) to propose two types of AD. He proposed that AD-1 was characterised by onset in old age, a more insidious course, fewer parietal lobe signs, less ventricular enlargement and less severe neuropathological and neurochemical changes. AD-2 was described as having an onset in middle age, a more rapid course, more parietal lobe signs, greater ventricular enlargement and more severe neuropathological and neurochemical changes than AD-1. The evidence he cites, while empirically supporting the differentiation of AD, does not justify its categorisation into this rigid dichotomy.

These observations were extended by Bondareff et al (1987) in a further examination of the histopathological evidence for
heterogeneity in AD. Neuronal counts in the locus coeruleus were studied in relation to a number of other variables including additional neuropathological and biochemical data and age at death. The results (on 46 patients which presumably included the 20 in the original study) did not confirm a significant difference in age between AD-1 and AD-2. The authors went on to perform three discriminant analyses (on the 27 patients in whom adequate data were available) in an attempt to separate the two groups further. First, the patients were separated into those with more than, or those with less than, 65 neurones per section in the nucleus coeruleus. Noradrenaline concentration along with tangle and plaque counts were successful in discriminating between the groups, and 74% of cases were successfully categorised. Second, the groups were divided into age at death (greater or less than 79 years). In this way, 87% of cases were classified correctly using the same variables, with the addition of choline acetyl transferase activity in Brodmann's area 24. A third analysis was performed excluding patients who died between the ages of 76 and 82 in an attempt to provide better separation of the groups. Using this result, group membership was predicted successfully in 100% of cases using plaque and tangle counts, cholineacetyltransferase (ChAT) activity (in Brodmann's area 21) and the number of neurones in the nucleus locus coeruleus. The authors cited other work to emphasise the paradox of more severe neurochemical and neuropathological changes occurring in younger AD patients. They admitted (as indicated previously) that the measures employed may simply have reflected differences in severity at extremes of a continuum.
Thus, their description is of quantitative rather than qualitative subtypes. Two findings confound this. First, there was no correlation between the degree of dementia during life and any of the variables used. Second, neither duration of dementia nor the dementia score improved the differentiation of the groups when added to the discriminant analyses. Their argument was thus strengthened that they had demonstrated both quantitative and qualitative differences.

The results of neurochemical studies also lend support to the evidence for heterogeneity. The first to do this were Rossor et al (1981). The ChAT levels of 25 cases of histologically confirmed AD were compared to 26 normal controls. The AD cases were divided into young and old groups (age of death less than or greater than 79 years). Both groups had significantly lower activities of the enzyme in the temporal cortex but only the younger group had significant decrements in the frontal cortex. Enzyme activity increased with age in the AD group whilst decreasing with age in the control group. Two possible inferences could be made from these findings. First, that the relative preservation of enzyme activity with increasing age reflected the relative absence of cerebral atrophy seen in this group (Hubbard and Anderson, 1981). Second, that the older group represented a discrete subtype.

In an extension of their earlier work, Rossor et al (1984) reported the levels of neurochemical activity in 49 patients with AD and 54 non demented controls. The findings of the earlier study were confirmed showing a decrease in ChAT activity which
was more widespread in younger patients. Similarly, aminobutyric acid, somatostatin and noradrenaline levels were decreased in younger patients compared to normal controls while the only significant difference between the older group and normal controls was a decrease in somatostatin in the temporal lobe. Although the existence of subtypes might be inferred from the data, the authors suggested that the older group might be dying earlier due to intercurrent illness and therefore have a less severe form of the disease. However, the dementia scores were similar in the two groups but unfortunately no information on duration of illness was provided.

Bird et al (1983) presented a full account of ChAT activity in 16 patients with AD and correlated the findings with clinical features. The control group consisted of 32 non demented patients and 17 patients with Huntington's Disease. The five areas examined were the frontal and temporal cortices, hippocampus, putamen and cerebellum. The findings of this important paper can be summarised thus:

1) the AD group had a 40% decrease in ChAT in the frontal and temporal cortices, hippocampus and cerebellum when compared to the control group;  
2) patients with early onset AD (onset less than 65 years, N=8) had lower Chat levels only in the temporal cortex compared to late onset patients (N=8). Compared to controls, the early onset group had lower levels in all areas except the putamen while the late onset group had lower levels only in the hippocampus;  
3) patients with myoclonus (N=4) had lower levels of ChAT in
all areas except the putamen compared to those AD patients without myoclonus and

4) there was a tendency for patients with a family history of dementia to have lower ChAT levels but these levels were not significantly different from those patients without a family history of dementia.

The duration of dementia was the same in the early and late onset groups which disproved the idea put forward by Rossor et al (1984) that older patients were simply dying earlier in the course of their illness.

While most neurochemical studies are based on post-mortem material, some biological markers can be measured in vivo. Platelet membrane fluidity (PMF), which reflects cell membrane structure and function, is one such marker which has been investigated in SDAT. Zubenko et al (1988a) found increased PMF in 50% of DAT subjects attending an AD Research Centre all of whom met NINCDS/ADRDA criteria. Those with increased PMF had more evidence of left parietal dysfunction (based on psychological test results) than patients with normal PMF. The authors concluded that they had discovered a biological subtype of DAT. Other evidence from the same group to supports this hypothesis.

DAT patients with the abnormality have an earlier age of onset and deteriorate more rapidly than those without (Zubenko et al, 1987a). Zubenko and Teply (1988) assessed PMF in 15 patients and ten controls over a 12 month period. No significant changes took place in individual subjects suggesting that it was a stable
biological marker. This result is somewhat contradictory to an earlier finding (Zubenko et al, 1987b) where a correlation was found between dementia severity and increased PMF. Zubenko and Teply's (1988) explanation of this fact was that increased PMF represents a subtype of the disorder with a more rapidly progressive course. Zubenko et al (1988b) showed that the number of relatives with dementia was the same in patients with or without increased PMF. However, the age of onset of the disorder in affected relatives was earlier in the group with the abnormality. This evidence suggests strongly that PMF may be a biological marker for a subgroup of the disease. The evidence is, however, less convincing that this subgroup is characterised by anything other than increased PMF, apart from age of onset. The more rapid deterioration and the psychological test results of parietal dysfunction could be explained by the earlier age of onset. This in itself may be simply a manifestation of quantitative subtypes. Zubenko et al (1988b) discussed the inheritance of both DAT and the PMF trait, suggesting that either two genes give rise to DAT (one of them also resulting in increased PMF) or that increased PMF may modify the clinical picture of DAT (ie by causing an earlier age of onset). The work on PMF is interesting but, so far, falls short of proving biological subtypes of DAT.

Two recent studies provided interesting and additional neurochemical support for the clinical observations of Chui et al (1985) and Mayeux et al (1985b) with regard to myoclonic and extrapyramidal subtypes of SDAT. Kaye et al (1988,a) studied CSF neurochemistry in 32 patients with SDAT - eight with
myoclonus and 24 without. All patients satisfied NINCDS-ADRDA
criteria. Patients with myoclonus were more severely demented (as
assessed by the MMSE) and had larger lateral and third ventricles
than those without myoclonus. Duration of dementia did not
differ significantly between the groups, but the myoclonic
subgroup had a younger age of onset (54.0 years compared to 63.4
years). The following biochemical measures in CSF were
significantly lower in the myoclonic subgroup - homovanillic
acid, biopterin and 5 hydroxyindole acetic acid. To take into
account severity of dementia, the authors examined two subgroups
matched for cognitive impairment (N=7 in each group). The groups
became matched for age, age of onset, and lateral ventricular
size. However, the significance of the neurochemical differences
remained.

In another study, the same group (Kaye et al, 1988b)
examined two groups of patients with SDAT - one with
extrapyramidal signs and one without. Lumber punctures were
performed in 27 SDAT subjects without extrapyramidal signs, ten
SDAT subjects with extrapyramidal signs and 14 age-matched
controls. The following neurotransmitters were measured -
homovanillic acid (HVA), biopterin, 5-hydroxyindole acetic acid
(5 HIAA) and 3 methoxyl 4 hydroxy phenethyleneglycol (MHPG).
In addition, plasma MHPG was measured to obtain a corrected value
which was said to reflect more accurately the CNS contribution of
total MHPG. Taking the SDAT group as a whole, only CSF
Homovanillic acid was significantly lower when compared to the
age-matched controls. A separate analysis showed no difference
between levels of CSF HVA in patients without extrapyramidal signs and controls suggesting that the difference seen in the group as a whole was entirely due to SDAT patients with extrapyramidal signs. This latter group was more demented (as assessed by the MMSE). To counteract this factor, the authors matched, for degree of cognitive impairment, nine subjects who had extrapyramidal signs with ten subjects free from extrapyramidal signs. The decrease in CSF HVA remained significant but in addition CSF biopterin and 5 HIAA were significantly lower in the group with extrapyramidal signs. An analysis of the patients CT scans showed that this difference was not due to a difference in cerebral atrophy.

The authors argued that these results strongly suggested that a subgroup of SDAT patients with extrapyramidal signs existed, characterised by more severe disease, more rapid deterioration (although no evidence was presented in support) and a distinct neurochemical profile. The results of two post-mortems on patients with extrapyramidal signs were given. One had changes of AD and Parkinson's Disease and the other had multisystem atrophy. Thus, the heterogeneity of patients within the subgroup showing extrapyramidal signs was emphasised. One methodological flaw existed in the study. Although CSF was extracted using a very thorough protocol, the possibility of concomitant drug effects was not properly taken into account. Although patients were drug free for two weeks before the examination, no mention was made of drug treatment prior to that time. As the patients with extrapyramidal signs were more demented, it is possible that they were on drugs to control
behavioural problems (such as phenothiazines). Since these drugs remain in the body for weeks or months, a washout period of two weeks might be inadequate. However, this cannot be overcome easily and does not detract significantly from the findings.

Jorm (1985) made two important points regarding heterogeneity defined by neuropathological and neurochemical data. First, differences in severity of a variety of characteristics does not necessarily mean that qualitative subtypes exist. Quantitative differences would explain most of the observations in the studies described in this section. Quantitative subtypes may exist but no data have yet been published to make a definitive judgement on this. Whilst some authors (eg Rossor et al, 1984) have argued that late onset cases may appear less severe because they are dying at a later stage, data such as those presented by Bird et al (1983) dispute this conclusion. Jorm (1985) suggested that another way to answer this question would be to examine early onset cases dying early in the disease (from causes other than AD) and to compare them to late onset cases. Second, all the studies (with the exception of that by Mayeux et al, 1985b) have examined cross sectional data. While it is possible to perform longitudinal studies on neuropsychological examinations, such studies on pathological data are impossible. However, neuroimaging techniques lend themselves to investigation of the results of neuropathological processes and can be repeated over time to follow the course of the disease.
2.9 NEURORADIOLOGICAL HETEROGENEITY

Naguib and Levy (1982a) followed 40 patients diagnosed as having senile dementia. CT scans were repeated between 18 to 36 months after the initial assessment. Two subgroups emerged - one showed increasing ventricular brain ratios over time while the other did not (this paper will be dealt with in more detail in Chapter 3.3).

Burns et al (1989) using Single Photon Emission Tomography (SPECT) and hexamethylpropyleneamineoxime (HMPAO) have shown differences within a group of 20 patients with DAT. Subjects with aphasia and apraxia (N=12) had lower cerebral blood flow bilaterally in the lateral temporal and posterior parietal cortices than patients without these features. The two groups were of the same age and had similar duration of dementia, suggesting that the differences were not merely a manifestation of severity of illness. The status of these subtypes with regard to longitudinal course has yet to be fully defined.

Martin et al (1986) reported the results of Positron Emission Tomography (PET) in 19 of the subjects who underwent neuropsychological assessment described in Section 2.3. The profiles were strikingly different in the groups. Those with global impairments showed no significant left/right differences in either frontal, temporal or parietal lobe metabolism. Subjects with word finding difficulty, but relative preservation of visuo constructive performance, had lower left temporal lobe metabolism and those with visuo-constructive impairment had lower metabolism in the right temporal and parietal regions.
Grady et al (1987) assessed 18F Deoxyglucose PET in 34 patients with DAT, 21 of whom had early onset disease. Right parietal lobe metabolism was significantly lower in the early onset group. This finding, along with the lack of difference found in the psychological test results (see Chapter 2.3) led the authors to postulate that early onset DAT had more cortical reserve ie despite metabolic deficits, cognitive function was intact.

2.10 SUMMARY

Clinical heterogeneity in DAT can be considered in terms of qualitative and quantitative subtypes, the former representing true clinical subtypes and the latter differences along a continuum from mild to severe disease. There is compelling evidence from a variety of clinical and other sources that considerable heterogeneity exists in DAT. The traditional dichotomy between age of onset below and above the age of 65 has shown that younger subjects have more aphasia and a shorter survival time than older patients. Detailed neuropsychological testing has revealed possible left hemisphere damage in younger patients and right hemisphere damage in the older group. Younger patients have also been shown to have right parietal hypometabolism compared to elderly subjects. Even when studies concentrate on either young or elderly patients alone, neuropsychological heterogeneity has been demonstrated with specific subgroups characterised by language, visuo-constructional and attentional focusing deficits.
Psychiatric symptoms are also important in suggesting clinical heterogeneity - the presence or absence of symptoms such as hallucinations, delusions, misidentifications or disorders of affect clearly distinguish clinical groups. Each is associated with a particular clinical profile and some have been found to have prognostic implications. Depressed DAT patients who come to post mortem have been found to have a neuropathology different from non-depressed subjects. Behavioural disturbances are traditionally associated with advanced dementia and are probably more indicative of quantitative subtypes. The Kluver-Bucy syndrome may indicate specific damage to the temporal lobes and so may be a clinical manifestation of a neuropathological subtype.

Although certain neurological signs (eg primitive reflexes) are common in both normal ageing and DAT, abnormalities such as myoclonus and extrapyramidal signs are associated with advanced dementia and with rapidly progressive disease. Low CSF levels of biopterin and homovanillic acid have been found in patients with extrapyramidal signs and myoclonus.

There is considerable genetic heterogeneity in DAT as evidenced by an association between agraphia and a positive family history of dementia (and in one study a negative association between a family history of dementia and aphasia). The new genetics offer the possibility of determining the gene (or genes) responsible for the clinical syndrome and thus the discovery of true heterogeneity.

Neuropathological and neurochemical studies support the hypothesis that DAT is a heterogeneous condition.
Neuronal counts in both the locus coeruleus and the basal nucleus of Meynert suggest that patients dying younger have a more severe loss. Neurochemical studies of cholineacetyltransferase (ChAT) and other neurotransmitters show similar results and ChAT levels have been shown to be lower in patients with a family history of dementia and with myoclonus. Platelet membrane fluidity appears to be a peripheral biological marker for a subgroup of DAT patients associated with an earlier age of onset (both in the probands and their affected relatives) and with a more rapid course. However, all neuropathological and neurochemical studies may be explained in terms of quantitative subtypes. Neuroradiological investigations show that neuropsychological profiles are associated with changes in regional cerebral glucose metabolism.
CHAPTER 3

THE NATURAL HISTORY OF SENILE DEMENTIA OF THE ALZHEIMER TYPE

3.1 INTRODUCTION

A review of the natural history of any psychiatric illness in the elderly must start with the pioneering work of Roth (1955). A satisfactory classification of mental disorders in the elderly was made and an assessment of their natural history performed. This reappraisal was deemed necessary in view of the increasing size of the problem and the fact that the success of the new treatments was challenging long held beliefs (eg those of Kraepelin) that psychiatric illness in old age was the inevitable consequence of underlying cerebral pathology. The case notes of 450 patients over 60 years of age admitted to Graylingwell Hospital in West Sussex during the years 1934, 1936, 1948 and 1949 were examined. Each case was assigned to one of five categories - affective psychosis, senile psychosis (approximately equivalent to Senile Dementia of the Alzheimer Type, SDAT), paraphrenia, acute confusion and arteriosclerotic psychosis (equivalent to vascular dementia). A follow-up study determined the status of the patients at six months and again at two years after admission (the two year follow up was performed only on the 1948/49 sample). Clear differences in prognosis were seen in the five groups. At six months, patients with a diagnosis of senile psychosis had the highest mortality of all - 58% were dead. After two years, the patterns were broadly similar to those at six months with the exception that, in the arteriosclerotic psychosis
category, the death rate had risen dramatically to 93% (the highest of the five groups). The mortality rate in senile psychosis had risen to 82%. It was found that women had a significantly lower mortality across all diagnostic groups (except confusional states). However, this finding was of statistical significance only in senile psychosis.

The study concentrated exclusively on hospital inpatients and no attempt was made to take into account cases seen as out-patients or on home visits. This selection tended to bias the results towards more severely affected patients. Also, little detail was given concerning the method of classifying cases. No mention was made of interrater reliability nor is it certain whether the rules for classifying the patients were set down beforehand. If they were not, knowledge of the outcome in a particular case may have introduced a significant source of bias. Despite these criticisms, the work is unique as it was the first to give a satisfactory classification of mental disorders affecting the elderly and as such its importance cannot be overemphasised.

The natural history of SDAT can be studied from two vantage points - survival studies giving information on mortality and thence the natural history and longitudinal studies following individual patients over time and assessing specific changes (eg in cognitive function or Computed Tomography (CT) scan appearances).
3.2 SURVIVAL

There have been many studies over the past 40 years examining the survival of elderly patients. Inevitably, questions of comparability arise due mainly to the different methods employed and to the different populations under investigation. Survival in dementia has been the subject of two recent excellent reviews (Christie, 1985, 1987). A summary of the relevant papers appears in Table 3.1.

One of the earliest inquiries into the fate of elderly hospitalised patients was by Camargo and Preston (1945). Six hundred and eighty-three first admissions to all the State Mental Hospitals in Maryland, USA, in the years 1938 to 1940 were followed up for three years. The main part of the paper concentrated on demographic characteristics (age, sex and race) but some information was provided about diagnosis. Forty-eight percent were said to suffer from senile psychosis - 70.7% of these were dying within three years. A higher death rate was observed in males. In view of the lack of diagnostic information, the work is of limited value to the present investigation. However, it was the first study to demonstrate the very high mortality in patients with senile dementia.

Post (1951) examined new admissions to an observation ward in four consecutive months during 1946. Of 214 patients, all over 60 years of age, 56 (26%) had functional disorders and 158 (74%) suffered from organic conditions. The latter group was not subdivided into different types of dementia. At the time of follow up, 42 months later, 61% of the organic cases had died. Death was more likely in patients with 'schizoid symptoms' than
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Key:
- 100: Not stated
- 1947-57: Community

Notes:
- Mortality in Senile Dementia of the Alzheimer Type

Table 3.1 (continued overleaf)
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in those with 'simple' dementia. It is possible that organic cases with a better prognosis (e.g., acute confusional states) were included, resulting in a mortality rate less than expected had only 'senile dementia' cases been assessed.

Roth and Morissey (1952) examined the case-records of 150 patients admitted to Graylingwell Hospital (in West Sussex) during 1948. A diagnosis was made retrospectively on information in the case-records (not necessarily corresponding to the diagnosis of the consultant in charge). Follow up was performed either by letter or by a visit from a psychiatric social worker. 24% of the sample were diagnosed as having senile psychosis. Six months after admission, 53% of these were dead (compared to 22% of the whole sample) and two years after admission 73% were dead (compared to 37% of the whole sample). Increased mortality was seen in males with senile psychosis—six months after admission, 75% were dead (compared to 46% of females) and after two years, 88% were dead (compared to 75% of females). This paper was clearly the forerunner of the later work (Roth, 1955) which put the nosology of mental illness in the elderly on a firm footing. There was no information on how a particular diagnosis was reached and it was stated that psychometric testing was available only on a small number of the patients.

Kay (1962) studied patients who had been admitted to the Psychiatric Hospital, Stockholm during the years 1931-1937. Patients were divided into 5 groups: - senile dementia, arteriosclerotic dementia, late paraphrenia and two groups of patients with affective disorder (onset before and after the age
of 60 years). This division was made on the basis of psychiatric symptomatology. Comparing the mortality rates with figures for the standard population (mortality rate 1.0), Kay showed that survival in senile dementia was 0.23 men and 0.33 for women. The mean survival time from admission to death was 2.6 years for men and 2.3 years for women. Patients admitted over the age of 70 had a higher life expectancy than those admitted between the ages of 60 and 70. Non-demented psychiatrically ill patients had a life expectancy only marginally less than the general population. Although the main aim of the paper was to examine the part played by organic cerebral disease in the genesis of mental disorder, the study demonstrated effectively the very significant decreased life expectancy in subjects with senile dementia. Although the two year mortality rate was smaller (68% compared to 82%), the rest of the results confirmed Roth's (1955) work.

Kay and Bergmann (1966) reported a four year follow up study of a group of elderly patients living at home. The main aim of the paper was to examine the relationship between physical and mental health in old age. Twenty-nine patients (10% of the total) had been given a diagnosis of 'organic brain syndrome', which included both acute and chronic conditions. However, for practical purposes, the cases can be regarded as due to chronic conditions (Bergmann, personal communication). Follow-up revealed that 69% of the sample had died (79% of the men and 60% of the women). It was found that both organic and functional illnesses in men were associated with a mortality rate higher than normal control subjects. The study was important because it was one of the few community samples dealing with mortality. The death rate
was very similar to that in other reports. Goldfarb (1969) performed a seven year prospective study of 1280 subjects over the age of 64 in institutions (old age homes, nursing homes and state hospitals) in New York in 1957 and 1958. Those patients with 'chronic brain syndrome' (diagnostic criteria not defined) were divided into 'moderate' and 'severe' (determined by a psychiatrist but not operationally defined). Patients with 'moderate' brain syndrome had a mortality rate of 23% and 88% at one and seven years respectively. Of those with 'severe' brain syndrome, 37% were dead after one year and 94% after seven years. From the late 1960's onwards, there was growing speculation that elderly demented patients were living longer than previously. Several authors addressed this question specifically. Shah et al (1969) reported on 38 patients with senile dementia admitted in the five years between 1955 and 1960 to Saxondale Hospital, Nottingham. The findings were not significantly different from Roth (1955), although the mortality rate was slightly less (at six months, 42% compared to 58%; at two years, 71% compared to 82%). As in other studies, it was found that women survived longer than men. These differences were most marked six months after admission (71% of women surviving compared to 20% of men). Two years after admission the gap had narrowed, the additional deaths being all female (32% of women surviving, 20% of men surviving).

Gruenberg (1978), in reviewing the epidemiology of senile dementia, quoted his own work concerning the Lundby study in Southern Sweden. He looked at two cohorts of demented patients,
1947-57 and 1957-67. Although the number of cases was small (14 and 27 respectively) the differences were quite striking. All the cases in the 1947-57 cohort were dead after six years but nearly 20% of the 1957-67 cohort were alive after ten years. The author emphasised that this apparent increase in survival could not be explained in terms of an increase in survival of the general population or in a change of diagnostic criteria. The increased prevalence rate of senile dementia observed in the 1957-67 cohort could be explained entirely in terms of increased survival, not of increased incidence. The main drawbacks to the study were the small numbers involved and the lack of diagnostic information given on the groups.

Kaszniak et al (1978) presented data on 47 hospitalised patients and their mortality one year after hospitalisation. While the title of the paper suggested that it dealt with subjects suffering from pre-senile and senile dementia, it included patients with hypertension, an abrupt onset and a fluctuating course. In this way, patients with significant vascular disease were involved. In view of these drawbacks and the fact that the follow up was incomplete (over one-quarter were lost to follow up after one year), the contribution of the study was limited. However, two findings of interest emerged. First, mortality was associated with EEG abnormalities but not with cerebral atrophy as assessed by CT scan, and second, some cognitive deficits, in particular expressive aphasia, were associated with increased mortality.

The question of increased survival in SDAT was addressed by Thompson and Eastwood (1981) who examined data from a home for
the aged over a ten year period from 1969 to 1978. Patients were categorised according to their diagnosis on admission or discharge and those categorised as "senile", "senile dementia", "pre-senile" or "Alzheimer's Disease" were examined. The percentage mortality rate in four time periods (0-6 months, 6 months-2 years, 2-4 years and over 4 years) following admission to the home was calculated for each year. There were large variations (eg 5% dying within 6 months in 1971 compared to 43% dying within 6 months in 1978). However, none of the findings were significant and no particular trend emerged over the years. The authors noted no apparent increase in survival time. They recognised that other factors might have influenced their results. They examined the age and sex composition of the residents and ascertained whether any change in admission policy had taken place. Although there had been no significant changes during the period, the study may have missed more subtle variations. The authors recognised this and other limitations of the study, not least the accuracy of the diagnoses given. They were appropriately cautious in their conclusions.

Duckworth et al (1979) examined 100 patients admitted to hospitals in Toronto, of whom 23 were diagnosed as having senile dementia. Carefully excluded were patients in whom physical illness had been erroneously diagnosed as mental illness. The authors compared the mortality rate to that described by Roth (1955). After six months, only 13% were dead (compared to Roth's 61%) and the two year mortality was 48% (compared to Roth's 84%). Statistically, both differences were highly significant.
Mortality figures for 'demented' patients (including those with vascular dementia) were given for three and four year mortality and so cannot be compared directly to the group at six months and two years for senile dementia only. Median life span for the demented group as a whole was three years and five months, while for the group with senile dementia, it was just over two years. This finding confirmed the better prognosis for patients with vascular dementia who were included in the group. The paper did not explain why the prognosis had improved so markedly compared to Roth's (1955) work but concluded that 'treatment facilities' had improved for the organic conditions. Although a genuine reduction in mortality may have been demonstrated, the two studies were incomparable in several respects. The Canadian work was prospective, used different diagnostic instruments, specifically excluded patients with severe physical illness and took place in a different country, two decades after Roth's work. However, other workers have sought to replicate Roth's findings using more comparable methods.

Blessed and Wilson (1982) applied Roth's (1955) criteria to 320 patients aged 65 and over admitted to St. Nicholas Hospital in Newcastle in 1976. 90% were successfully allocated to one of the original five categories. 30% of the cases were diagnosed as having senile dementia (equivalent to the original 'senile psychoses' in Roth, 1955). The mortality at six months was 31%, half that of Roth's (1955) study. This change was highly significant. Mortality at two years had risen to 68% compared to Roth's 82%, not a significant difference. There was an increase in the overall numbers of patients admitted - notably elderly.
women with senile dementia. The highly significant difference in
mortality at six months with a non significant difference at two
years suggested that treatment available immediately on admission
to hospital (eg antibiotics) improved short term prognosis but
had little effect in the long term. Also, the fact that patients
in Blessed’s study were older (16% over 80 years compared to 5.5%
in Roth’s study) may have been a contributory factor to increased
mortality, leading to a narrowing of the gap at the two year
follow-up.

Christie (1982) took great care to ensure comparability
between his study of admissions to Crichton Royal in 1974-1976
and that of Roth’s (1955) Graylingwell sample. It was necessary,
in view of current practice, to examine those over 65 in the
Crichton Royal sample. Roth gave figures by age only in ten year
cohorts. Therefore, in order to obtain directly comparable
groups, Christie looked at patients 70 years and over and
extrapolated the equivalent sample from Roth’s data. In
addition, as noted previously, two year follow up was performed
only on Roth’s 1948-1949 group. The net effect was that only 143
of the original 450 Graylingwell subjects were used as a
comparison group. The death rate at six months and two years for
the Crichton admissions was 15% and 50% respectively. The
Corresponding figures for the Graylingwell admissions were 63%
and 88%. Table 3.2 summarises the data from Christie (1982),
comparing mortality rates in senile dementia to that of Roth
(1955) – the significance levels have been calculated as they do
not appear in the original paper. They show, quite strikingly,
the improvement in survival between the two studies. Christie argued cogently that the studies were comparable though separated by 25 years during which time significant social, medical and demographic changes had taken place. Evidence was presented to show that the two hospitals were similar in their admission policy, diagnosis and outcome which further strengthened his argument. Christie (1982) therefore seemed justified in claiming that the differences were due to a genuine change in the natural history of mental disorder.

**TABLE 3.2**


<table>
<thead>
<tr>
<th></th>
<th>NUMBER OF PATIENTS DEAD AFTER SIX MONTHS</th>
<th>NUMBER OF PATIENTS DEAD AFTER TWO YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DEAD</td>
<td>ALIVE</td>
</tr>
<tr>
<td><strong>GRAYLINGWELL</strong></td>
<td>40</td>
<td>24</td>
</tr>
<tr>
<td><strong>CRICHTON</strong></td>
<td>15</td>
<td>85</td>
</tr>
<tr>
<td><strong>(1974-1976, CHRISTIE,1982)</strong></td>
<td></td>
<td>Chi-Square X=39.5</td>
</tr>
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<td></td>
<td></td>
<td>df=1, p&lt;0.001</td>
</tr>
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</table>
Whitehead and Hunt (1982) followed 45 cases of 'chronic brain syndrome' (not further defined) for a period of five years after admission. The death rate in the first year for those aged 75 and over was 42%, and for those aged 64-75 the rate was 24%. The combined death rate for all ages was 35% after one year and 77% after five years.

The drawbacks of assessing survival on hospital based populations have been noted (Christie, 1987). These subjects represent a biased sample. It is possible that mortality is overestimated when data are obtained from this population. Molsa et al (1986) followed 218 patients with DAT from a community sample - all subjects alive on a particular prevalence day were traced six years later. Survival in DAT was 21.1% compared to the expected rate of 48.5%. The mean duration of illness was 5.7 years. Mortality was independent of age but was greater with increased severity of dementia. The study confirmed, in a representative community sample, that DAT was a malignant condition.

This "malignant" aspect of DAT has been addressed specifically by two authors. Katzman (1976) emphasised the poor prognosis and made the point that as DAT was often not stated on the death certificate, both its prevalence and its contribution to the death rate were being seriously underestimated. Go et al (1978) entitled their study "The malignancy of dementias". A large group of patients (N=982) had all undergone post mortem examinations in the University Hospital in Geneva over a ten year period. Survival time for those with AD (proven at post mortem) was one third that of the normal population and was 10% of that
expected from the time of admission to hospital. The presence of neurofibrillary tangles in the neocortex was associated with a longer survival time.

More recent studies on survival have taken a slightly different approach. Instead of reporting comparative survival rates, some have used more sophisticated statistical tests in an attempt to identify specific factors within groups which are predictive of survival.

An early contribution to this field was by Naguib and Levy (1982a). Forty patients with SDAT who had been studied in an earlier CT project (Jacoby and Levy, 1980a) were followed up for a mean of 29 months. One patient could not be traced, 27 had died and 12 survived. The deceased group had performed worse on a scale of parieto-temporal dysfunction, suggesting that parietal lobe changes were an indicator of a poor prognosis (thus confirming the earlier work of McDonald, (1969) and Hare, (1978, see Chapter 2.3). The work of Constantinidis (1978) suggested that subjects with parietal lobe signs had a better prognosis than those who did not show the signs. However, the younger age of onset of the former group and the failure to take age into account in the analysis means that their conclusion could not be validly drawn.

Barclay et al (1985,a) used life table analyses to compare survival times over five years in patients with three types of dementia - DAT (N=199), MID (N=69) and 43 patients with "mixed" DAT/MID. Fifty per cent survival for the groups was 3.4 years for DAT, 2.6 years for MID and 2.5 years for the mixed category.
These results confirmed (using a powerful statistical technique) the poor prognosis in DAT compared to normals but also emphasized the even worse prognosis in vascular dementia. It is interesting to note that patients with mixed dementia had a prognosis almost identical to that of the pure vascular group.

In an accompanying paper (Barclay et al, 1985b), the same group presented a more detailed analysis of the DAT population. They were divided into subgroups, depending on the presence or absence of a particular characteristic. Lowered survival was associated with being male, having an age of onset of less than 65 years and having a high rating on a behavioural abnormality scale. Duration of illness, cognitive function and the presence of vascular disease had no influence on survival. This study confirmed the work of Seltzer and Sherwin (1983) by showing that an early age of onset had a significant negative effect on survival but, surprisingly, found that impaired cognition had no such effect. The authors postulated that this result was due to the relative insensitivity of the instrument used (The Kahn-Goldfarb Mental Status Questionaire, Kahn, 1960).

McLaren et al (1986) used two cognitive tests (the Paired Associate Learning Test (PALT, Inglis, 1958) and the cognitive section of the Clifton Assessment Procedures in the Elderly, CAPE) and one behavioural test (the behavioural section of the CAPE) to predict outcome in 107 elderly demented patients. The non-survivors had worse scores only the "easy" tests of the PALT and the CAPE; in the other tests there were no differences between those patients who died and those who survived. The population under study included subjects with both vascular and
degenerative dementia and served to emphasise the poor prognostic significance of cognitive impairment.

Heyman et al (1987) confined their investigations to early onset DAT and assessed predictive features of institutionalisation and death. The study had the advantages of being prospective with 100% follow up and also that all the patients satisfied the NINCDS/ADRDA criteria for DAT. Death was predicted by poor cognitive function (particularly language dysfunction) and overall dementia ratings. Age had a significant modifying effect - the younger the patient, the greater the risk of death for the same degree of cognitive impairment. The Cox proportional hazards model and the Kaplan-Meier technique were used to show that aphasia was associated with institutionalisation for younger subjects but not for older ones.

Christie and Wood (1988) described the course of the illness in two groups of SDAT subjects - those aged 65 to 74 years and those 85 years old and above at the time of their terminal admission to hospital. The two groups were significantly different with regard to survival. The older group had a more benign course, surviving for at least 70% of their disease outside the hospital. Once admitted, however, survival time was short. In contrast, the younger group spent about 50% of their time in hospital and survived longer than the older group after admission. A behaviour rating scale correlated with survival in the young group but not in the older subjects. Christie and Wood (1988) presented compelling evidence of the differences in survival between young and old SDAT patients. The differences did
not appear to be due to social factors - the reasons for hospitalisation and the social characteristics of the two groups were similar, suggesting that the elderly group lived at home for a shorter time. The correlation of the behaviour scale with subsequent mortality may simply reflect the presence of items on the scale which measure more accurately disease characteristics associated with dementia in the young but not in the elderly (possibly due the confounding effect of more physical illness in the latter group).

Knopman et al (1988) reviewed the survival of 101 DAT subjects between two and four years after their assessment in a dementia clinic. Using the Kaplan-Meier technique, it was found that 92% of subjects with mild dementia were alive after three years compared to 69% with advanced dementia (severity of dementia was defined as a score of above or below 16 on the Information, Memory and Concentration scale (IMC), Blessed et al, 1968). Being male and rated as irritable or exhibiting nocturnal disruptive behaviour were associated with significantly higher mortality. The study confirmed clinical sense and suggested that disruptive behaviours may be specifically identified which are predictive of death. One explanation is that behaviours such as "nocturnal wandering" and "irritability" may be indicative of confusional states, and therefore underlying physical illness, leading to a higher mortality.
2.3 LONGITUDINAL CHANGES IN COGNITION

Recognition of the decline in cognitive function associated with the progression of SDAT is so widely accepted that it is included as a defining characteristic in the major diagnostic schemata (McKhann et al, 1984; DSM IIIR, 1987). The rate of the decline depends on the population under investigation and on the assessment instruments employed. A summary of studies looking at longitudinal change in cognitive function appears in Table 3.3. Some assess cognitive change over a short period of only of a few weeks. These results cannot be considered real evidence in support of an investigation into the natural history of SDAT. They are mentioned briefly for the sake of completeness and because they raise interesting issues concerning the assessments used and methods employed. Studies in which the diagnostic criteria suggest that a significant number of subjects, without SDAT, have been included will not be discussed.

One of the earliest investigations into change in cognitive function was by Walton (1958). Walton reanalysed the results obtained two years previously on the Wechsler Memory Scale for patients in the placebo group of a six week trial of Parenterovite. All suffered from memory impairment, but the group included patients with both functional and organic diagnoses. The memory deficit in the former group was attributed to either a 'pseudodementia' (apparent dementia resulting from depression) or to the effects of prolonged hospitalisation. However, the author re-examined the case notes two years later in order to substantiate the diagnosis. Of 14 patients thought initially to have an organic dementia, three had changed
<table>
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<tr>
<th>NS</th>
<th>BDS</th>
<th>18-42 months</th>
<th>None</th>
<th>34</th>
<th>Trial and Grampian not stated</th>
<th>1986</th>
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<tr>
<td>NS</td>
<td>*</td>
<td>BDS</td>
<td>None</td>
<td>6 months</td>
<td>26</td>
<td>Little et al. HO</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>None</td>
<td>48 months</td>
<td>13</td>
<td>Kessels et al. V</td>
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<tr>
<td></td>
<td></td>
<td>CDR</td>
<td>None</td>
<td>30 months</td>
<td>43</td>
<td>Kessels et al. HO</td>
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<td></td>
<td></td>
<td></td>
<td>None</td>
<td>24 months</td>
<td>10</td>
<td>Naujoks and Levy HI</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Rabins et al. HO</td>
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<td></td>
<td>Mather and (1977) I HO</td>
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<td></td>
<td></td>
<td>(Cowan et al. (1979) HO</td>
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<td></td>
<td></td>
<td>Kendrick et al. (1972) HO not stated</td>
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<td>Marion (1978) HI</td>
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**Table 3.3 (continued overleaf)**
**Key:** I = may contain subjects with dementia other than Alzheimer's disease.

<table>
<thead>
<tr>
<th>Measure of Cognitive Function</th>
<th>Group</th>
<th>StudySubjects</th>
<th>Population of Study</th>
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<tbody>
<tr>
<td>Short Portable Mental Status Questionnaire</td>
<td>Control</td>
<td>16</td>
<td>48 months</td>
</tr>
<tr>
<td>Short Portable Mental Status Questionnaire</td>
<td>Control</td>
<td>77</td>
<td>3 months</td>
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<tr>
<td>Short Portable Mental Status Questionnaire</td>
<td>Control</td>
<td>43</td>
<td>6 months</td>
</tr>
<tr>
<td>Short Portable Mental Status Questionnaire</td>
<td>Control</td>
<td>26</td>
<td>3 months</td>
</tr>
<tr>
<td>Short Portable Mental Status Questionnaire</td>
<td>Control</td>
<td>496</td>
<td>12 months</td>
</tr>
<tr>
<td>Times Psychological Test (from BPS)</td>
<td>Control</td>
<td>161</td>
<td>26 months</td>
</tr>
<tr>
<td>Times Information, Memory and Battery, PTH</td>
<td>Control</td>
<td>126</td>
<td>12 months</td>
</tr>
<tr>
<td>Times Information, Memory and Battery, PTH</td>
<td>Control</td>
<td>54</td>
<td>None</td>
</tr>
<tr>
<td>Not Specified</td>
<td>Control</td>
<td>0</td>
<td>None</td>
</tr>
</tbody>
</table>
sufficiently to be rediagnosed as having functional disorders. One patient considered to have senile dementia had become depressed. The reanalysis confined itself to the 12 patients diagnosed as having a definite organic disorder two years after the trial. Scores on the Wechsler Memory Scale did not deteriorate significantly in the organic group over the six week trial. When compared to the functional group, it was found that the difference in change was significant between the two groups. Although the diagnostic criteria used are open to criticism, the follow up was a clever way of validating the diagnosis. In that sense, it is similar to the work of Roth (1955).

Kendrick (1972), in a paper discussing the theoretical assumptions behind the Kendrick Battery of tests, examined 38 demented patients with the Digit Copying Test (DCT) and the Synonym Learning Test (SLT). The main aim of the paper was to assess different cognitive deficits in three groups of patients - demented, depressed and those with pseudodementia and to compare them with normal elderly controls. It was found that the DCT (a test of sensorimotor performance) was significantly decreased compared to controls only in the demented group. The SLT (a test of intermediate memory) was similarly lowered in subjects with pseudodementia compared to the normals and the depressed. The demented group had the lowest scores. Over a six week test-retest period, some improvement was noted in cognitive function of the group with pseudodementia but no change in the others. The short duration of the study (six weeks) and the insensitivity of the assessment (ie a grading of 'organic' or 'non-organic')
detracted from the importance of this conclusion. The non-significant change cannot be assumed to be a true finding and may have reflected inappropriate methods. However, one may infer from the results that these tests showed a consistency when administered to patients over a period of weeks, emphasising their test-retest reliability.

Cowan et al (1975) presented psychometric data from the US/UK Diagnostic Project from Queens County, New York and from Camberwell, London. Patients were assessed using the PALT, the Digit Copying Test (DCT, Kendrick, 1965) and the Bender-Gestalt Test (BG, Shapiro, 1956). In an attempt to compare diagnostic practice between the two countries and to validate the Geriatric Mental State Schedule (Copeland et al, 1976) as an instrument capable of differentiating depression and dementia, the three psychological tests were administered one week, one month and three months after admission to hospital. A comparison using nonparametric statistics showed no significant change in the demented group over the three month period for either country. As age and baseline score differed in patients with dementia and affective disorder, these two variables were used as covariates in a multivariate analysis of covariance. It was found that in all three tests, there was significant differential change in patients with dementia and affective disorder, the former showing significantly less improvement than the latter.

These early studies (Walton, 1958; Kendrick, 1972; Cowan et al, 1975) suffer from similar drawbacks which diminish their ability to support the hypothesis that cognitive function declines in SDAT. First, in common with many other studies on
dementia, the diagnostic criteria are not provided. It is therefore probable that patients with dementia due to causes other than SDAT were included. Second, the duration of the follow up period is too short to assess change adequately. Third, duration of dementia is not given and so it is difficult to judge whether patients are in an early or late stage of the illness where ceiling and floor effects may be anticipated. These criticisms cannot be levelled with the same force at subsequent investigations.

Whitehead (1977) reported follow-up data on 15 patients with chronic brain syndrome who had been assessed on two occasions, one year apart. Many different ratings were made of behaviour, mobility and self-care skills as well as cognitive function. Performance on the following cognitive tests showed a significant decline over the test period: an overall clinical rating of intellectual impairment; WAIS vocabulary; digits forward; general orientation; general events; total learning score and a parietal scale. Verbal fluency showed no change. This report was one of the first studies to show a well documented decline in cognitive function in SDAT over time. However, it was possible that patients other than those with degenerative dementia were included. Also, data were available on only a small number of the total, hence there may be a degree of sample bias. One further criticism was that some of the tests used had no proven reliability or validity.

From the 1980's onwards, more rigorous clinical criteria for SDAT were employed and follow up periods tended to be longer.
Rabins et al (1984) followed patients with dementia, pseudo
dementia and depression for two years. They demonstrated that
using the MMSE (Folstein et al, 1975) patients with dementia
deteriorated significantly over time (mean initial MMSE 11.2,
mean after two years, 4.2). Patients with pseudodementia
improved on the MMSE but depressed patients remained the same.
This sophisticated study was the first demonstration of the
validity of the MMSE as a measure of cognitive decline in
dementia.

Naguib and Levy (1982,a) investigated 10 of the 12
survivors of an earlier study (Jacoby and Levy, 1980a) and
performed repeat psychological tests, using the Mental Test Score
(MTS, Hodkinson, 1973) and CT scans after two years. All patients
satisfied strict criteria for SDAT. A summary of the MTS results
is shown in Table 3.4.

**TABLE 3.4**

**SUMMARY OF FINDINGS ON MENTAL TEST SCORE IN NAGUIB AND LEVY (1982,a).**

<table>
<thead>
<tr>
<th></th>
<th>Initial MTS Mean(SD)</th>
<th>Final MTS Mean(SD)</th>
<th>Difference in MTS</th>
<th>Significance of change in MTS *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (N=5)</td>
<td>14.4(3.6)</td>
<td>13.6(3.0)</td>
<td>-0.8 £</td>
<td>p=0.345</td>
</tr>
<tr>
<td>Group 2 (N=5)</td>
<td>14.0(2.7)</td>
<td>4.6(3.3)</td>
<td>-9.4 £</td>
<td>p=0.043</td>
</tr>
<tr>
<td>Total (N=10)</td>
<td>14.2(3.0)</td>
<td>9.1(5.6)</td>
<td>-5.1</td>
<td>p=0.016</td>
</tr>
</tbody>
</table>

Key: MTS- Mental Test Score.

* - assessed by Wilcoxon matched-pairs signed-ranks test.
£ - significance of difference in MTS between group 1 and 2,
p=0.008 (Mann-Whitney U test, two tailed).
Two subgroups emerged - one with no deterioration in MTS and a small increase in Ventricular Brain Ratio (VBR, Group 1) and a second group with a significant deterioration in MTS and increase in VBR (Group 2). The number of subjects was small and may be a biased sample in that they represented survivors who had a milder form of illness than those who died (Naguib and Levy, 1982b). Despite the small sample, this study raised the exciting possibility of two subtypes of SDAT - one showing significant cognitive decline over time, the other showing no decline.

Berg et al (1984) classified 43 SDAT subjects as having mild dementia using the CDR (Hughes et al, 1982). They followed the sample over 12 months to assess who would progress to moderate or severe dementia. Twenty-one patients did deteriorate and while EEG and CT measures were not helpful in predicting which patients would deteriorate, the Digit Symbol Substitution Test of the WAIS and an aphasia test predicted correctly the subsequent stage of dementia in 95% of cases. These results essentially replicated the work of Naguib and Levy (1982b) in showing the poorer prognosis in subjects with aphasia.

Using a new rating scale for DAT (the Alzheimer's Disease Assessment Scale, ADAS), Rosen et al (1984) retested ten subjects over a period of one year. The criteria were stated in the paper and approximated to DSM IIIR criteria for degenerative dementia. On the cognitive subscale of the ADAS, the ten DAT subjects deteriorated significantly over one year. In contrast, normal elderly subjects showed no decline over the year.

Knesevich et al (1985) described 43 patients with DAT
diagnosed in accordance with the NINCDS/ADRDA criteria (McKhann et al, 1984). The patients were divided into those with, and without, aphasia and were followed up for 30 months. All patients were described as 'mild' (category 1) on the CDR (Hughes et al, 1985), at the start of the study. For ease of reference, the results are summarised in Table 3.5.

**TABLE 3.5**

**SUMMARY OF FINDINGS OF KNESEVICH ET AL (1985)**

<table>
<thead>
<tr>
<th></th>
<th>AD patients- with aphasia</th>
<th>AD patients- without aphasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (N)</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>Errors on BDAE</td>
<td>9.55</td>
<td>1.08</td>
</tr>
<tr>
<td>Errors on BDS</td>
<td>5.30</td>
<td>4.61</td>
</tr>
<tr>
<td>At 30 month follow up:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N progressed to CDR 2</td>
<td>23</td>
<td>11</td>
</tr>
<tr>
<td>N developing aphasia</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Progression in BDS</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>N dead at follow up</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>% risk of developing dementia to age 79:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siblings of probands</td>
<td>7.5</td>
<td>26.3</td>
</tr>
<tr>
<td>Parents of probands</td>
<td>17.7</td>
<td>34.5</td>
</tr>
</tbody>
</table>

Key: BDAE - Boston Diagnostic Aphasia Examination  
BDS - Blessed Dementia Scale  
CDR - Clinical Dementia Rating  
NS - not significant at p<0.05.
After 30 months, 80% of the sample had progressed to moderate dementia (CDR 2). 96% of those with, and 58% of those without, aphasia had progressed (statistically significant at $p < 0.001$). A deterioration in cognitive performance, as measured by the BDS, had occurred in both groups, with a tendency (not statistically significant) to greater impairment in the aphasic group. The work was important in that it documented progressive cognitive decline in a rigorously selected sample of DAT patients. It also showed clear differences in patients with and without aphasia. However, there was incomplete information given on the two cognitive scales used, possibly as not every subject was tested. The method of evaluating non-progression on the BDS was to define an error score regardless of initial score which may have masked a true decline.

An uncontrolled descriptive study of the decline in 13 patients with DAT was presented by Dastoor and Cole (1985). The Hierarchic Dementia Scale (HDS, Cole et al, 1983) was used to trace the natural history of the patients over four years. There was wide inter-subject variation in the rates of decline, all but one subject showing a decrease over time. While there was a trend for younger subjects to decline more rapidly, there were many exceptions. This descriptive study was useful in that it emphasised the variability of cognitive decline. However, the small numbers involved and the relatively unknown scale employed makes it difficult to draw definite conclusions.

The early studies described in this section (Walton, 1958; Kendrick, 1972; Cowan et al, 1975) showed no decline in patients with SDAT over a number of weeks. Although no decline
was shown, there was a significant absence of a 'practice effect' in demented patients. This aspect was examined in detail by Little et al (1986) using two different subtests of the PALT (Inglis, 1958). Memory was assessed using both a repeated and parallel form of the PALT in 26 subjects fulfilling strict criteria for SDAT. If new learning were possible in SDAT, performance on the former (where the same material was repeated) would have shown a different pattern to that on the latter (where different material was repeated). Five test sessions over six months did show that, where items were changed (the parallel form), there was a progressive deterioration in performance. In the repeated form, scores remained the same. Thus, this 'masking of deterioration' using the repeated form suggested that, at least to some extent, new learning was shown in SDAT patients. This observation has important implications for repeated neuropsychological assessment in SDAT subjects.

Botwinick et al (1986) studied 18 DAT patients extensively using 16 cognitive tests annually over four years (although curiously these were referred to as 'behavioural tests'). All 18 were rated as CDR 1 (ie mild dementia) at the start of the study. The neuropsychological battery consisted of the Wechsler Memory Scale (mental control and logical memory), digit span backwards and forwards, associate learning, word fluency, Boston naming, visual retention (recall and copying), Bender Gestalt, four subscales of the Wechsler Adult Intelligence Scale (information, comprehension, digit symbol and block design), the Trailmaking test (Part A) and Crossing-Off. All tests showed significant
decline in the DAT patents over the four years, the greatest
decline being in logical memory (79%) and the smallest in digit
span forward (51%). The control group showed no significant
decline. A subgroup of five SDAT patients declined only on the
Bender Gestalt test, with no significant deterioration in the
other measures. They did, however, show more decline than normal
controls in three other tests. Four possible explanations for
the results in this subgroup were put forward:

1) that decline in SDAT has a normal distribution and the
group was simply at one end of the distribution;
2) that the group had milder disease (although the same CDR
rating) at the start of the study. This theory was partly
supported by an analysis of the initial scores;
3) that although they had the same CDR rating, their disease
was of shorter duration than the others, and therefore, in
time, they would 'catch up' on their deterioration. The
results did not, however, support this and
4) that they represented a clinical subgroup of SDAT patients.

Reisberg et al (1982) applied the Global Deterioration Scale
(GDS) to 106 community residents and studied them prospectively
for three years. Although "dementia of the Alzheimer type" was
discussed, no specific information (other than a description of
the exclusion criteria) was given. Thus, it was not possible to
be certain of the precise diagnostic criteria employed. The main
finding was an increased risk of death and institutionalisation
in those subjects rated as 'deteriorated' on the GDS.

The most recent five papers to be described in this section
represent a new level of enquiry into the longitudinal assessment
of SDAT. Patients were diagnosed using the most stringent criteria for the clinical diagnosis of DAT (McKhann et al, 1984). Determination of decline was no longer based on simple descriptive statistics comparing an initial score and a final score on a particular cognitive test. Complicated statistical methods were employed to calculate the predictive value for decline of various cognitive tests and numerical values obtained to quantify rates of decline. Three of these papers present results which are part of large and well organised longitudinal studies into the natural history of SDAT.

Huff et al (1987) challenged the traditional view that early onset DAT progressed more rapidly than late onset disease. Data were collected on 165 consecutive out-patients attending a memory clinic. The authors found a bimodal distribution of age at onset of dementia, with one peak around 56-60 years and another around 68-70 with a relative trough occurring at 65. This led them to the conclusion that two discrete populations existed. Progression of the disease was assessed by the BDS, repeated at intervals of three months on 77 of the sample (the exact number of follow ups and their timing was not stated). There was no correlation between rate of progression and age of onset, chronological age or duration of dementia in the senile onset group compared to the presenile group. Also, although the two groups were of equal severity at the first examination, the senile onset subgroup had a significantly shorter duration of illness than the presenile subgroup. The report seemed to be at odds with traditional teaching (although agreed with a study
published in the same year by Grady et al (1987), discussed in Chapter 2.2) yet did not explore the possible explanations for the results. Information about the samples was inadequate and it was not clear if both the dementia scale and the IMC test of the BDS were performed. If both of these tests had been carried out, the functional and cognitive subscales should have been analysed separately. Also, fewer than half the patients received follow-up examinations. Consequently, the sample was not sufficiently representative. Despite these drawbacks, the paper contributed important information about age and rate of progression of early and late onset DAT.

Berg et al (1987) evaluated three scales in 43 patients with DAT over a period of 30 months. Only 26 patients completed the tests. The tests consisted of the BDS (the observed behaviour scale only, not the IMC scale), Pfeiffer's Short Portable Mental Status Questionnaire (SPMSQ, an 11 item scale testing mostly memory but having one item on concentration, Pfeiffer, 1975) and the Face Hand Test (FHT, Zarit et al, 1978). The CDR was used as a rating of severity of dementia throughout the study, all subjects starting with a rating of I (ie mild dementia). From the initial values on the three rating scales, it was not possible to predict how severely demented the patients would be at the end of the study. Indeed, the agreement between the CDR rating and the scores on the three questionnaires at the end of the study was far from convincing. Differential progression was found in the group - of the patients completing the study, five remained mildly demented, ten had progressed to moderate dementia and 13 had progressed to severe dementia. (The figures provided
in the paper did not tally, possibly because not every patient performed all of the tests). The authors claimed that their results provided evidence for heterogeneity within the SDAT group. This assumption seemed premature as the CDR is not a widely validated instrument. In addition, the findings were similar to those of Botwinick et al (1986). This similarity was not surprising as the samples were drawn from the same group of patients.

The same sample was described again by Berg et al (1988). On this occasion, the results were given of five brief questionnaires - the BDS (both the dementia scale and the IMC subscale), the SPMSQ, an aphasia battery and the FHT. In addition, the results of the "sum of boxes" was produced, thus giving a composite score ("sum") on each of six cognitive categories ("boxes"). This forms the basis of the CDR score. The natural history of the disorder was measured by the deterioration on the cognitive scores, age at death and age at placement in a nursing home. The method employed by Berg et al (1988) to indicate the deterioration in cognitive function was to report the results as percentiles, ie the percentage of the sample scoring above a certain level. In the majority of the tests, the ceiling level was reached by 50 months indicating that the disease had progressed to an advanced stage. Correlations between the various tests were low and this result led the authors to the conclusion that they each represented discrete cognitive defects. It is interesting to note that the correlation coefficients increased dramatically as the study progressed.
Four of the tests showed similar patterns of decline (the "sum of boxes", the BDS (both functional and cognitive components and the aphasia battery). The FHT showed great variability in the scores (i.e., even some mildly demented patients did badly on it) and the SPMSQ reached its ceiling very early on. Consequently, these two tests were considered unsuitable for the longitudinal assessment of SDAT. The authors' main conclusion from the paper was that the "sum of boxes" was the most informative measure to assess the natural history of SDAT. This conclusion did not seem justified as it was based on a relatively crude and insensitive scale such as the CDR. Some criticisms may be levelled at this paper, on the basis of the instruments used. The "sum of boxes" which was claimed to be the best instrument represents a clinician's rating of the degree of disability. As to be expected, the clinicians' rating showed deterioration as the disease progressed. The authors quoted reliability statistics for the CDR (which is derived from the "sum of boxes") but to claim that reliability statistics may be interchanged in this way seems presumptuous. The authors included tests which were dependent on the patient's performance in a test setting as well as scales relying on observer rating. The "sum of boxes" is a mixture of cognitive abilities (memory and orientation) and functional status. Although the various cognitive measures decline with time, the authors correlated this with the CDR which they employed as their "gold standard". Despite the complicated and involved method of its rating, the CDR is simply a severity scale of mild, moderate, and severe. Within the limitations indicated, the paper was valuable in that
it addressed the issue of which tests are most appropriate for use in the longitudinal assessment of SDAT.

Katzman et al (1988) presented results from one of the largest investigations into the natural history of SDAT. The annual rate of change in the IMC was assessed in 161 patients with either DAT or autopsy proven AD. Four different groups were studied — patients in a nursing home, patients attending a private practice out-patients service and two groups of volunteers involved in an ageing study and an AD Research Centre. All subjects were followed for at least one year. The IMC showed a ceiling effect on error scores of 24 and above. When subjects with these scores were excluded (leaving 142 subjects), two interesting results emerged. First, rate of change in the IMC score (an average of 4.4 additional errors per year) was not significantly different in the four sites. Second, the rate of change was independent of sex, education and most importantly, age. Thus, there was no evidence to support the hypothesis that a difference existed between early and late onset DAT (the age range of the sample was 52 to 96 years).

Two minor criticisms may be made of this important paper. First, the changes were calculated for the groups as a whole and no attempt was made to assess the significance of individual differences (eg by using a paired non-parametric statistic). Individual assessments would have provided important information about the differences in individual patients. Second, a case vignette was provided of a patient whose IMC score improved by five points throughout the year. The improvement was attributed
to the patient's habituation to the effects of large doses of Clonidine with which the patient's hypertension had been treated. This subject would not, in my view, have fulfilled the NINCDS-ADRDA criteria although the authors claimed that all their patients did so.

Ortof and Crystal (1989) reported the rate of cognitive decline over 12 months, as assessed by the IMC, in 54 patients with DAT. The average rate of increase was 4.1 Blessed points per year and showed a normal distribution. Age of onset, duration of illness and family history of dementia had no influence on the rate of progression. The absence of an effect on progression by age of onset agrees with earlier work (Grady et al, 1987; Huff et al, 1987) but the lack of an influence on progression by duration of illness disagrees with the study of (Thal and Grundman, 1986).

Recently, an interesting study has measured decline in cognitive function over time and has related it to a biochemical marker. Urakami et al (1989) studied 26 patients with SDAT and divided them into three groups, depending on their decline as measured by the Functional Assessment Staging method of Reisberg et al (1985). Eleven patients had a rapid decline, six an intermediate decline and nine a slow deterioration. CSF concentrations of acetylcholinesterase and somatostatin were measured in each of the three groups and compared to the levels in both younger patients with DAT and age matched controls. Activity of both neurotransmitters was decreased in the younger patients and in the SDAT subgroup who deteriorated rapidly. There was no difference in the CSF activity between the other SDAT
groups and the age matched controls. The CSF examination had been performed at entry to the study. This, coupled with the fact that CSF acetylcholinesterase is known to be relatively stable over time and independent of dementia severity, makes the findings most important and raises the exciting possibility of a biological marker to indicate subsequent course of the disease. The study requires replication on a larger sample.

3.4 LONGITUDINAL CHANGES IN COMPUTED TOMOGRAPHY SCANS

Very few studies have been done which have looked at longitudinal changes in CT scans over time. While a single CT scan is of limited diagnostic use, serial scans on individual patients have been performed in an attempt to improve diagnostic accuracy and to follow the course of the disease. Studies which have involved the longitudinal assessment of CT scans are summarised in Table 3.6.

Naguib and Levy (1982a) were the first to perform serial scans of patients with SDAT. Their findings (in ten patients) suggested that there were two subgroups of patients - one with relatively stable ventricular size and little deterioration of cognitive function over time, and the second with a marked increase in ventricular size associated with significant cognitive decline. Gado et al (1983) scanned 45 DAT patients one year apart. They found that a significant degree of ventricular enlargement occurred over that time but was not present in non-demented controls. They observed that computer-assisted volumetric measures of CSF space were a more sensitive indicator of change than linear measures. Brinkman et al (1984) showed, in
controls.

Verticulat

Partners. From

discrimination make

verticulat

increased.

Increased

Volume.

Twosubgroups emerged.

<table>
<thead>
<tr>
<th>INTERVAL</th>
<th>PATIENTS (FEMALE)</th>
<th>PATIENTS (MALE)</th>
<th>CONTROLS</th>
<th>CONTROLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLLOW-UP</td>
<td>70.8 (FEMALE)</td>
<td>62.8 (MALE)</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>6-60 months</td>
<td>71.2</td>
<td>12</td>
<td>6 female</td>
<td>12 male</td>
</tr>
<tr>
<td>62-200 weeks</td>
<td>76.0</td>
<td>27</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15-35 months</td>
<td>60.6</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>12 months</td>
<td>71.0</td>
<td>12</td>
<td>45</td>
<td>10</td>
</tr>
<tr>
<td>18-36 months</td>
<td>76.2</td>
<td>0</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

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Table 3.6---

Longitudinal CT scan changes in dementia of the Alzheimer type.
five patients with DAT, that the increase in ventricular size was significantly greater than in normal ageing. Bird et al (1986), in a unique study, re-scanned 27 subjects who four years earlier, had been part of the control group in another CT study (Jacoby et al 1980). A reduction in the MTS of more than three points was associated with an increase in VBR and lower attenuation numbers in the left thalamic region at follow-up. Luxenberg et al (1987) re-scanned 18 patients with DAT and 12 healthy controls from between six months to five years after the first scan. The increase in size of the lateral ventricles in male DAT patients was such that it completely separated the male group from the control group. Finally, de Leon et al (1989) found an annual increase in ventricular size of 9% in DAT patients compared with 2% in normal controls.

3.5 SUMMARY

It has been known for some time that elderly psychiatric patients have a much reduced survival time when compared to healthy age matched controls. Survival has been used to validate disease classification in old age psychiatry and patients with vascular or degenerative dementia, delirium or functional psychoses have demonstrated differing survival patterns. It is therefore reasonable to postulate the presence of subtypes of SDAT on the basis of different survival times. DAT has been described as a "malignant" condition and survival studies confirm that view, although there is some evidence to suggest that DAT patients are living longer than they did 20 years ago. Factors found to be associated with reduced survival include male sex,
younger age of onset, longer duration of illness and increased cognitive impairment and behavioural disturbance.

A progressive deterioration in cognitive function over time is one of the hallmarks of dementia and is a defining characteristic in most of the major diagnostic schemata. Cognitive function does not deteriorate significantly over a matter of weeks and testing at least three months apart is necessary to demonstrate significant differences. There is wide variation in the degree of cognitive decline. Several studies have reported a subgroup of patients in whom progression of cognitive impairment is very slow. Global ratings of dementia (which include measures both of cognitive and functional impairment) appear to be more effective at demonstrating decline than detailed psychological tests. CSF neurochemical profiles have been shown to be different in patients with differing patterns of decline.

Changes in CT scan appearances also take place over time. Subgroups have been found with some subjects who have virtually no longitudinal change in CT indices, but the majority of studies report significant increases in ventricular size (both in the third and lateral ventricles) and in CSF spaces over 12 months. The increase in third ventricular size has been shown to separate completely male DAT subjects from controls. Thus, a repeat CT scan may be of more diagnostic value than a single scan.
CHAPTER 4
METHODS OF THE CURRENT STUDY

4.1 PATIENTS

Recruitment

All patients were resident in the Camberwell Health Authority area in south east London (comprising the London boroughs of East Lambeth and South Southwark). All had been in contact with the psychiatric services based at the only two psychiatric hospitals in the area, the Bethlem Royal and Maudsley Hospitals (known as the Joint Hospital) and Dulwich Hospital. The patients recruited might be divided into two broad categories - those already in contact with the hospital services in October 1986 and those who had their first hospital contact between October 1986 and September 1988. Patients were recruited from the following sources -

Inpatients - patients admitted for assessment to the old age psychiatry wards at the Joint Hospital and Dulwich Hospital. After assessment, patients were discharged to their own homes, to private nursing homes or to Part III homes (local authority residential homes). A number continued in long stay hospital care either at Dulwich Hospital or at Cane Hill Hospital in Surrey (about 15 miles south of the catchment area). At the beginning of the study all those in hospital were included, resulting in a sizeable "backlog" of patients already in long-stay care, many of whom had been there for some years.

Day-patients - as an alternative to hospital admission some patients were seen on a day basis at the two hospitals. Such patients were generally less severely demented and disturbed than
inpatients. After assessment, they were discharged to either their own or residential homes. Contact was maintained through two local authority day centres where day care was provided (Holmhurst Day Centre for South Southwark and Stockwell Day Centre for East Lambeth).

Domiciliary Visits - a number of patients were visited at home at the request of their general practitioners. A regular review of domiciliary reports was performed to include these patients. However, the majority of these were normally referred as either inpatients or day-patients and only a minority circumvented the hospital system (eg occasionally a patient was seen on a domiciliary visit and referred directly to a Part III home).

Out-patients - a few patients were referred directly to out-patients and these were included.

Other sources of referral - contact was made with the local departments of geriatric medicine and neurology and referrals of patients for the study were requested. Two cases, one unknown to the psychiatric or medical services, were first degree relatives of patients in the study and were found following contact with the probands.

The referral of patients was often at the instigation of the consultant in charge of the case. The author had the advantage of personal acquaintance with the consultants responsible for the care of the elderly and all were keen to involve their patients in the research. It is considered, therefore, that the population examined was free of any significant sampling bias and
that virtually all patients in contact with the hospital services were included. It should be noted, however, that many patients with senile dementia are unknown to the hospital services and so this study does not claim to be representative of all elderly demented subjects.

**Inclusion Criteria**

Information, gathered from the source of referral concerning the history and clinical findings was used to assess whether or not the patient was suffering from senile dementia of the Alzheimer type (SDAT). If there was evidence to suggest that the patient, although demented, was unlikely to have SDAT (e.g., a clear history of cerebrovascular accident), the case was excluded. All other cases were considered. Initially, a letter of introduction was sent to the next of kin outlining the study and asking permission to visit and gather additional information. An interview was then arranged and the history evaluated. Following this, the patient was interviewed and examined physically.

The criteria employed in this study have been fully outlined previously (Chapter 1.3) and are those of the NINCDS/ADRDA (McKhann et al, 1984). A decision whether or not to include a case in the study was taken only after the relatives had been interviewed. If blood tests had not been performed as part of the patient's initial investigation, they were done at this stage. The justification for the use of these criteria is twofold. First, as has been demonstrated in Chapter 1.3, they are the best available and predict Alzheimer pathology at post mortem in 80% to 100% of cases. Second, as a measure of internal audit, the results of post mortem examinations of subjects in the current
study will be presented in Chapter 10.

The application of these criteria requires explanation on two points. First, it is stated that these are criteria for AD and purists would argue that these are not the same as criteria which should be used to diagnose Dementia (or Senile Dementia) of the Alzheimer Type. However, they are clinical criteria and as such define a clinical syndrome - Dementia of the Alzheimer type. I shall therefore use these criteria to define a syndrome in which one might expect to find Alzheimer pathology at post mortem. Second, one has to accept that attempts to predict pathology during life are often wrong. This uncertainty is present in every branch of medicine and is not unique to psychiatry. Thus, a clinical diagnosis of Dementia (or Senile Dementia) of the Alzheimer type accurately defines a clinical syndrome - whether or not Alzheimer pathology is found in all cases at post mortem is a separate issue.

4.2 ASSESSMENTS

The assessment procedure can be broken down into several sections-

Cognitive assessment - the main instrument used was the CAMCOG, which forms part of a larger assessment battery for the detection of dementia in the elderly, the CAMDEX (Roth et al, 1986). The CAMDEX (Cambridge Mental Disorders of the Elderly Examination) was developed to provide, in one assessment schedule, an approach to three related issues in the diagnosis and assessment of dementia - to give an accurate diagnosis, to provide a valid and reliable measure of the central feature of dementia ie cognitive
impairment and to devise a reliable rating scale of behaviour and adaptation in everyday life. The instrument consists of eight sections: an interview with the patient; a cognitive examination (the CAMCOG); interviewers' observations; physical examination; results of laboratory tests; record of medication taken; a section for additional information and a structured interview with an informant (the history schedule).

Roth et al (1986) presented details of the reliability and sensitivity/specificity of the CAMDEX. Interrater reliability (on 40 subjects) was between 0.83 and 0.94 for the sections. Using a total CAMCOG score of 79/80 out of 107, the sensitivity of correctly diagnosing an organic mental disorder was 92% and the specificity was 96% (sensitivity refers to the number of true positives ie 92% of cases scoring 79 or less were clinically diagnosed as having an organic mental disorder and specificity refers to the number of true negatives ie 96% of cases scoring 80 or above had been diagnosed as functionally ill). Actual figures for test retest reliability were not given but were described as "good".

The CAMCOG consists of 72 questions and is divided into several subsections, each testing one aspect of cognitive function. These are: orientation; language (comprehension and expression); memory (recall, recognition, retrieval of recent and remote information); attention and concentration; praxis (copying, ideational and ideomotor); perception; calculation and abstract thinking. The total score possible is 107. Additional questions are included to allow the Mini Mental State Examination
(MMSE, Folstein et al, 1975) and Abbreviated Mental Test Score (AMTS, Thompson and Blessed, 1987) to be computed. The MMSE is reproduced in Appendix 1 and the AMTS in Appendix 2.

The use of the CAMCOG in the present study was based on the second issue addressed by its developers - a valid and reliable measure of cognitive impairment. All the subjects involved in the study had already been clinically diagnosed as suffering from SDAT and all met the NINCDS/ADRDA criteria. Thus, the CAMCOG was not used as a diagnostic instrument but as a rating of the degree of dementia. The range of cognitive functions assessed made it superior to the other shorter tests available (the MMSE and AMTS). As the population under study was already moderately to severely demented, other more sophisticated psychological tests such as the Welscher Adult Intelligence Scale or the Wisconsin Card Sorting Test were clearly inappropriate.

It is reasonable to ask why the CAMDEX was not used in its entirety in the assessment of the population. The instrument was very recently developed and had, in fact, not been published at the start of this study. Subsequent work has consolidated the use of the CAMDEX as an effective assessment schedule in the elderly. Thus, it was reasonable at the start of the study to be slightly cautious about the implementation of the CAMDEX. Also, existing schedules were utilised where they demonstrated an obvious advantage over the CAMDEX. For example, in the assessment of psychiatric symptoms, a great deal of information was available about the Geriatric Mental State Schedule (GMSS, vide infra) and it was well known in the Department in which this study was undertaken. With regard to the behaviour rating scale,
many of the patients were in hospital and there was a need for a rating scale to assess behaviours associated with more advanced dementia. The Stockton Geriatric Rating Scale was therefore employed. Basic demographic data, the findings on physical examination and medication history were recorded on sheets specifically designed for this study. The history schedule of the CAMDEX was used. The History and Aetiology Schedule developed in conjunction with the GMSS, was considered inappropriate for this study as it did not focus particularly on the history of a demented person.

Psychiatric Symptoms - these were assessed using the Geriatric Mental State Schedule (GMSS, Copeland et al, 1976; Gurland et al, 1976). The GMSS is a standardised interview for assessing psychopathology in patients over the age of 65 and was adapted from the Present State Examination (PSE, Wing et al, 1967). It contains 436 items and a factor analysis revealed 21 independent factors assessing individual symptom complexes (Gurland et al, 1976). The factors used in this study were - depression, anxiety, paranoid delusions, visual and auditory hallucinations, reported belligerence, observed belligerence, anxiety, insight, non-social speech, hypomania, somatic concerns and incomprehensibility. The factors disregarded were mainly concerned with cognitive function (eg impaired memory, disorientation) and were regarded as superfluous as cognitive function was more fully assessed by the CAMCOG. In addition to their assessment in the GMSS, certain psychiatric symptoms were assessed by the history schedule of the CAMDEX. This was done in
order to record symptomatology which had been present at some point during the illness but not necessarily at the time of the clinical interview. These symptoms will now be separately defined.

Delusions were defined according to Fish (1985) and Cummings (1985). Their presence required that the ideas be firmly held and impervious to evidence to the contrary. Delusions were recorded as present (a) if they had occurred "at any time" since the onset of the illness and (b) if they had occurred within the twelve months prior to entry to the study (this time period was used as it corresponded to the time period of follow-up). Thus, (b) represented a subset of (a). To avoid erroneously attributing symptoms to an acute delirium, delusions had to be present for at least seven days. They were divided into three categories - delusions of theft, delusions of suspicion (e.g. believing the spouse was being unfaithful or believing him/herself to be watched) or (3) 'other' delusions which could not be assigned to categories (1) or (2). Thus, delusions of theft and suspicion correspond to the simple persecutory delusions of Cummings (1987) whereas 'other' delusions correspond to "complex, bizarre or multiple" described by Cutting (1987). In two of the six patients with "other" delusions, they could also be categorised as delusions based on specific neurological deficits as described by Cummings (1987).

Persecutory ideation was defined as ideas of persecution, not held with delusional intensity and present for at least seven days.

Auditory hallucinations were regarded as present if the
subject reported hearing voices in the absence of an external stimulus or if he or she had been observed clearly engaging in a dialogue while no one else was present. Visual hallucinations were regarded as present if a subject reported seeing something or someone in the absence of an external stimulus or if he or she had been observed to interact clearly with a non-existent person or object.

Three misidentification syndromes were identified following the definitions used by Rubin et al (1988):

1) people in the house - this is a variant of the "phantom boarder syndrome" and consisted of the belief, based on misrecognition, that others were living in the house;

2) misidentification of mirror image - evidence of this was gleaned from the history of an inability to recognise the subject's own reflection or a statement such as "someone else is in the mirror" and

3) misidentification of television - this was usually apparent with the story of the patient talking to the television or being fearful that an event on the screen (eg a fight or fire) was taking place in the room.

To these three syndromes, described by Rubin et al (1988), I have added a fourth:

4) misidentification of people - this was recorded if a subject mistook a relative or friend for another eg mistaking a spouse for a daughter or brother.

In order to exclude symptoms associated with an intercurrent delirium, hallucinations and misidentifications were required to
last for at least seven days. As with delusions, hallucinations and misidentifications were recorded (a) "at any time" since the onset of illness and (b) in the twelve months prior to entry into the study. Thus, (b) was a subset of (a).

History of the illness - this was taken using the appropriate section of the CAMDEX (Roth et al, 1986). Details were taken of memory loss, personality change, functional activity (from which the Blessed Dementia Scale could be obtained), depression, history of stroke, episodes of confusion, paranoid symptoms and visual and auditory hallucinations. The duration of each symptom and the nature of its onset (gradual or sudden) was recorded. In addition, details of past history, family members and a family history of dementia, Down's syndrome, cerebrovascular disease and other mental illness was noted. For the purposes of this study, a family history of DAT was defined with three degrees of certainty - definite, probable or possible. A family history was considered definite if I was able to see the patient personally, if a post mortem had been performed with AD as the diagnosis or if the death certificate mentioned "Senile Dementia" or "Alzheimer's Disease". A probable family history was recorded if I had spoken to a relative who knew the patient in question and was able to give a clear account of the illness suggesting it was AD. A possible family history was defined as a history from a relative that another member of the family had been demented but there was no clear account of the illness available.

Physical examination - this was performed in the standard way, the details of which appear in Appendix 3.
Hachinski score - (Hachinski et al, 1975) each patient was assigned a score on the basis of the history and examination as a measure of possible vascular dementia.

Behaviour rating - the Stockton Geriatric Rating Scale (Meer and Baker, 1966) was used. This is a 33 item scale originally tested on 1,081 patients in Stockton, California. Although described as a "geriatric" rating scale, the population on which it was validated consisted of elderly patients in a psychiatric hospital, of whom approximately half had "chronic brain syndromes" and half functional psychoses. The scale has both internal consistency and interrater reliability (0.94 and 0.87 respectively). The predictive validity of the scale (ie the association of scores with subsequent discharge from hospital or death) is excellent. A factor analysis of the items revealed four factors - physical disability, communication failure, socially irritating behaviour and apathy. The physical disability subscale encompasses features such as incontinence and the inability to eat, dress or bathe unaided. The apathy subscale describes patients who do not help others and who do not interact with others and communication failure refers to the inability of patients to understand others or to be understood. Thus, one would expect subjects with advanced dementia to score highly on these subscales. Socially irritating behaviour refers to patients making accusations against others, threatening harm to others and being objectionable.

Particular characteristics of dementia which have hitherto remained unmeasured are those of the "Kluver-Bucy Syndrome"
(Kluver and Bucy, 1937). In view of this, seven additional questions were devised in an attempt to rate these behaviours and they were added to the end of the Stockton Geriatric Rating Scale using the same three point format. The seven additional questions are in Appendix 5. In a separate reliability study (based on 480 individual observations), 24 hour testing retest reliability and interrater reliability achieved Kappa values of 0.74 and 0.72 respectively (a factor analysis and measures of internal consistency and validity of this scale are discussed in Chapter 6.1). In addition to the above, one question was added concerning wandering behaviour (see Appendix 5). Each behaviour rating scale was completed by the author in a semi-structured interview to ensure correct understanding of the questions.

Severity of dementia - a global rating was made using the Clinical Dementia Rating (CDR, Hughes et al, 1982). This rating is a simple measure of the severity of dementia (mild, moderate and severe or CDR I, II, III). The rating was based on assessments of six areas - memory, orientation, judgement and problem solving, community affairs, home/hobbies and personal care. Inter-rater reliability of the scale was 0.89 and validity was suggested by highly significant correlations between the CDR and other cognitive and behavioural assessments. The scale was updated by Berg et al (1984).

Computed Tomography (CT) scan of the head - this was performed in the Department of Neuroradiology at the Maudsley Hospital using the GE 9800 whole body CT scanner. The patient lay supine on a movable examination table with the head supported in a head-rest, stabilisation straps being used to immobilise the head during the
examination. Positioning in the gantry of the CT scanner was achieved using two lazer cross lights - one through the medial saggital plane and one along the interorbital line. The height of the patient was determined by a third cross light positioned over the external auditory meatus. Using a scout view of the skull, the gantry was angled parallel to the floor of the anterior cranial fossa to avoid irradiating the orbits.

Ten millimetre contiguous slices were taken from the floor of the anterior cranial fossa to the top of the head. The dose of radiation was approximately 50 mSv (millisieverts) and was comparable to that in a set of standard skull X-rays. No contrast enhancement was used. Each slice took about four seconds to scan but could be reduced to two seconds with an uncooperative patient. The total scanning time was about five minutes. The output was displayed in a 256 x 256 matrix and interpolated on to a 512 x 512 screen.

Images were transferred to a computer tape and later analysed using an independent viewing console attached to the main computer. The scans were analysed in two ways - visual ratings and computer-assisted ratings. Visual ratings were performed comparing the scans to standards of predetermined severity (selected from a population not in the study). Seven regions were assessed on a four point scale of atrophy or widening: none; mild; moderate or severe. The regions assessed were the frontal, parietal, temporal and occipital lobes, right and left sylvian fissures and the interhemispheric fissure (IHF, which was rated on a 3 point scale). The scores from these
individual regions were summated to give a "total cortical score". White matter changes (periventricular lucencies) were also recorded using a four point scale. Basal ganglia calcification was assessed bilaterally in the caudate, globus pallidus and putamen. The presence or absence of infarcts was also noted. All scans were rated independently by two raters. The following Kappa scores were computed for each region - frontal 0.84, parietal 0.75, temporal 0.74, occipital 0.88, IHF 0.76, sylvian fissure (right) 0.75, (left) 0.72, white matter changes 0.85, basal ganglia calcification 0.85 and cerebral infarcts 0.85.

For the computer-assisted ratings, the numerical data from the scans were transferred using magnetic tapes and analysed on an independent viewing console. Using a movable cursor, regions of interest were outlined and then the area within the region which fell within predetermined Hounsfield Units (HU) densities was measured. The following regions were assessed - third ventricle (0-25 HU), right and left sylvian fissures (0-30 HU), ventricular size was assessed on the two slices where the bodies of the lateral ventricles were seen best (0-25 HU). Ventricular brain ratio (VBR) was calculated by dividing the area of the brain slice to the inner table of the skull by ventricular size and expressing the result as a percentage. The average of two slices was taken. These particular HU densities were chosen because of previous reports (eg Reveley, 1985) and because they corresponded best to the visual impression of the scan. A total of 127 regions were assessed by two raters and the Pearson Correlation Coefficient between the ratings was 0.99. A test-
A retest reliability measure was made by analysing 60 scans chosen at random seven days after the initial assessment. The Pearson Correlation Coefficient of the two ratings was 0.99.

Two regions were rated by both the visual and computer-assisted method (the right and left sylvian fissure areas) which allowed for a cross validation of the techniques. The results are presented in Table 4.1 and show excellent agreement between the two methods.

There are several methodological difficulties associated with the interpretation of CT scans. These have been well summarised by Jacobson et al (1985).

**Partial Volume Effect** - each two-dimensional CT image actually represents a 3-dimensional structure (a voxel, the two dimensions of the image plus the slice thickness). Thus, in the two-dimensional representation (the pixel), areas at the CSF/brain interface will contain both structures and the resulting attenuation value (and hence the hue on the grey scale) will be a mixture of the two. While essentially an insoluble problem in the analysis of CT scans, the use of predetermined values to delineate CSF and brain help to reduce its effects.

**Beam Hardening Effect** - this situation obtains when X-rays are attenuated by passage through bone and so areas of tissue next to the skull will have falsely raised values. The effect is reduced by using pixels of predetermined density.

**Visually Detectable Artefacts** - these are due to a restless and uncooperative patient moving during the scan. There were few of these in the present study and, where such an
artefact significantly interfered with the interpretation of the scan, the scan was discarded.

Scanner Drift - This is due to differences in attenuation values secondary to changes which take place within the CT scanner over time. In this study, phantoms of predetermined density were scanned at each session and it was shown that the change in attenuation values over the period in which the study was performed was less than 5%.

Other Operating Factors - any changes in the software of the computer programs may affect the results. No such changes took place during the present study.

Timing of assessments - All the above assessments were performed at entry to the study, within 14 days of each other. The CAMCOG, GMSS, physical examination, behaviour rating scale and CT scan were repeated annually.

Neuropathology - as part of a full post-mortem examination, brains were removed, examined externally and either fixed in their entirety or sliced fresh, in which case individual slices were frozen or fixed in 10% formol saline. Following at least two weeks fixation, blocks of tissue were taken from standardised areas of frontal, parietal, temporal and occipital lobes, from basal forebrain, striatum, midbrain, pons, medulla and cerebellum, all according to the protocol of the Medical Research Council Alzheimer's Disease Brain bank in the Department of Neuropathology, Institute of Psychiatry. Sections were stained with haematoxylin and eosin, luxol fast blue/cresyl violet and impregnated with silver according to Marsland and Glees.

Immunohistochemistry for glial fibrillary acidic protein was
carried out. In some instances, further investigations included the Gallyas silver method, Congo red and immunohistochemistry for A4 protein.

The histopathological diagnosis of AD may be approached in a number of ways. In this study, the diagnosis of AD was dependent upon finding widespread neocortical involvement with plaques and/or neurofibrillary tangles. Diffuse Lewy body disease was diagnosed when Lewy bodies were found not only in the substantia nigra and locus coeruleus but also in the cortex, particularly in the parahippocampal gyrus. Vascular damage, whether secondary to cerebral atherosclerosis, embolic disease or congophilic angiopathy, was considered to be significant when multiple and widespread macroscopic and/or microscopic lesions were identified. However, none of these diagnoses was considered to be mutually exclusive and when none was present and no other recognised neurodegenerative disease was identified, cases were placed into the "no diagnosis" group.

4.3 ANALYSIS OF DATA

This was performed using an IBM PC AT computer with the Statistical Package for the Social Sciences, personal computer version (SPSSPC+). Additional analyses were performed on the mainframe version of SPSS (SPSSX) using the Amdahl computer at the University of London Computing Centre. The survival analysis was performed using an EGRET programme on the IBM PC.

Standard statistical test were performed. Paired t-tests were used to compare changes in groups of individuals over time, unpaired t-tests were used to compare group means and one
way anova was applied when the means of three or more groups were being compared. Chi-square tests (with Yates correction where appropriate) assessed the strength of the association of categorical variables. The strength of association of continuous variables was tested by a Pearson product moment correlation. Cluster analysis employed Ward's method using squared Euclidean distances on standardised scores. Other statistical tests used will be described in the appropriate results section.

With regard to the survival analysis (Chapter 9), the Standardised Mortality Ratios were calculated using the Camberwell Health Authority All Cause Mortality Rates. The rates were derived from the number of deaths reported for 1987 by the Office of Population Censuses and Surveys (OPCS, 1989). The population estimates were provided by the South East Thames Regional Health Authority (mid-year estimates, 1988). Confidence intervals were calculated using tables or the normal approximation to the Poisson distribution.

The survival times were analysed according to the proportional hazards model of Cox (Cox and Oakes, 1984). The study of survival times has considerable advantages over more simple analytic methods which, for instance, treat the outcome as a binary variable (dead or alive) at the end of the follow-up period. In brief, the model assumes that the hazard or risk of death for all individuals is proportional throughout the study. The second assumption of the model is that the effect of explanatory variables is multiplicative. The use of the proportional hazards model allows a multi-variate approach.
The coefficients generated by the proportional hazards model are exponentiated and the hazard ratios can be interpreted as relative risks (a relative risk of greater than 1 indicates an increased death rate while a relative risk of less than 1 corresponds to a reduced death rate, compared to the baseline). The final model for predictors of survival was determined by adding variables which were included if they were significant at the 5% level.

4.4 ETHICAL APPROVAL

All procedures were approved by the Ethics Committees of the Joint Hospital, Dulwich Hospital and Cane Hill Hospital.
CHAPTER 5

GENERAL DESCRIPTION OF THE SAMPLE

In total, 186 patients satisfying the NINCDS/ADRDA criteria were approached for inclusion in the study. Eight relatives refused permission for patients to be included (the commonest reason being they felt the patients had been "through enough"). Therefore, 178 subjects were evaluated in the study (96% of those approached). Their demographic characteristics are shown in Table 5.1. Due to lack of information, it was not possible to allocate a Clinical Dementia Rating (CDR) to three subjects.

The reasons for 40 of the patients being placed in the possible category were: diabetes (controlled with diet and oral hypoglycaemic drugs, nine patients, 22%); past or current hypertension (on antihypertensive medication, nine patients, 22%); evidence of cerebrovascular disease (temporally unrelated to the dementia syndrome, eight patients, 20%); heart disease (two patients, 5%); other physical illness (eg temporal arteritis, subacute bacterial endocarditis, epilepsy, vitamin B₁₂ deficiency and malignancy, seven patients, 18%); previous significant alcohol intake (two patients, 5%) and an atypical clinical picture (three patients, 8%).

Ninety-five percent of subjects had a Hachinski score (Hachinski et al, 1975) of four or less. Five patients had a score of five, two scored six and one patient had a score of seven. The score could not be calculated on two subjects due to
### TABLE 5.1
CHARACTERISTICS OF THE SAMPLE

<table>
<thead>
<tr>
<th>All Subjects</th>
<th>Number</th>
<th>(% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL SUBJECTS</td>
<td>178</td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>140</td>
<td>(79%)</td>
</tr>
<tr>
<td>male</td>
<td>38</td>
<td>(21%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean</th>
<th>Range</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE (years)</td>
<td>80.4, 56-99, 6.6</td>
<td></td>
</tr>
<tr>
<td>AGE OF ONSET (years)</td>
<td>75.2, 50-95, 7.4</td>
<td></td>
</tr>
<tr>
<td>DURATION OF ILLNESS (months)</td>
<td>63.0, 6-240, 42.6</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Probable' Alzheimer's Disease</th>
<th>Number</th>
<th>(% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>'Probable'</td>
<td>138</td>
<td>(78%)</td>
</tr>
<tr>
<td>'Possible'</td>
<td>40</td>
<td>(22%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Placement: Home</th>
<th>Number</th>
<th>(% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital</td>
<td>78</td>
<td>(44%)</td>
</tr>
<tr>
<td>Residential Care</td>
<td>26</td>
<td>(15%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Dementia Rating</th>
<th>Number</th>
<th>(% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (N=175)</td>
<td>12</td>
<td>(7%)</td>
</tr>
<tr>
<td>II</td>
<td>78</td>
<td>(45%)</td>
</tr>
<tr>
<td>III</td>
<td>85</td>
<td>(48%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Family History of Dementia of the Alzheimer Type in:</th>
<th>Number</th>
<th>(% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parents</td>
<td>21</td>
<td>(12%)</td>
</tr>
<tr>
<td>Siblings</td>
<td>31</td>
<td>(17%)</td>
</tr>
<tr>
<td>2nd Degree Relatives</td>
<td>3</td>
<td>(2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Existing ('Prevalent') Cases</th>
<th>Number</th>
<th>(% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New ('Incident') Cases</td>
<td>99</td>
<td>(56%)</td>
</tr>
</tbody>
</table>

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lack of information. "Existing" cases refer to those subjects who were already known to the services at the beginning of the study (1 October 1986). "New" cases consisted of those patients presenting for the first time to the hospital between 1 October 1986 and 30 September 1988. As the study finished on 1 October 1989, recruitment ceased at the end of September 1988 to allow at least 12 months follow-up on all cases. The mean follow-up interval was 18.4 months (range 12-36 months).

Table 5.2 outlines the results of the cognitive testing and CT scan examinations for the whole sample at entry to the study. All patients received cognitive tests. CT scans were obtained on 138 subjects (78%). The reasons for scan refusal were: the patient refusing the scan after discussion (5%), the relatives refusing permission for the patient to be scanned (10%), the patient being too uncooperative due to aggression or behaviour disturbance (58%) and the scan not possible for physical reasons (eg arthritis preventing the subject lying flat, 27%).

Follow up of the patients was 100% complete. Details of the follow-up are presented in Chapter 7.
<table>
<thead>
<tr>
<th>Table 5.2: Cognitive Function and Computed Tomography Findings in the Sample (At Entry to the Study)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COGNITION</strong></td>
</tr>
<tr>
<td>Mini-Mental State Examination (Max=30)</td>
</tr>
<tr>
<td>Mean: 8.0, Range: 0-24, Standard Deviation: 6.7</td>
</tr>
<tr>
<td>Abbreviated Mental Test Score (Max=10)</td>
</tr>
<tr>
<td>Mean: 2.5, Range: 0-10, Standard Deviation: 2.9</td>
</tr>
<tr>
<td>CAMCOG:</td>
</tr>
<tr>
<td>Memory (Max=27)</td>
</tr>
<tr>
<td>Mean: 3.3, Range: 0-16, Standard Deviation: 3.8</td>
</tr>
<tr>
<td>Language (Max=30)</td>
</tr>
<tr>
<td>Mean: 11.4, Range: 0-26, Standard Deviation: 9.1</td>
</tr>
<tr>
<td>Praxis (Max=12)</td>
</tr>
<tr>
<td>Mean: 4.0, Range: 0-12, Standard Deviation: 3.8</td>
</tr>
<tr>
<td>Orientation (Max=10)</td>
</tr>
<tr>
<td>Mean: 1.8, Range: 0-9, Standard Deviation: 2.1</td>
</tr>
<tr>
<td>Attention (Max=7)</td>
</tr>
<tr>
<td>Mean: 1.3, Range: 0-7, Standard Deviation: 2.0</td>
</tr>
<tr>
<td>Calculation (Max=2)</td>
</tr>
<tr>
<td>Mean: 0.7, Range: 0-2, Standard Deviation: 0.8</td>
</tr>
<tr>
<td>Abstract Thinking (Max=8)</td>
</tr>
<tr>
<td>Mean: 0.6, Range: 0-4, Standard Deviation: 0.9</td>
</tr>
<tr>
<td>Perception (Max=11)</td>
</tr>
<tr>
<td>Mean: 3.6, Range: 0-4, Standard Deviation: 3.2</td>
</tr>
<tr>
<td>Total (Max=107)</td>
</tr>
<tr>
<td>Mean: 26.6, Range: 0-75, Standard Deviation: 22.6</td>
</tr>
<tr>
<td><strong>COMPUTED TOMOGRAPHY</strong></td>
</tr>
<tr>
<td>Ventricular - Brain Ratio (%)</td>
</tr>
<tr>
<td>Mean: 15.0, Range: 3.4 - 34.4, Standard Deviation: 5.4</td>
</tr>
<tr>
<td>III Ventricle (cm²)</td>
</tr>
<tr>
<td>Mean: 1.9, Range: 0.7 - 4.5, Standard Deviation: 0.6</td>
</tr>
<tr>
<td>Total Cortical Store (Max=23)</td>
</tr>
<tr>
<td>Mean: 6.5, Range: 1-16, Standard Deviation: 2.8</td>
</tr>
<tr>
<td><strong>% of Subjects with:</strong></td>
</tr>
<tr>
<td>Basal Ganglia Calcification</td>
</tr>
<tr>
<td>25.1%</td>
</tr>
<tr>
<td>White Matter Changes</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>39.5%</td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>36.6%</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>20.1%</td>
</tr>
<tr>
<td>Severe</td>
</tr>
<tr>
<td>3.8%</td>
</tr>
<tr>
<td>Infarcts</td>
</tr>
<tr>
<td>2%</td>
</tr>
</tbody>
</table>
CHAPTER 6

PSYCHIATRIC SYMPTOMS AND BEHAVIOUR DISTURBANCE

6.1 RESULTS

Disorders of Thought Content

Table 6.1 outlines the proportion of subjects with delusions and persecutory ideas. No significant differences in the prevalence of symptoms were found between subjects with "probable" and those with "possible" AD. In view of this, and for the sake of clarity, the results are presented for the sample as a whole. 16% had experienced delusions since the onset of the illness and 11% in the 12 months prior to entry into the study. Delusions of theft were the commonest type of delusion followed by delusions of suspicion. Six subjects had "other" delusions. These consisted of: a conviction that a pet budgie had been burnt; the idea that the patient had become a father at age 90; the belief that the patient was in Korea fighting a war; an idea held by one man that people came in at night and cut his throat; a woman who was convinced that people came into her house and added objects and a belief that someone was playing a tape machine in a local street which was giving the patient messages. 20% of the sample had experienced persecutory ideas. One-third of the sample had some form of disorder of thought content. A greater proportion of men than women suffered delusions of theft.

Table 6.2 gives a summary of the main CT findings in relation to the symptoms. One hundred and thirty-eight patients had CT scans including only five of the six patients with "other" delusions. Subjects with simple delusions or persecutory ideation did not differ significantly from those without these features on
### TABLE 6.1

<table>
<thead>
<tr>
<th>Disorder of Thought Present</th>
<th>N(%)</th>
<th>M:F</th>
<th>% of Males Affected</th>
<th>% of Females Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any delusions</td>
<td>28(15.7)</td>
<td>13:15 ***</td>
<td>35%</td>
<td>11%</td>
</tr>
<tr>
<td>Any recent delusions (within previous 12 months)</td>
<td>19(10.7)</td>
<td>9:10 ***</td>
<td>24%</td>
<td>7%</td>
</tr>
<tr>
<td>Delusions of theft</td>
<td>16 (9.0)</td>
<td>7:9 **</td>
<td>19%</td>
<td>6%</td>
</tr>
<tr>
<td>Delusions of Suspicion</td>
<td>10 (5.6)</td>
<td>4:6</td>
<td>11%</td>
<td>4%</td>
</tr>
<tr>
<td>Other Delusions</td>
<td>6 (3.4)</td>
<td>3:3</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Persecutory Ideation</td>
<td>36(20.2)</td>
<td>9:27</td>
<td>24%</td>
<td>19%</td>
</tr>
<tr>
<td>Any Disorder of Thought</td>
<td>53(29.8)</td>
<td>16:37 *</td>
<td>43%</td>
<td>26%</td>
</tr>
</tbody>
</table>

**KEY:**

*Any disorder of thought' represents the total number of subjects with either delusions, persecutory ideation or both.

Statistics - Chi-square test, disorder more common in men -

*: p<0.05

**: p<0.02

***: p<0.01

All others non-significant at p<0.05
"OTHER" DELUSIONS IN SDAT - CT FINDINGS

<table>
<thead>
<tr>
<th>DELUSIONS</th>
<th>PRESENT (N = 5)</th>
<th>ABSENT (N = 133)</th>
<th>SIGNIFICANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>R (Mean ± SD)</td>
<td>8.6 ± 3.0</td>
<td>15.4 ± 5.3</td>
<td>p&lt;0.006 1</td>
</tr>
<tr>
<td>Lceration with Basal Ganglia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ft: Present</td>
<td>2</td>
<td>8</td>
<td>p&lt;0.004 2</td>
</tr>
<tr>
<td>Absent</td>
<td>3</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>ght: Present</td>
<td>2</td>
<td>9</td>
<td>p&lt;0.007 2</td>
</tr>
<tr>
<td>Absent</td>
<td>3</td>
<td>124</td>
<td></td>
</tr>
</tbody>
</table>

Y: SD - standard deviation
VBR = ventricular-brain ratio
Statistics - 1: students' 't' test
2: Chi-square test.
any of the CT variables assessed. However, those with "other" delusions differed from those without on two measures – they had significantly smaller VBR’s and more often had basal ganglia calcification. Neither cognitive score at entry to the study nor change in cognitive score over the succeeding 12 months differed for subjects with and without disorders of thought content.

Disorders of Perception

Table 6.3 outlines the frequency for disorders of perception in the sample. Visual hallucinations (13%) were slightly more common than auditory hallucinations (10%). Misidentification syndromes occurred more frequently with 30% of the sample having had one misidentification at some point in their illness and 19% having had the experience in the preceding 12 months. Misidentification of other people and the belief that others were in the house were more common in men.

Table 6.4 shows a comparison of age, age of onset and duration of illness in those with misidentification syndromes. No significant differences were seen in those with or without hallucinations but, as can be seen from Table 6.4, subjects with misidentifications involving mirror image and people in the house were significantly younger than those without. Their illnesses had started at a younger age but there was no relationship to duration of illness.

Table 6.5 outlines the results of neuropsychological testing. No differences were seen in either cognitive score at entry to the study or change in cognitive score over the succeeding 12 months between those with or without
DISORDERS OF PERCEPTION IN SDAT

DISORDERS OF PERCEPTION PRESENT

<table>
<thead>
<tr>
<th>Hallucinations: (N=177):</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sex Ratio</td>
<td>% of Males</td>
<td>% of Females</td>
</tr>
<tr>
<td></td>
<td>N(%)</td>
<td>M:F</td>
<td>Affected</td>
</tr>
<tr>
<td>Hallucinations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ly recent hallucinations</td>
<td>20(11.3)</td>
<td>6:14</td>
<td>16%</td>
</tr>
<tr>
<td>Recent hallucinations</td>
<td>23(13.0)</td>
<td>6:17</td>
<td>16%</td>
</tr>
<tr>
<td>Ly misidentification</td>
<td>17(9.6)</td>
<td>3:14</td>
<td>8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Identification Syndromes: (N=178)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sex Ratio</td>
<td>% of Males</td>
<td>% of Females</td>
</tr>
<tr>
<td></td>
<td>N(%)</td>
<td>M:F</td>
<td>Affected</td>
</tr>
<tr>
<td>Ly misidentification</td>
<td>54(30.3)</td>
<td>19:35 **</td>
<td>51%</td>
</tr>
<tr>
<td>Ly recent misidentification</td>
<td>34(19.1)</td>
<td>12:22 *</td>
<td>32%</td>
</tr>
<tr>
<td>Recent misidentification</td>
<td>21(11.8)</td>
<td>10:11 **</td>
<td>27%</td>
</tr>
<tr>
<td>Ly identification of people</td>
<td>31(17.4)</td>
<td>12:19 **</td>
<td>32%</td>
</tr>
<tr>
<td>Identification of people in the home</td>
<td>11(6.2)</td>
<td>1:10</td>
<td>3%</td>
</tr>
<tr>
<td>Ly television</td>
<td>7(3.9)</td>
<td>3:4</td>
<td>8%</td>
</tr>
</tbody>
</table>

**Statistics (Chi-square test), disorder more common in men -

*: p<0.02

**: p<0.01

1 others, non-significant at p<0.05
All others, non-significant at $p > 0.05$

Younger age of onset compared to those without - $p < 0.05$

All statistical tests were done with matched-pair analysis where younger and had

SD - Standard deviation

KEY:
- No
- Yes

<table>
<thead>
<tr>
<th>Illusion of mirror image</th>
<th>Illusion of television</th>
<th>People in the home</th>
<th>Any recent misidentification</th>
<th>Any recent misidentification</th>
</tr>
</thead>
<tbody>
<tr>
<td>69.4 ± 4.3 (1)</td>
<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
</tr>
<tr>
<td>68.6 ± 6.4</td>
<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
</tr>
<tr>
<td>69.4 ± 4.3 (1)</td>
<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
</tr>
<tr>
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<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
</tr>
<tr>
<td>63.9 ± 6.4</td>
<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
</tr>
<tr>
<td>68.6 ± 6.4</td>
<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
</tr>
<tr>
<td>63.9 ± 6.4</td>
<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
</tr>
<tr>
<td>68.6 ± 6.4</td>
<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
</tr>
<tr>
<td>63.9 ± 6.4</td>
<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
</tr>
<tr>
<td>68.6 ± 6.4</td>
<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
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<tr>
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<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
</tr>
<tr>
<td>68.6 ± 6.4</td>
<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
</tr>
</tbody>
</table>

**TABLE 6.4**

<table>
<thead>
<tr>
<th>Illusion (mean ± SD)</th>
<th>Illusion (years)</th>
<th>Illusion of age (years)</th>
<th>Illusion of duration of illness (years)</th>
<th>Illusion of age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>69.4 ± 4.3</td>
<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Illusion (mean ± SD)</th>
<th>Illusion (years)</th>
<th>Illusion of age (years)</th>
<th>Illusion of duration of illness (years)</th>
<th>Illusion of age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>69.4 ± 4.3</td>
<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
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<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
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<tr>
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<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
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<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
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<td>63.9 ± 6.4</td>
<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
</tr>
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<td>68.6 ± 6.4</td>
<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
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<td>68.1 ± 6.4</td>
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<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
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<tr>
<td>68.6 ± 6.4</td>
<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
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<td>63.9 ± 6.4</td>
<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
</tr>
<tr>
<td>68.6 ± 6.4</td>
<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
</tr>
<tr>
<td>63.9 ± 6.4</td>
<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
</tr>
<tr>
<td>68.6 ± 6.4</td>
<td>75.0 ± 5.6</td>
<td>71.4 ± 6.1</td>
<td>63.9 ± 6.4</td>
<td>68.1 ± 6.4</td>
</tr>
</tbody>
</table>
Indicating that a deterioration in cognitive function has taken place.

<table>
<thead>
<tr>
<th>Change in 1 year</th>
<th>Initial Score</th>
<th>CANSOC Total (max = 100)</th>
<th>Initial Score</th>
<th>CANSOC Total (max = 100)</th>
<th>Initial Score</th>
<th>CANSOC Total (max = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.6</td>
<td>-1.2</td>
<td>-1.1</td>
<td>-1.2</td>
<td>-1.3</td>
<td>-1.2</td>
<td>-1.3</td>
</tr>
<tr>
<td>0.4</td>
<td>-1.1</td>
<td>-1.2</td>
<td>-1.2</td>
<td>-1.2</td>
<td>-1.2</td>
<td>-1.3</td>
</tr>
<tr>
<td>-1.6</td>
<td>-1.7</td>
<td>-1.2</td>
<td>-1.2</td>
<td>-1.2</td>
<td>-1.2</td>
<td>-1.2</td>
</tr>
<tr>
<td>4.5</td>
<td>4.0</td>
<td>4.2</td>
<td>4.2</td>
<td>4.2</td>
<td>4.2</td>
<td>4.2</td>
</tr>
<tr>
<td>1.9</td>
<td>3.2</td>
<td>3.2</td>
<td>3.2</td>
<td>3.2</td>
<td>3.2</td>
<td>3.2</td>
</tr>
<tr>
<td>3.1</td>
<td>3.3</td>
<td>3.3</td>
<td>3.3</td>
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<td>3.3</td>
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<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>2.5</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>5.3</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
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<td>2.8</td>
<td>2.8</td>
<td>2.8</td>
<td>2.8</td>
<td>2.8</td>
</tr>
</tbody>
</table>

**Table 6.5**

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

Cognitive function in daily with and without hallucinations.
misidentifications. Initial cognitive function was not significantly different in those with or without hallucinations. However, in those experiencing either visual or auditory hallucinations within 12 months of entry to the study, the deterioration in cognitive function over the succeeding year was significantly greater than in those not hallucinating. Neuroleptic medication was prescribed for 34% of hallucinating subjects and 46% of those with misidentifications. 34% of non-hallucinators were taking these drugs as were 33% of those without misidentification syndromes - there was no statistically significant difference in these proportions.

After 36 months, 84 of the subjects had died but the only significant association between death and the presence of perceptual disorders was that 35.1% of those with misidentification syndromes had died, compared to 52.4% of those without these symptoms (significant at \( p < 0.05 \), chi-square test). This difference remains significant after controlling for age. There was no difference in the proportion of subjects with or without perceptual disorders across the three levels of dementia rating.

Disorders of Affect

Table 6.6 outlines the rates for mood disturbances. Observations were recorded in 174 patients and relatives were able to give ratings in 163 patients. Seventy of the patients were unable to cooperate with the direct questioning involved in the GMSS and so they were excluded from this part of the analysis. Although nearly two-thirds of patients had at least one symptom of depression and nearly half were rated as depressed by
<table>
<thead>
<tr>
<th>DISORDERS OF MOOD IN SDAT</th>
<th>DISORDERS OF MOOD PRESENT</th>
<th>% OF MALES AFFECTED</th>
<th>% OF FEMALES AFFECTED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N(%)</td>
<td>SEX RATIO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>M:F</td>
<td></td>
</tr>
<tr>
<td>PRESSION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>served by Rater</td>
<td>41(23.5%)</td>
<td>6:35</td>
<td>17%</td>
</tr>
<tr>
<td>served by Rater</td>
<td>41(23.5%)</td>
<td>6:35</td>
<td>17%</td>
</tr>
<tr>
<td>served by Patient</td>
<td>68(63%)</td>
<td>12:56</td>
<td>36%</td>
</tr>
<tr>
<td>served by Relative</td>
<td>70(42.9%)</td>
<td>14:56</td>
<td>42%</td>
</tr>
<tr>
<td>previous history</td>
<td>17(9.5%)</td>
<td>1:16</td>
<td>3%</td>
</tr>
<tr>
<td>NIA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>served by Rater</td>
<td>6(3.5%)</td>
<td>0:6</td>
<td>0%</td>
</tr>
<tr>
<td>served by Patient</td>
<td>1(0.6%)</td>
<td>0:1</td>
<td>0%</td>
</tr>
</tbody>
</table>
their relatives. No patient satisfied DSM IIIR for major depressive disorder. Subjects on antidepressants were more likely to be rated as depressed by an observer (p < 0.002, chi-square test) but there was no relationship between antidepressant prescribing and either relatives' reports of depression or complaints by the patient. There was no association between a past history of depression and current depression as assessed by any of the three methods.

Signs and symptoms of mania were rare - only six patients had evidence of observed mania and only one patient reported manic symptoms.

Table 6.7 outlines the results of cognitive testing in those with and without depression. The main findings were: patients who reported depression were less cognitively impaired than those who did not; observed depression was unrelated to either cognitive function or to deterioration in cognitive function; there was a tendency for subjects rated as depressed by their relatives to be less impaired and there was a tendency (statistically significant only for the MMSE) for those with a previous history of depression to deteriorate less quickly. Manic symptomatology was unrelated to cognitive function.

Table 6.8 summarises the main CT findings in relation to mood disorders. First, those patients in whom depression was reported by the relatives had smaller third ventricles and VBRs. Second, observed manic symptoms were strongly related to visual ratings of widening of the Interhemispheric Fissure (IHF) and depressive symptoms were inversely related to IHF widening.
Table 6.7
MOOD CHANGES IN SDAT - SUMMARY OF CT FINDINGS

**Table 6.8**
Depressive symptoms correlated negatively (Spearman correlation) with three indices on CT scanning – third ventricular size \((-0.22, p < 0.05)\), right sylvian fissure size \((-0.23, p < 0.02)\) and VBR \((-0.20, p < 0.05)\). Observed depression did not correlate with any of the CT findings.

The following GMSS factors were more common in patients with severe dementia (CDR III, 3x2 Chi-square test) – retarded speech \((p < 0.0001)\), nonsocial speech \((p < 0.005)\), incomprehensibility \((p < 0.0001)\), anxiety \((p < 0.0001)\) and loss of insight \((p < 0.05)\). Retarded speech, incomprehensibility and anxiety were more common in hospitalised patients (all \(p < 0.0001\), 3x2 Chi-square test).

Behavioural Disturbance

Table 6.9 outlines the frequency with which the main behavioural disturbances were seen (full data were not available on four patients). Three signs of the Kluver-Bucy syndrome were relatively uncommon (binge eating, hyperorality and sexual disinhibition). Incontinence occurred in nearly 50% of the sample. Subjects with aggression were more likely to be on neuroleptic medication but there was no association between binge eating and the prescribing of neuroleptics.

Table 6.10 shows the prevalence of behavioural abnormalities in relationship to the overall severity of dementia as assessed by the CDR. As would be expected, behavioural disturbances became more common as severity of dementia increased. The exceptions were binge eating, hypermetamorphosis and "rage" behaviour. There was a non-significant trend for aggression to increase with severity of dementia. 34% of hospitalised patients
### Table 6.9

**Behavioural Disturbance in SDAT**

<table>
<thead>
<tr>
<th>Behavioural Disturbance Present</th>
<th>N(%)</th>
<th>Sex Ratio</th>
<th>% of Males Affected</th>
<th>% of Females Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aggression</strong> (N=178)</td>
<td>35(19.7%)</td>
<td>15:20 **</td>
<td>40%</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Wandering</strong> (N=178)</td>
<td>33(18.5%)</td>
<td>7:26</td>
<td>19%</td>
<td>21%</td>
</tr>
<tr>
<td><strong>Urinary Incontinence</strong> (N=174)</td>
<td>83(47.7%)</td>
<td>17.66</td>
<td>47%</td>
<td>48%</td>
</tr>
<tr>
<td><strong>Elements of 'Kluver Bucy Syndrome':</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Binge Eating</strong> (N=174)</td>
<td>17(9.8%)</td>
<td>8:9 *</td>
<td>22%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Hyperorality</strong> (N=174)</td>
<td>11(6.3%)</td>
<td>2:9</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Sexual Disinhibition</strong> (N=174)</td>
<td>12(6.9%)</td>
<td>3:9</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Misrecognition of Nurses/Relatives</strong> (N=174)</td>
<td>77(44.3%)</td>
<td>13:64</td>
<td>36%</td>
<td>46%</td>
</tr>
<tr>
<td><strong>Going into 'Rages'</strong> (N=174)</td>
<td>62(35.6%)</td>
<td>13:49</td>
<td>36%</td>
<td>45%</td>
</tr>
<tr>
<td><strong>Hypermetamorphosis</strong> (N=174)</td>
<td>54(31%)</td>
<td>12:42</td>
<td>33%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Withdrawal/Apathy</strong> (N=174)</td>
<td>71(40.8%)</td>
<td>13:58</td>
<td>36%</td>
<td>42%</td>
</tr>
</tbody>
</table>

**Key:** Statistics, Chi-square test  
Behaviour more common in men, * p<0.01  
** p<0.001
### Relationship of Behavioural Disturbance to Overall Severity of Dementia

<table>
<thead>
<tr>
<th>Clinical Dementia Rating</th>
<th>Mild (N=12)</th>
<th>Moderate (N=77)</th>
<th>Severe (N=85)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(with each behaviour)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>8.3%</td>
<td>16.7%</td>
<td>23.5% NS</td>
</tr>
<tr>
<td>Xdering</td>
<td>0%</td>
<td>10.2%</td>
<td>27.0% **</td>
</tr>
<tr>
<td>Incontinence</td>
<td>8.3%</td>
<td>2.6%</td>
<td>94% ***</td>
</tr>
<tr>
<td>Symptoms of Kluver-Bucy Syndrome:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age eating</td>
<td>8.3%</td>
<td>10.4%</td>
<td>9.4% NS</td>
</tr>
<tr>
<td>Perorality</td>
<td>0%</td>
<td>0%</td>
<td>13.0% **</td>
</tr>
<tr>
<td>Sexual disinhibition</td>
<td>0%</td>
<td>2.6%</td>
<td>11.8% *</td>
</tr>
<tr>
<td>Recognition of nurses/relatives</td>
<td>8.3%</td>
<td>26.0%</td>
<td>65.9% ***</td>
</tr>
<tr>
<td>Ing into 'rages'</td>
<td>25%</td>
<td>28.6%</td>
<td>43.5% NS</td>
</tr>
<tr>
<td>Permetamorphosis</td>
<td>8.3%</td>
<td>28.6%</td>
<td>36.5% NS</td>
</tr>
<tr>
<td>Intermittent apathy</td>
<td>50%</td>
<td>28.6%</td>
<td>50.1% *</td>
</tr>
<tr>
<td>Subjects with any features of the Kluver-Bucy Syndrome</td>
<td>75%</td>
<td>66.2%</td>
<td>96.5% ***</td>
</tr>
</tbody>
</table>

Statistics - 3 x 2 Chi-square

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$
NS - not significant at $p < 0.05$
were aggressive compared to 11% of those at home and 4% in residential homes (p > 0.001, chi-square test). Of the 83 subjects with incontinence 51 were dead at 36 month follow up, compared to 23 of those who were not incontinent (p > 0.001, chi-square test). Patients dead at follow-up had significantly higher scores on the communication failure, apathy and physical disability subscale of the Stockton Geriatric Rating Scale.

Table 6.11 shows the patterns of cognitive function in subjects with or without aggression, wandering and binge eating. Patients with aggression and wandering behaviour were significantly more cognitively impaired on all measures than those without these features. However, there was no significant difference in cognitive function in those with or without binge eating. Deterioration in cognitive function over the follow up showed no differential decline in any of the groups. (Cognitive function in patients without other behavioural disturbances showed a similar pattern to those with aggression and wandering and have not been detailed separately).

With regard to associations with CT findings, these have been summarised in Table 6.12. Aggression was associated with more temporal lobe atrophy, excess wandering behaviour with increased sylvian fissure size and hyperorality with third ventricular size. Hyperorality was also associated with frontal, parietal and occipital atrophy but was not associated with temporal lobe atrophy. There were no differences in the CT measures of those with or without sexual disinhibition. Patients with incontinence had
In all cases non-significant at p>0.05 MNS - Abbreviated Mental Test Score

Indicating that a deterioration in Cognitive function has taken place.

\( \text{Change in 1 year shows the mean change in score for the group over 12 months - the negative sign} \)
\( \Rightarrow \text{p}<0.01 \)
\( \Rightarrow \text{p}<0.001 \)

**KEY:**

<table>
<thead>
<tr>
<th></th>
<th>P/U</th>
<th>Initial Score</th>
<th>Change in 1 year</th>
<th>P/U</th>
<th>Initial Score</th>
<th>Change in 1 year</th>
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<td>Anxiety</td>
<td></td>
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<td><strong>VISCERAL</strong></td>
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<tr>
<td>Aims (Max = 10)</td>
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<td>Initial score</td>
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<tr>
<td><strong>MINI-INDICATED STATE</strong></td>
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<td></td>
</tr>
<tr>
<td>Cognitive FUNCTION</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioural Disturbance in Somatic - Cognitive Function</td>
<td></td>
<td></td>
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### Table 6.11

<table>
<thead>
<tr>
<th>NO</th>
<th>YES</th>
<th>NO</th>
<th>YES</th>
<th>NO</th>
<th>YES</th>
<th>NO</th>
<th>YES</th>
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</thead>
<tbody>
<tr>
<td>10</td>
<td>157</td>
<td>13</td>
<td>33</td>
<td>96</td>
<td>143</td>
<td>13</td>
<td>35</td>
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</table>

**Score**
### BEHAVIOURAL DISTURBANCE IN SDAT - SUMMARY OF CT FINDINGS

<table>
<thead>
<tr>
<th></th>
<th>Present (N=22)</th>
<th>Absent (N=114)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hippocampal Atrophy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Mild</td>
<td>13</td>
<td>58</td>
</tr>
<tr>
<td>Moderate</td>
<td>7</td>
<td>44</td>
</tr>
<tr>
<td>Severe</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Callosal Malaria Size</strong> (mm, mean ± SD)</th>
<th>Present (N=22)</th>
<th>Absent (N=114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>8.8 ± 2.9</td>
<td>7.1 ± 2.7 **1</td>
</tr>
<tr>
<td>Left</td>
<td>9.7 ± 2.9</td>
<td>8.2 ± 2.9 *1</td>
</tr>
<tr>
<td>Total</td>
<td>18.6 ± 5.4</td>
<td>15.3 ± 5.2 ***1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Periorbital</strong></th>
<th>Present (N=5)</th>
<th>Absent (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular size (mm², mean ± SD)</td>
<td>2.55 ± .91</td>
<td>1.89 ± .61 **1</td>
</tr>
<tr>
<td><strong>Periorbital</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>Mild</td>
<td>3</td>
<td>78</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Cerebral Atrophy</strong></th>
<th>Absent</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>2</td>
<td>53</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mild</td>
<td>1</td>
<td>65</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Statistics:
1. Students' *t* test
2. Chi-square test

- * p<0.05
- ** p<0.02
- *** p<0.01

**SD:** Standard deviation
significantly more atrophy in all regions and more ventricular enlargement than continent patients (incontinent patients' mean VBR 16.9, Standard Deviation (SD) 6.0; continent patients' mean VBR 13.7, SD 4.4, p < 0.001, students' 't' test).

Subjects were divided into those who had at least one feature of the Kluver-Bucy syndrome (N = 142) and those who had no features (N = 32). Patients in the former group were more likely to have moderate or severe atrophy of the temporal lobes (chi-square test with Yates correction, p < 0.04).

The relationship between the seven elements of the Kluver-Bucy syndrome were analysed to see if they formed a discrete cluster which may have indicated a subtype. The findings were as follows:

1) 18.4% had none of the symptoms, 29.3% had only one symptom, 24.7% had two, 17.2% had three and 8.6% had four. Only one patient had all seven;

2) a Spearman correlation showed significant correlations between disinhibited sexual behaviour and hyperorality (0.30, p < 0.001); hypermetamorphosis and apathy (0.23, p < 0.001) and between binge eating and hyperorality (0.24, p < 0.001);

3) a factor analysis using a Varimax Rotation revealed three factors accounting for 57.1 of the variance. These are shown in Table 6.13 and

4) a Cronbach's Alpha Coefficient to assess internal consistency was low (0.43) confirming that the scale was not assessing a unified construct.
### Factor Analysis of Behaviours Associated with the Klüver-Bucy Syndrome

<table>
<thead>
<tr>
<th>Factor 1</th>
<th>Factor 2</th>
<th>Factor 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.24</td>
<td>0.25</td>
<td>0.45</td>
</tr>
<tr>
<td>0.49</td>
<td>0.72</td>
<td>0.36</td>
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<tr>
<td>0.75</td>
<td>0.67</td>
<td>0.15</td>
</tr>
<tr>
<td>0.10</td>
<td>0.14</td>
<td>0.19</td>
</tr>
<tr>
<td>0.69</td>
<td>0.18</td>
<td>0.15</td>
</tr>
<tr>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

**Sexual Disinhibition**

**Apathy**

**Hypochondriasis**

**Reactive Behaviour**

**Binge Eating**

---

**Table 6.13**
Therefore, the individual items on the scale were significantly associated with each other but the scale was assessing three different factors. Binge eating appeared to be least associated with the other items.

6.2 DISCUSSION

Disorders of Thought Content

The main findings were:

1) a significant proportion of subjects with SDAT suffered from associated delusions of persecutory ideas;
2) delusions of theft were relatively more common in men;
3) some types of delusion were associated with preservation of ventricular size and with basal ganglia calcification as seen on the CT scan and
4) cognitive function bore no direct relationship to the presence of these symptoms.

Frequency of Symptoms

Generally, this present work has found a lower frequency of delusions than other studies. For example, Cummings et al (1987) reported that 30% of DAT patients had evidence of current delusional ideas; Rubin et al (1988) found 31% to be deluded and Berrios and Brook (1985) reported delusions in 37%. Possible explanations for these differences need to be considered. The current study differs from these in two main respects. First, the current sample was an epidemiologically representative one from a catchment area rather than being made up of volunteers attending a research centre (Rubin et al, 1988) or consecutive referrals to an acute service (Cummings et al 1987; Berrios and
Brook, 1985). Both of these methods of selection may have led to a sample biased in favour of patients with more acute psychiatric disturbance. Second, the method of ascertainment of the symptoms in this study was similar to that used by Rubin et al (1988). However, only current symptomatology was investigated by Cummings et al (1987) and the high rate for delusions was attributed to the use of leading questions about their presence. Also, the group described by Cummings et al (1987) was less demented than the current sample and patients were able to co-operate more easily with an interview. Thus, the relatively high rate in other studies may be explained both in terms of the nature of the population and the method by which symptoms were ascertained. I believe the current study, by examining a representative sample, has revealed a more realistic frequency of delusions which accords with clinical experience. One other possibility for the differences is that some of the patients referred to in the present study as suffering from persecutory ideation may have been regarded as delusional by other authors.

**Sex Difference**

No other studies have commented on a differential sex distribution of delusions. In most papers insufficient information is given to enable this to be calculated. In the 20 patients with organic delusions described by Cummings (1985), 16 were male. This apparent high proportion was not commented on by the author and was most likely due to the sample being drawn from a Veterans' Administration facility. In the present study, there is no reason to suppose that there was any systematic bias towards the overreporting of delusions in males. This finding of a
higher prevalence of delusions in males therefore remains unexplained and requires further investigation.

Relationship with CT Scan findings

The anatomical substrate of delusions has been investigated by a number of authors. Cummings (1985) postulated that pathological processes involving the limbic system and basal ganglia were particularly associated with the development of delusions. In this study, "other" delusions were found to be associated with less ventricular enlargement. Although some other studies of DAT subdivide delusions into different types (e.g., stealing and suspicious delusions, Rubin et al. 1988; delusions of abandonment and impostering, Reisberg et al., 1987), no other studies have divided them according to the "simple" or "complex" categories proposed by Cutting (1987) and Cummings (1985). It seems logical that simple delusions (possibly based on an understandable psychological process e.g., mislaying of a handbag leading to a belief that it has been stolen) have a less complex pathophysiological substrate than more systematised and bizarre delusions. Other work has shown that delusions in dementia are inversely related to cortical atrophy in dementia (Jacoby and Levy, 1980a) or to impaired cortical perfusion (Gustafsson and Risberg, 1974). Patients with late paraphrenia (a condition characterised by delusions and hallucinations) have been shown to have no significant cortical atrophy when compared to normal age matched controls (Burns et al, 1989) and these findings have been interpreted as an indication that a relatively intact cortex may be a prerequisite for the development of delusional ideation.
This hypothesis requires confirmation. However, this is the first study to show an inverse relationship between delusions and ventricular enlargement. The association between basal ganglia calcification and delusions has been noted previously (Cummings, 1983, Frances, 1979). Although basal ganglia calcification is a recognised accompaniment of ageing (Murphy, 1979), no studies have looked systematically at its clinical correlates in DAT. The number of patients with basal ganglia calcification in this study was small, but nevertheless there appeared to be a significant relationship between this and "other" delusions.

**Relationship with Cognitive Changes**

There was no direct relationship between the presence of delusions and cognitive function. Although some studies have reported a significant decline in cognitive function in subjects with psychosis (Drevets and Rubin, 1989), this was not subcategorised in terms of delusions or hallucinations. The main methodological problem in this study was the means by which information about the phenomenology was obtained. The severity of illness in the population made reliance on relatives' and caregivers' reports essential. There are difficulties associated with the elucidation of phenomenology in demented patients and most other studies on this type of population have relied on reports of symptoms which might ideally be obtained through a direct interview with the patient (Rabins et al, 1982; Rubin et al, 1988; Reisberg et al, 1987; Merriam et al, 1988).

**Disorders of Perception**

The main findings were:

1) disorders of perception occurred commonly in SDAT;
2) misidentification syndromes were more often found in men;
3) subjects with misidentification syndromes were younger and
   had a younger age of onset but a lower death rate and
4) hallucinations were associated with a more rapid cognitive
decline.

Frequency of Symptoms

Hallucinations are a common accompaniment of SDAT. Their
reported frequency varies from between 3% (Cummings et al, 1987)
and 49% (Rabins et al 1982). Of the smaller number of
publications differentiating visual and auditory hallucinations,
three have found a greater prevalence of visual hallucinations
and two the reverse (Wragg and Jeste, 1989). There is a tendency
for the number of patients with hallucinations to be higher in
those studies describing acute referrals (eg Rabins et al 1982;
Leuchter and Spar, 1985) compared to those reporting subjects who
attend AD research centres (Rubin et al 1988). Results may vary
according to the definitions used, ie the parsimonious definition
used by Cummings et al (1987) resulted in a prevalence rate of 0%
for visual hallucinations and 3% for auditory hallucinations
while Rabins et al (1982), relying on care givers' accounts,
found a rate of 49%. Cummings et al (1987) ignored questionable
hallucinations while Rabins et al (1982) made no mention of such
exclusions. The present study relied largely on caregivers'
accounts and ephemeral visual and auditory hallucinations were
excluded. This may explain why the rate in this study is between
hallucinations have been described rarely (eg 2% in Rubin et al
1988) but were not found in this study.

Berrios and Brook (1984), working with general hospital referrals, described visual hallucinations in 30% of 150 referrals to a psychogeriatrician of whom 43% suffered from SDAT. Hallucinations were usually fleeting and were strongly associated with eye pathology and delusions. No association was found between visual hallucinations and either impairment of vision or delusions in the present study. Berrios and Brook (1984) also described "a new subtype of perceptual disorder" in seven patients who felt television images were real.

Perceptual disturbances, other than hallucinations, have also been described in DAT. Rubin et al (1988) examined these in detail and described them as misidentification syndromes, although they had been described separately in the early literature (Mayer-Gross et al, 1960). Three were documented: misidentification of television (originally described by Berrios and Brook, 1984); misidentification of mirror image and the conviction that someone else is in the house. This last syndrome is difficult to categorise unambiguously - it can be argued that it could also represent a delusion or visual hallucination. In agreement with Rubin et al (1988), but recognising that its exact nosology is debatable, I have chosen to include it as a misidentification. The justification for this is:

a) it often fails to fulfil the definition of a delusion;
b) it occurs frequently without definite evidence that the other person in the house has been seen;
c) it is associated with other misidentifications eg with misidentification of mirror reflection, p < 0.0001 and with
misidentification of television, p 0.08, (both statistics chi-square tests) and
d) it is more systematised and iterative than confabulation.

Rubin et al (1988) described misidentification in 23% of their sample - 7% misidentified their mirror image, 12% misidentified images on the television and 12% felt that others were in the house. These figures are very similar to the rates in the current study. Merriam et al (1988) found extremely high rates of perceptual disturbances with 50% and 40% misidentifying people and places respectively. 17% of their sample displayed the Capgras syndrome, while this occurred in only one person in the present study. The population described by Merriam et al (1988) appears unusual and unrepresentative in view of the extremely high rates of psychiatric symptoms (eg 56% with persecutory ideas and 86% with depression). Misidentification of people occurred in 12% of the current sample which is almost identical to that described by Cutting (1987) in his 74 patients with organic psychoses.

**Sex Distribution**

There was a significant excess of males with misidentification syndromes in this study. No other work has addressed this issue, although Teri et al (1989) found that men were reported to have more problems as described by relatives (which included behaviour such as aggression and symptoms such as loss of interest and muteness). In common with the situation for delusions, there seems no reason to suppose there was any systematic bias in the reporting of misidentifications in men.
However, this merits further investigation as theoretically, altered sensitivity or tolerance on the part of their female carers may result in overreporting in males (Teri et al, 1989).

**Relationship to Age and Mortality**

No previous studies have reported age and age of onset of illness in subjects with misidentification syndromes. Drevets and Rubin (1989) found no difference in age in subjects with or without psychoses but did not subdivide psychotic features into delusions, hallucinations or misidentification syndromes. The association between age and misidentification in this study may be due to involvement of the parietal lobe. Younger age of onset in DAT is associated with parietal lobe damage (Seltzer and Sherwin, 1983) as is agnosia (Lishman, 1987). The association between reduced mortality and misidentification in this study replicates a finding by Drevets and Rubin (1988). These authors found that 'psychotic' patients (those with delusions, misidentification or hallucinations) had a mortality rate of 20% at 66 months compared to 60% in non-psychotic patients (p < 0.05). On the other hand, parietal lobe involvement has been reported to be a predictor of rapid deterioration and higher mortality (McDonald, 1969, Naguib and Levy, 1982a). Since mortality was decreased in patients with misidentifications, there may be some intervening variable involved which was not identified in this study. Decreased mortality in patients with misidentifications may be a manifestation of different underlying cerebral pathology or an indication that a different pattern of care is given to patients with psychotic symptoms and that this in some way reduces mortality.
Relationship to Cognitive Function

The relationship between psychotic symptoms and cognitive function has been investigated in several publications. Generally speaking, psychotic features (including delusions) are said to occur early in the course of the disease while cognitive function is relatively intact (Rothschild, 1941; Cummings, 1985). However, there are conflicting reports about this issue in the literature. Merriam et al (1988) reported a significant association between the degree of cognitive impairment on the IMC and the presence of perceptual disturbances and hallucinations. On the other hand, Teri et al (1988) found no difference in the proportion with hallucinations across three levels of dementia severity, a finding which is in agreement with the present investigation.

Three studies have examined the rate of cognitive decline in DAT and have related this to the presence of psychotic features. Mayeux et al (1985a) found in a longitudinal study of 62 patients with DAT, that the 27 psychotic patients deteriorated much faster on neuropsychological and functional ratings. "Psychosis" was curiously defined as "persistent or recurrent thought disorder". Stern et al (1987), in an extension to the study by Mayeux et al (1985) presented information on 65 subjects examined over a follow up period of up to seven years. An association was noted between psychotic symptoms and myoclonus and extrapyramidal signs. Psychotic subjects deteriorated more quickly than non-psychotic subjects and reached a predetermined 'cognitive endpoint' sooner than their non-psychotic counterparts.
Drevets and Rubin (1989) compared ten subjects who had displayed psychotic symptoms early in the course of DAT with 15 subjects who had never experienced psychosis. The two groups were followed up for 66 months. By 15 months, the previously 'psychotic' group had deteriorated much faster on cognitive function and functional ability and in an overall rating of severity of dementia. The current work replicates the findings of increased cognitive deterioration in 'psychotic' subjects but narrows this down to subjects specifically experiencing hallucinations and not delusions or misidentifications.

**Disorders of Affect**

The main findings were:

1) depressive symptoms occurred commonly in subjects with SDAT but objective signs of depression were much less common;

2) in contrast, symptoms and signs of mania were rare;

3) patients complaining of depressive symptoms were less cognitively impaired but their disease progressed at a similar rate to those without depression and

4) mood changes had neuroanatomical correlates - depression was associated with relative preservation of the third and lateral ventricles and with less widening of the IHF and widening of this region was more marked in subjects with manic symptomatology.

**Frequency of Depression**

Comparisons of the frequency of depression in this and other studies must be judged in the light of differing populations studied and assessment instruments employed. For example, some publications report only the mean number of symptoms (eg Burke et
al 1988), while others give a categorical measure of whether the subject was depressed or not (eg Knesevich et al 1983). Some compare relatives' reports and patient's complaints (eg Burke et al 1988). The present work reports three separate ratings of depression (from patient, relative and trained observer) carried out in a standardised way.

Reports of depressed mood in DAT vary from between 0% (Knesevich et al 1983) and 87% (Merriam et al 1988). Samples drawn from acute care settings tend to have higher rates than those obtained through research clinics. Symptoms tend to be more frequent when relatives' reports are used (Burke et al 1988; Merriam et al 1988) than when these are based on direct interview with the patients (Lazarus et al 1987). The findings of the present study are surprising in that the patients themselves reported more symptoms than the relatives. One possible explanation is the very low threshold used for diagnosing depressive symptoms on the GMSS (ie one symptom) and the comparative insensitivity of the question addressed to the relatives (ie a yes/no answer was required to the question "do you think your relative is depressed?"). The proportion of subjects regarded as depressed by the observer (23.5%) is similar to those regarded as suffering from depressive disorders in other studies (eg Reifler et al 1982; Birkett, 1972). 5.6% of patients were taking antidepressant medication - no other reports are available with which to compare this. Theoretically, treatment with an antidepressant may have masked depressive features, but in view of the small number taking such a drug this
would not significantly affect the results of the present study. The absence of any DSM IIIR cases of major depression is in agreement with reports by Cummings et al (1987) and Knesevich et al (1983). However, it should be noted that the diagnostic categories of primary degenerative dementia of the Alzheimer type and major depressive disorder are mutually exclusive in DSM IIIR.

Mania

In contrast to the frequency of depressive symptomatology, elevated mood in DAT is less common. Bucht and Adolfsson (1983) described it in three out of 18 patients (17%) and Rothschild (1941) noted it in only one of 31 subjects (3%). No standardised instruments have been used to assess manic symptomatology in DAT before the use of the GMSS in the present study. However, the rates of elevated mood revealed are comparable to Rothschild (1941). Subjective evidence of elevated mood occurred in only one subject in the present study.

Relationship between Disorders of Mood and Cognitive Impairment

Subjects who complained of depression were less cognitively impaired than those who did not. This is in agreement with the observations by Reifler et al (1982) and Merriam et al (1988) who found that depressive symptoms were more common in DAT patients with less cognitive impairment. Cummings et al (1987) found little relationship between depression and cognitive function but noted that some features of depression (crying, diminished sleep) were discernible in subjects with all degrees of dementia but that certain symptoms (eg guilt, hopelessness and anxiety) were difficult to assess in those with severe dementia. Thus, the apparent paucity of depressive symptoms in patients with severe
dementia may be an artefact due to the insensitivity of the assessment instruments employed or may be due to the inability to experience such complex integrated emotions and abstract ideas due to advanced brain disease. The present work suggests that patients with severe cognitive impairment have less complaints of depression but do not differ in terms of observed depression (by an interviewer or relative) or previous history of depression. Theoretically, the cholinergic deficit in DAT may protect patients from severe depressive episodes. The deterioration in cognitive function was similar in subjects with or without depression, suggesting that depressed subjects do not have a discrete biological subtype of DAT. However, those with a past history of depression had a tendency to deteriorate less quickly which may suggest that those patients, irrespective of current symptomatology, have a less severe form of the illness. The only other study to present information on the proportion of DAT patients with a past history of psychiatric morbidity is by Agbayewa (1986). In total, 18% of 188 subjects had a previous history of psychiatric problems. When only those with a history of depression are included, the figure is remarkably similar to the present study - 9.6% compared to 9.5% in the current sample. No additional information was given in the paper to allow comparisons with the present sample.

Anatomical Correlates of Affective Disorder

The CT scan changes seen in subjects complaining of depression concur with the cognitive findings in suggesting that these subjects, when compared cross sectionally to a group
without depression, have a less severe form of dementia. Also, there was a negative correlation between the number of depressive symptoms and both third and lateral ventricle size. Patients whose relatives felt that they were depressed had smaller values for these same two indices. This is the first study, as far as I am aware, which has assessed CT findings in depressed and non-depressed SDAT subjects, although Jacoby and Levy (1980a) found no correlation between depressive symptoms on the GMSS and CT variables in demented subjects. Several reports have appeared concerning CT changes in subjects with affective disorder alone (eg Jacoby and Levy, 1980b, Dolan et al 1986) and comparisons between depressives with and without cognitive impairment (eg Pearlson et al, 1989).

Two papers have described the neuropathological changes in AD patients with and without depression. Zubenko and Moossy (1988) examined degenerative neuropathological changes in the locus coeruleus and substantia nigra. In 14 out of 37 patients with AD, depression (based on DSM III criteria) had occurred during life. No differences were found between those with or without depression in terms of age, duration of dementia, brain weight or global rating of SP and NFT. However, degenerative changes in the locus coeruleus and substantia nigra were much greater in patients with depression and a combination of the findings in both nuclei was a better predictor of depression than those in each nucleus separately.

Zweig et al (1988) found evidence of depression during life in eight patients out of 21 with neuropathologically proven AD. They were characterised by having more neuronal loss in the
nucleus coeruleus and dorsal raphe nucleus than non-depressed subjects. Both Zubenko and Moossy (1988) and Zweig et al (1988) suggested that catecholamine depletion due to damage in these aminergic nuclei might be responsible for the clinical features of depression. Zweig et al (1988) suggested that this supports the hypothesis that the presence of depression in AD is representative of a biological subtype of the disorder.

**Behavioural Disturbance**

The main results were:

1) behavioural disturbances occurred in a significant proportion of patients suffering from SDAT;

2) the majority were directly associated with more severe disease, as measured in terms of cognitive function and overall severity;

3) some had anatomical correlates as measured by changes in CT scan and

4) the complete 'Kluver-Bucy' syndrome, even in advanced dementia, was rare but individual items associated with the syndrome were common and tended to be interrelated with the exception of binge eating.

**Proportion of Patients with Behavioural Disturbance**

Aggression is the behaviour causing most distress to carers, both at home and in hospital. The proportion of patients exhibiting this behaviour varies according to the definition used. The one used in the present study (as behaviour liable to cause physical injury to others) is very similar to that used by Swearer et al (1988) and the percentage of subjects demonstrating
aggression is almost identical (20% of the current study, 21% by Swearer et al). Likewise, Reisberg et al (1987) found "violence" to occur in 19% of their sample. Ryden (1988) found 65% of a community sample of 183 subjects to have at least one form of aggression (most commonly verbal aggression). Closer inspection of her results show that acts which would be deemed aggressive in other studies were much less frequent, eg pushing/shoving (21%); pinching/squeezing (15%) and hitting/punching (14%). Thus, it would appear that predominantly physical, as opposed to verbal, aggression showed a rate remarkably consistent at around 20%.

The neurophysiological basis for aggression is unknown, but human and animal studies have suggested circuits involving the medial nuclei of the hypothalamus (Moyer, 1971), the amygdala (Hitchcock and Cairns, 1973; Heath and Mickle, 1960) and hippocampus (Green et al, 1957). Two observations suggest that a link may exist between aggressive behaviour and neurochemical changes in DAT. First, there is evidence that the circuits mediating aggression are cholinergic (Smith et al, 1970) and the cholinergic deficit in DAT is well recognised (Rossor et al 1984). Second, serotonin metabolites have been shown to be reduced in aggressive patients with depression (Branchey et al, 1984) and schizophrenia (Lemoine et al, 1984). A reduction in serotonin metabolites has also been demonstrated in DAT (eg Adolfsson et al, 1979).

Wandering has received less attention as a disruptive form of behaviour in DAT - it was not even included as an item in the original Stockton Behaviour Rating Scale (Meer and Baker, 1966). However, it has been cited by over 70% of families as being a
problem (Rabins et al 1982). The only other study to offer a predetermined definition of wandering is that by Teri et al (1988) who found the behaviour in 26% of the 127 subjects. It was commoner (over 50%) in subjects with severe dementia (defined as an MMSE score of less than ten). Both the frequency of wandering and association with severe dementia have been replicated in the present study.

Urinary incontinence is another major problem both for relatives (Rabins et al, 1982) and care staff (Meer and Baker, 1966). The prevalence rate in out-patients varies from between 16% to 40% (Swearer et al, 1988, Rabins et al, 1982). In one study (Teri et al, 1988), its presence was clearly related to the severity of dementia. This is in agreement with the present work in which the vast majority of those rated as "severe" were incontinent. The grave prognostic significance of the feature has also been shown with 47% of incontinent patients having died within 30 months of follow-up.

Binge eating is one of the features of the Kluver-Bucy syndrome (Sourander and Sjogren, 1952). Increased eating in dementia has been described (Hope et al, 1989) but was not considered to be associated with other signs of the Kluver-Bucy syndrome. A recent study by Morris et al (1989), found increased eating in 26% of 33 patients with dementia. However, the sample was mixed with 27 subjects suffering from DAT and six from other dementias. Swearer et al (1988) found "dietary change" (either decreased or increased eating) in 46% of his subjects. Binge eating differed from other behaviour described here in that the
proportion of the subjects exhibiting this feature did not increase with the severity of dementia. There appeared to be no association with other features of the Kluver-Bucy syndrome, except with the related disorder of hyperorality, which is not surprising.

Sexual disinhibition was seen in 7% of the current sample. Like binge eating, this is considered by some an integral part of the Kluver-Bucy syndrome (Cummings and Duchen, 1981). An identical frequency of sexual disinhibition has been reported by Kumar et al (1989).

Association with Severity of Dementia

The majority of behavioural disturbances, unlike psychiatric symptoms (such as depression, delusions and hallucinations) were positively associated with the degree of dementia. Thus, such behaviour is likely to be a result of advanced cerebral pathology and so the neuropathological substrates may be qualitatively and quantitatively different from those of psychiatric symptoms. The distinction between disturbed behaviour and specific psychiatric symptoms in DAT is often not made (Reisberg et al, 1987, Teri et al, 1988). There was no evidence that disturbed behaviour was the result of prescribed medication.

Relationship with CT Scan Findings

Many of the behavioural disturbances were associated with regional changes in the CT scans. More specifically, aggressive subjects had more atrophy of the temporal lobes. This confirms an earlier report of a similar relationship (Swigar et al, 1985). Hyperorality was associated with widening of the third ventricle and atrophy of the frontal lobe. The proximity of the
hypothalamus to the third ventricle and its function as a regulator of dietary intake may suggest that hyperorality may result from damage leading to increased oral tendencies. Signs of the 'Kluver-Bucy syndrome' were associated with temporal lobe atrophy.

The 'Kluver-Bucy Syndrome'

Sourander and Sjogren (1970) describe individual components of this syndrome as having frequencies of over 70% in 132 post mortem verified cases of AD. Abnormal sexual behaviour was the least frequent with a rate of 17%. However, the various features were not operationally defined and no indication was given of the proportion of cases exhibiting two or more of the components. It has been argued that the full syndrome is unlikely to occur in man as it is specific for other primates and that the abnormal sexual behaviour is the least likely to occur (Sourander and Sjogren, 1970; Pilleri, 1966). Both these observations have been confirmed by the present study. The seven features have been shown to have a degree of interrelationship but the association was not strong and three individual factors emerged with binge eating being isolated. This confirms the impression of Fairburn and Hope (1988,b) that binge eating is not associated with other features of the syndrome. It should also be noted that some of the symptoms were not exclusively related to temporal lobe damage.

One of the problems in the present assessment of the 'Kluver-Bucy Syndrome' involves the way in which behaviour seen in animals is assessed in humans using a rating scale. For
example, it was very difficult to translate unequivocally abnormal sexual behaviour in the monkey (defined originally as increased sexual activity involving forms of heterosexual, homosexual and autosexual behaviour) to the sort of disturbance seen in the patients and to incorporate this into a rating scale. Nevertheless, an attempt to do this seemed worthwhile the questions asked did seem appropriate although there might obviously have been an overlap between this type of behaviour and that as seen in patients with frontal lobe damage.

6.3 SUMMARY

Delusions occurred in 16% of subjects since the onset of illness and had been present within the preceding 12 months in 11%. Simple delusions of theft and suspicion were the most common types and a greater proportion of men suffered delusions of theft. Subjects with other types of delusion had relatively well preserved lateral ventricular size and basal ganglia calcification. 20% of the group had experienced persecutory ideation short of delusions since the onset of the illness. Cognitive function at entry to the study and cognitive deterioration over the succeeding 12 months were not influenced by the presence of disorders of thought content.

Visual hallucinations had been experienced by 13% and auditory hallucinations by 10%. 30% had misidentification syndromes - these were associated with a younger age and younger age of onset of illness and proportionately more men than women were affected. There was a reduced 36 month mortality rate in this group. Subjects with hallucinations had a greater
deterioration in cognitive function at 12 month follow up which could not be accounted for by neuroleptic medication.

At least one depressive symptom was reported by 63% of the sample, 24% were rated as depressed by a trained observer and 43% were considered depressed by their relatives. 10% had a previous history of depression. In contrast, elevated mood was rare, occurring in only six patients (3.5%). Subjects with depressive symptoms had less cognitive impairment and less ventricular enlargement on CT compared with those without symptoms. Widening of the IHF was associated with symptoms of mania but was inversely related to the presence of depressive symptoms.

Aggression was present in 20%, wandering behaviour in 19%, binge eating in 10%, hyperorality in 6%, urinary incontinence in 48% and sexual disinhibition in 7%. Behavioural abnormalities were greater in those with more severe dementia. Temporal lobe atrophy correlated with aggression and widening of the third ventricle with hyperorality. Features of the Kluver-Bucy syndrome were commonly seen but the full syndrome occurred in only one subject. Patients with at least one feature of the Kluver-Bucy syndrome had greater temporal lobe atrophy than those without any of the features.
CHAPTER 7
LONGITUDINAL CHANGES IN COGNITIVE FUNCTION
AND COMPUTED TOMOGRAPHY

7.1 RESULTS

Cognitive Function

Assessment of longitudinal changes in cognitive function was confined to those patients who scored above zero on the CAMCOG examination at entry to the study - 142 were eligible for inclusion. Of these, 34 died during the next 12 month follow up and so data are presented on the remaining 108. Table 7.1 outlines the mean scores on the cognitive tests at entry to the study and 12 months later. There was a highly significant deterioration in cognitive function across the group. The relatively large sample size with an approximately normal distribution of scores justified the use of the paired t-test. Figure 7.1 shows the distribution of change in the MMSE score over 12 months. There were no significant differences between survivors and non-survivors in either cognitive tests or in age, age of onset or duration of illness. However, as would be expected, non-survivors were more likely to be in CDR III (Chi-square test, p<0.007) but no differences were seen in the two groups with regard to sex, family history of dementia, place of residence or CT variables.

Table 7.2 shows the effect on change in cognitive function of family history of dementia and initial cognitive score. A family history of dementia in parents was associated with a larger decline in cognition over one year, despite there being no difference in initial score. This was significant for the MMSE
<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Mean (SD)</th>
<th>Initial Score</th>
<th>Change in Cognitive Function in ADAT (N=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>Mean (SD)</td>
<td>Score after 12 months</td>
<td></td>
</tr>
<tr>
<td>Post</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>9.9 (6.0)</td>
<td>(max = 90)</td>
</tr>
<tr>
<td>3.0</td>
<td></td>
<td>6.9 (6.0)</td>
<td>(max = 90)</td>
</tr>
<tr>
<td>6.0</td>
<td></td>
<td>2.6 (2.6)</td>
<td>*</td>
</tr>
<tr>
<td>9.0</td>
<td></td>
<td>2.0 (2.0)</td>
<td>(max = 90)</td>
</tr>
<tr>
<td>12.0</td>
<td></td>
<td>1.1 (1.1)</td>
<td>(max = 90)</td>
</tr>
<tr>
<td>15.0</td>
<td></td>
<td>1.1 (1.1)</td>
<td>(max = 90)</td>
</tr>
<tr>
<td>18.0</td>
<td></td>
<td>1.1 (1.1)</td>
<td>(max = 90)</td>
</tr>
<tr>
<td>21.0</td>
<td></td>
<td>1.1 (1.1)</td>
<td>(max = 90)</td>
</tr>
<tr>
<td>24.0</td>
<td></td>
<td>1.1 (1.1)</td>
<td>(max = 90)</td>
</tr>
</tbody>
</table>

**Key:**
- **p < 0.05**  (N = 108)
- **p < 0.02**  (N = 108)
- **p < 0.01**  (N = 108)

**Scores:**
- **Total**
- **Perception**
- **Attention**
- **Calculation**
- **Praxis**
- **Language**
- **Memory**

**Notes:**
- **Abstract Thinking:**
- **Calculation (max = 2)**
- **Attention (max = 7)**
- **Praxis (max = 12)**
- **Language (max = 30)**
- **Memory (max = 27)**

**Notes:**
- **Mini-Mental State:**
- **Change in Cognitive Function in ADAT (N=108)**

**Table 7.1**
Figure 7.4

Distribution of change in Mini-Mental State Examination score over 12 months in Alzheimer's disease.
### Table 7.2

**Change in Cognitive Function - Effect of Family History of Dementia and Initial Cognitive Function**

<table>
<thead>
<tr>
<th>TEST (SCHRETER'S)</th>
<th>INITIAL COGNITIVE SCORE</th>
<th>FAMILY HISTORY OF DEMENTIA</th>
<th>FAMILY HISTORY OF DEMENTIA AND INITIAL COGNITIVE FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANOVUS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>34</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>N</td>
<td>43</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>N</td>
<td>43</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

**Key:**
- *: p < 0.005
- NS: no significant differences between the 3 groups at p < 0.05

All other non-significant at p < 0.05
test with a strong trend (not quite statistically significant) for the other tests. A family history in either mother or father both contributed equally to this significant result but was not affected by the degree of certainty with which the judgement of the dementia syndrome in the relative was made (possible, probable or definite, see Chapter 4). The score on the CAMCOG at entry to the study was used to divide the sample into three subgroups according to the degree of cognitive impairment. Subjects with moderate impairment (CAMCOG scores of between 30 - 50 out of 107) tended to have a greater decline in cognitive function than those with either mild or severe impairment. There was no significant correlation between duration of illness and decline. However, when the sample was divided into those with duration of illness above or below 24 months, there was a tendency for those with the shorter duration of illness to have a greater decline. This was significant for the memory subscale of the CAMCOG (-2.7 compared to -1.5 points per year, Students' 't' test, p<0.05).

Other factors which might have influenced the rate of cognitive decline were examined. Significant negative findings included no correlation between rate of cognitive deterioration and age at entry to the study, age of onset, years in education, sex, extrapyramidal signs, myoclonus and presence or absence of apraxia, aphasia or parietal lobe atrophy on CT scan.

To examine patterns of decline in more detail, a cluster analysis was performed using all the indices of change in cognition. Ward's method was employed using squared Euclidean
distances on standardised scores. Table 7.3 shows that three clusters resulted (N = 105 as incomplete data were present in three cases). The significant between the clusters using a one way ANOVA (Scheffe’s test), merely reflects the ability of the cluster analysis to separate the groups effectively. These results are shown graphically in Figure 7.2. The majority of the subjects showed mild or moderate decline. The nine subjects in the third cluster showed the most decline of the group. These nine were not significantly different from the others in their initial characteristics. The first cluster included six subjects whose MMSE actually increased over the follow-up period. The increase was small (two subjects each had an increase of 1, 2 and 3 out of 30). Three of these subjects were hospitalised for continuing care; two had very mild dementia and lived at home and the sixth was in a nursing home. There was no significant difference between these six subjects and the others in terms of age, age of onset, duration of illness or initial cognitive performance. Unexpectedly, they had significantly more atrophy of the frontal lobe (p<0.04, Chi-square test), parietal lobe (p<0.002) and left Sylvian fissure region (p<0.001) than the others.

An attempt was made to quantify the rate of decline over 1 year. To compare with other studies, it was necessary to convert the MMSE result into an IMC score using the formula of Thal et al (1986), which is only valid when the MMSE is between 10 and 26. 23 patients had scores falling in this range on both occasions. The mean decline in Blessed Score was 2.80 (SD 3.21) per year (ie an increase of 2.80 errors per year).
### Table 7.3: Change in Cognitive Function in SDAQ (N = 105)

<table>
<thead>
<tr>
<th>Cluster</th>
<th>N = 9</th>
<th>N = 33</th>
<th>N = 43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Decline</td>
<td>9.9% Confidence Interval</td>
<td>Mean Change</td>
<td>9.5% Confidence Interval</td>
</tr>
<tr>
<td>Moderate Decline</td>
<td>12.4% Confidence Interval</td>
<td>Mean Change</td>
<td>14.8% Confidence Interval</td>
</tr>
<tr>
<td>Mild Decline</td>
<td>16.2% Confidence Interval</td>
<td>Mean Change</td>
<td>18.5% Confidence Interval</td>
</tr>
</tbody>
</table>

All values in clusters differ from each other at p < 0.05 (One-Way ANOVA, Scheffe's Test)
There was no difference between the CAMCOG scores of the three groups at initial evaluation or follow up.

Initial Evaluation

12 month follow up

Severe (N = 9)

Moderate (N = 53)

Mild (N = 43)

Change in total CAMCOG score over 12 months in each of the 3 cluster groups.

Figure 7.2
Computed Tomography

Of the original sample of 138 who had been scanned at entry to the study, 36 had died and could therefore not be rescanned. Two of the repeat scans were discarded for technical reasons. It was not possible to rescan 37 patients who had been scanned at entry to the study and were still alive after one year. The reasons for scan failure in these 37 were: uncooperative, aggressive behaviour - 16 patients (43%); too physically ill to be scanned - 10 patients (27%); moved too far out of the district making it impractical to perform a second scan - 8 patients (22%) and relatives refusing permission for a second scan - 3 patients (8%).

Significant changes took place in the CT scan indices over the 12 month follow up period. The mean VBR increased from 15.1 to 16.5 (9.3% increase, Student's t test p < 0.0001), third ventricular size increased from 1.8 cm² to 2.1 cm² (16.6% increase, Student's t test p < 0.001) and Total Cortical Score (the summation of the regional atrophy scores) deteriorated from a mean of 5.9 out of 23 to 6.3 (6.8% increase, Student's t test p < 0.0001).

It was found that measures of the sylvian fissure area often showed a decrease in size over time which was due to different positioning of the patient at the second scan. These results were therefore not included in the analysis. There was a wide variation in the changes in the CT scan - 14 out of the 63 showed either no change or an actual decrease in size of the third and lateral ventricles suggesting that no statistically significant
overall change had taken place. A group of six patients, demonstrated a mean change in VBR of three or greater. A histogram of the distribution of changes in VBR suggested that these formed a subgroup and were not merely at one end of a normal distribution. Neither of these subgroups (those demonstrating large or negligible change in CT variables) showed any difference to the others in terms of demographic details or initial and follow-up cognitive or CT variables. The presence or absence of white matter changes did not affect the rate of increase in ventricular size. Changes in the CT indices were not related to initial severity of illness as assessed by the CDR.

The association between decline in cognition and change in CT scan variables was examined. A frequency distribution curve suggested that both the changes in cognitive function and in ventricular size were normally distributed, so a Pearson Product Moment Correlation was performed. The correlations between change in ventricular size and the cognitive tests were: total CAMCOG score -0.21 (p < 0.05); language -0.19 (p < 0.1); memory -0.24 (p < 0.05) and praxis -0.20 (p < 0.1). There was no significant correlation between age of onset of the disorder and increase in ventricular size (Pearson correlation, 0.0025).

7.2 DISCUSSION

Cognitive Function

Assessments of the decline in cognitive function showed:
1) a highly significant decline in cognitive function occurred over 12 months in the group;
2) the rate of decline had a relatively normal distribution with some patients having marked decline and others only minimal
deterioration;
3) initial cognitive function, duration of illness and family history of dementia in parents had some influence on rate of decline and
4) age, age of onset, parietal lobe atrophy, presence of aphasia and apraxia and previous educational attainment had no effect on rate of deterioration.

Rate of Cognitive Decline

Deterioration in cognitive function in SDAT has been documented previously and this is replicated by the present findings. It has also shown the ability of the CAMCOG scale to detect changes in cognitive function over one year. Other reports have demonstrated a non-significant decline when the follow-up period is three months or less (eg Cowan et al, 1975), but a significant decline is apparent when the follow-up period is six months or more (eg Naguib and Levy, 1982a, Katzman et al, 1988). Deterioration in SDAT and documentation of a variety of clinical stages has been reported by Reisberg et al (1982, 1986). The rate of decline was found to be relatively homogeneous as the histogram of the distribution of decline has shown (Figure 7.1). This is almost exactly the same shape as the distribution of decline in the IMC score in the paper by Ortof and Crystal (1989). At the extremes of this distribution were subjects whose decline was very rapid and others where the decline was negligible. This is in agreement with other studies (eg Dastoor et al, 1985; Botwinick et al, 1986). Botwinick et al (1986) described a subgroup of five out of 18 patients with mild DAT who
progressed very little over a four year period. Four possible explanations for this lack of progression were given. First, that these patients were at one end of a normal spectrum. Second, that they were less severely demented to start with. Third, the duration of disease was less in this group and fourth, that they represented an identifiable subgroup of DAT, ie "slow or non-progressive". In invoking the same explanations for the changes in the current population, it can be seen that the second and third explanations are not supported but both the first and last explanations remain possibilities.

The surprising finding of more atrophy in the frontal, parietal and left sylvian fissure region of the CT scans in the six patients who deteriorated most is difficult to interpret. Theoretically, if rate of decline of cognitive function (rather than actual degree of cognitive impairment) was related to cerebral atrophy (as suggested by Luxenberg et al, 1987), then one might argue that these patients had already reached a maximal level of cerebral atrophy ie a 'floor effect'. Thus, further deterioration in the atrophic process would be minimal and this is reflected in the relative non-progression of cognitive function. However, this is a theoretical explanation of a surprising finding and the question remains unresolved. Parietal lobe atrophy has been associated with a poor prognosis (McDonald, 1969, Hare, 1978, Naguib and Levy, 1982a). However, the outcome variable used was death rather than decline in cognitive function and these two indices may not necessarily be related. Naguib and Levy (1982a) showed a significant association between an increased VBR and cognitive decline and a small but not
A statistically significant association between cognitive decline and radiodensity in the right parietal region on CT scan. However, the number of patients was small (N=12), the follow-up period variable and the patients 3.6 years younger than in the present study. Further longitudinal studies of both cognitive decline and progression of cerebral atrophy are required to answer this question.

The finding of an association between initial cognition and decline concurs with that of Katzman et al (1988). These authors found that a ceiling effect occurred with an IMC score of 24 or above, which is equivalent to a floor effect (ie where a score is at, or sufficiently near zero, so that any further decline is not observed) seen with the MMSE (the IMC score is the number of errors while the MMSE and CAMCOG score is the number correct). In this study, patients with intermediate scores tended to deteriorate more quickly than those with either high or low scores. This may indicate that in the course of SDAT, there is a relatively small decline initially, followed by a more marked decline and then a slowing down later in the course of the disease. Alternatively, it may be due to a floor and ceiling effect on the MMSE and CAMCOG.

Quantification of Rate of Decline

Katzman et al (1988) quantified the annual rate of decline on the Blessed Scale in 161 patients drawn from four populations - a nursing home, an AD Research Centre, a private practice and an ageing study. The rate of decline in the present work (2.80 IMC points per year) is almost identical to that in the Nursing
Home and Research Centre subsamples. It is likely that these two populations had more in common with the present sample than those seen in the ageing study (who were all normal volunteers, some of whom developed dementia) or a private practice population. Ortof and Crystal (1989) found a mean decline of 4.1 Blessed points per year in a sample of 54 DAT patients. There are two possible explanations for this apparently high rate. First, the rate quoted was the mean for all 54 patients - when the group was split into those with an IMC score of 0-15 (similar to the present sample), the mean rate of decline was 2.70. Second, the average age of the group was 67, 13 years younger than this sample. The more rapid decline expected in younger patients (Becker et al, 1988) may therefore partly explain the differences between the studies.

Factors Affecting Decline

The relationship between family history of dementia and rate of decline has been examined in several studies and found not to affect rate of cognitive decline (Thal et al, 1986; Ortof and Crystal 1989). In this study, there was a strong trend (just statistically significant) towards an increased decline in subjects whose parents suffered from dementia. The fact that the siblings of the patients may themselves not have completed the period at risk may have affected the findings and the numbers involved are small. The results should therefore be interpreted with caution and require replication. However, one possible explanation is that these patients have a genetic predisposition to a more severe form of the disease. Duration of illness of less than two years was associated with increased decline in the
memory subtests of the CAMCOG, a result in agreement with that of Thal et al (1986).

In this work, several negative findings require explanation. Age of onset and age at examination were found not to be associated with more rapid rate of decline. This accords with other studies such as that of Thal et al (1986a), Becker et al (1988) and Ortof and Crystal (1989). Heyman et al (1987) and Christie and Wood (1988), found that a younger age of onset was predictive of death and institutionalisation. However, neither study used change in the cognitive score as the outcome variable and Heyman et al (1987) studied early onset cases. Huff et al (1987) reported an association between age of onset and progression. Paradoxically, they found that onset over the age of 65 was associated with more rapid progression. This was barely statistically significant and probably not clinically relevant. The lack of an association between age and decline in the present sample may have been due to the fact that all subjects were over 65 years of age.

The presence of aphasia has been associated with more rapid progression in two studies (Faber-Langendoen et al, 1988, Knesevich et al, 1985). However, both used the CDR as a measure of progression and Knesevich et al (1985) used a cut-off point on the IMC score at the time of the second examination, regardless of initial score. The CDR is a global rating of dementia and includes no specific cognitive tests. Therefore, neither study is strictly comparable to the present results. The lack of influence on progression of sex or previous education is in keeping with
the observations of Katzman et al (1988). With regard to neurological signs, all the subjects in the present study with either extrapyramidal signs or myoclonus were very demented and so a pronounced floor effect on the cognitive tests would explain the absence of an effect of these two physical signs on progression.

Four methodological drawbacks of the current work should be mentioned. First, many of the patients had advanced dementia and so a floor effect is seen on the cognitive tests, tending to underestimate cognitive changes. Second, the follow-up period was comparatively short (12 months). Although a longer follow-up period would be desirable, this would lead to an increase in the dropout rate and accentuate floor effects previously noted. Third, the patients were over age 65 which may account for the lack of an association between age of onset and progression. Finally, patients who died during the follow up period could obviously not be included in the calculation of change in cognitive score which may have influenced the rate of decline in some way.

Computed Tomography

The main findings were:

1) statistically significant changes in the CT indices measured took place over the 12 month period;

2) there was wide variation in degree of the changes and

3) a relationship existed between deterioration in cognitive function and increasing ventricular size.

There are four criticisms which can be levelled at this part of the study. First, because of attrition the population
examined was not unselected and the possibility of bias cannot be ruled out. Thus, only 63 of 100 patients could be re-scanned after one year. It is difficult therefore to be confident about extrapolating these results to a population of SDAT subjects. However, if serial scans are going to be of help in identifying subtypes of SDAT or to assess the natural history of the condition, it can obviously only be of use in those patients in whom it is possible to perform serial scans. SDAT is a progressive condition and deterioration in behaviour and therefore diminished ability to co-operate with investigations is to be expected over a 12 month period. It was decided, ab initio for ethical reasons, that no sedation for CT scans would be given in this research project.

Second, most of the patients suffered from moderate to severe dementia and as such the changes may be different than if the group had mild dementia (due to a CT 'floor' effect).

Third, is the problem of repositioning patients after 12 months. Although the scanner employed was the same at both parts of the study, difficulty was experienced in positioning the patients correctly and, as was shown by the measures of the sylvian fissure, small changes in the position of the patients can produce misleading results. In three of the other studies assessing change in CT (Gado et al, 1983, Brinkman et al 1984, de Leon et al, 1989), the machines used were different at entry and follow up and in this regard the present study may be considered to be better. The effects of technical changes in the scanner itself were felt to be minimal, as shown by the lack of
scanner 'drift' over time (Jacobson et al, 1985). Also, the 
assessment of total cortical score by visual rating and the use 
of the mean of two slices to measure ventricular size probably 
help to minimise further these confounding factors. Finally, it 
was not possible in this study to rescan normal adults over 12 
months. However, these is sufficient information available from 
other studies to suggest that changes due to normal ageing are 
minimal and that changes in SDAT are as a result of the disease 
process and not a consequence of ageing (Brinkman et al, 1984, 
Gado et al, 1983). Despite these drawbacks in method, useful 
results were obtained in this study.

First, it was shown that significant changes in CT scan 
appearance occurred in the SDAT group, as a whole, over 12 
months. Both ventricular enlargement was remarkably similar (9% 
per annum) to that described by de Leon et al (1989) who 
estimated total ventricular volume. Luxenberg et al (1987) 
assessed both third and lateral ventricular enlargement - the 
increases were of the order of 20-50%. However, the numbers 
studied were small (N=12).

The second finding, similar to that of Naguib and Levy 
(1982a), was that a significant minority of patients (14 out of 
63) showed no deterioration in the CT scan. Why is this? It may 
be that two subgroups do exist as suggested by Naguib and Levy, 
(1982a) - one with patients in whom minor or no change in CT 
indices takes place and another marked changes. A further 
possibility is that the patients who did not change had reached a 
predetermined level of brain atrophy and so the lack of 
continuing atrophy was due to a "floor effect". However, it is
noteworthy that the patients whose atrophy did not progress were no more cognitively impaired than those who did show further CT changes. The CT methods used in this study may also be criticised, but the same applies to other work in this field. I felt it is unlikely that any shortcomings in the CT method contributed significantly to the results of this study. Test - retest, interrater and concurrent validity have been proven with the current technique and it has also been shown that there has been no significant alteration in the CT attenuation numbers over time. Also, this study had the advantage of using the same machine at entry and follow up while other studies (eg Brinkman et al, 1984, and de Leon et al 1989) used different machines.

The third finding was that there is a relationship between cognitive deterioration and increasing ventricular size. This accords with other studies which have shown an association between cognitive and radiological deterioration (Naguib and Levy, 1982a, Luxenberg et al 1987, de Leon et al 1989). The specific association between increasing ventricular size and apraxia just failed to reach statistical significance. McDonald (1969) and Hare (1978) stressed that parietal lobe involvement was a poor prognostic sign and Naguib and Levy (1982,b) provided radiological evidence to support this.

In conclusion, significant changes in CT scan indices take place over 12 months in patients with moderate to severe dementia. Although there is wide variation in the changes seen over time, the evidence for the presence of specific subgroups of
SDAT is small as the changes were not related to other indices of the disease.

**Special Problems encountered in Longitudinal Studies**

There are currently several major studies being undertaken, mainly in the USA, investigating dementia of the Alzheimer type employing a longitudinal study design (La Rue, 1988). The rationale for utilising this method in the study of dementia is straightforward. It is irrational to attempt to characterise in a cross-sectional fashion an entity which changes over time. Thus, in longitudinal studies "the entity under investigation is observed repeatedly and evolves over time" (Baltez and Nesselroade, 1979). The natural history of the disorder can thus be assessed. This has been defined as "biobehavioural changes over time in groups of individuals not subjected to a systematic intervention" (La Rue, 1988). The longitudinal method has its own drawbacks. Influences which may detract from the validity of such investigations have been outlined by La Rue (1988) and are summarised below with a note on how the present study attempts to overcome them.

1) **Reliability and Stability of Instruments:** the measures used require to possess reliability (interrater and internal consistency) in common with non-longitudinal designs. Measures must also be stable over short periods and yet be sensitive enough to assess any difference due to decline consequent on the natural history of the disorder. For the methods used in this study, test-retest and interrater reliability have been established (eg CAMDEX, Roth et al 1986, GMSS Copeland et al, 1976). For measures developed for this study (eg Kluver-Bucy
symptoms on the behaviour rating scale and quantitative CT scan analysis), reliability statistics have been computed and appear in the relevant results section.

2) **Instrument Bias**: the most obvious way of introducing such bias is by changing instruments partway through a study (e.g. by using updated versions of tests or by adding new tests or examinations). This is not an issue on the work reported here as the measures are the same throughout the study. The effects of instrumentation bias may appear in other ways. In the course of a study it is likely that subjects will become more demented. Thus, there is a risk of floor effects whereby the test is not sufficiently sensitive to measure changes in very demented patients. In the current study, the aim was to assess heterogeneity in SDAT and so subjects of varying degrees of dementia were included. Thus, some were still living independently in the community and suffered from mild dementia whereas others were suffering from extreme dementia and were often hospitalised and unable to speak. For the tests requiring co-operation from the patient, e.g. tests of cognitive function, no single test exists which would be as equally applicable to every patient in the study. Thus, tests spanning a variety of functional and organic domains were employed. The cognitive tests may show a floor effect and some of the behavioural assessments were too crude for the mild cases and so a ceiling effect was apparent. Another source of bias, slightly different to floor and ceiling effects, applies to the CT scan. Although equally applicable to all subjects, it did require a significant
amount of co-operation. Some patients were too severely demented to co-operate in the scanner and some patients were sufficiently mildly affected to be able to say they did not wish to co-operate. Thus, the instrument is biased to those able to undergo the procedure but those excluded were not simply as a manifestation of a degree of dementia (this was unavoidable as it was considered unethical to sedate a patient for a research scan).

3) **Repeated Testing:** A practice effect may be apparent on testing normal subjects or mildly impaired subjects over a short time interval. These are not concerns of the present study because of the presence of amnesia which was inherent in the selection process. The time interval between testing (12 months) was considered sufficiently long to make a practice effect unlikely. Other effects such as a change of setting for the examination were unavoidable.

4) **Subject Attrition:** This can take two forms, refusal by a subject to participate in a follow-up or death of a subject. There is evidence that these can occur non-randomly, eg less able people are more likely to refuse repeated testing and are more likely to die than more able people. Thus, at each successive testing, there may be an underestimation of decline as less impaired people survive and take part in the follow-up.

Botwinick et al (1988) studied the question of subject attrition in research in great detail. They reported on their own data concerning patients with DAT and normal controls participating in a longitudinal study. Two main conclusions were drawn. First, subjects who opt out of the research were of
similar cognitive impairment to those who remained. This was true both of the normal subjects and the demented patients. Second, the authors compared results from two groups of patients - those in a longitudinal study of SDAT and those in a cross-sectional study. Each was given a rating of dementia (mild, moderate or severe on the CDR) as well as more detailed neuropsychological tests. The results were similar for individuals assessed longitudinally at various levels of the global rating as for those assessed cross-sectionally. Thus, studying a group of patients cross-sectionally with dementia of varying severity gives no less information than studying a single group of patients longitudinally. However, as the authors mention, longitudinal studies are essential when assessing individual subject change or the rate of change.

In the current project, death was the only reason for subject attrition. This high follow-up success rate was obtained using two strategies - a willingness to travel considerable distances to examine patients and, most importantly, maintaining close contact with the patient and family providing support and advice and thus facilitating co-operation.

5) Cohort Effects and Sampling Bias: individuals born at different times and in different areas have experienced influences which distinguish them from others. Thus, cohort effects (assessing patients over a wide age range, often 50 to 80 years), and sampling bias (recruiting subjects for a study depending on volunteers who may be of a higher socioeconomic group and more willing to pursue research opportunities) may
influence the results. The current study avoids sampling bias by investigating patients from a defined catchment area and was thus not dependent on volunteers (a very small number of people did refuse to take part in the study, less than 3%, but these did not differ significantly in major demographic variables from those included).

7.3 SUMMARY

A highly significant deterioration in cognitive function was observed in the group over the 12 month follow up period. Decline in cognitive scores was relatively normally distributed. An increased rate of decline was seen in patients whose parents suffered from dementia, in subjects who had moderate dementia and who had been ill for less than 24 months. Age, age of onset and the presence or absence of aphasia and apraxia had no influence on rate of progression. A cluster analysis revealed three patterns of decline.

Significant deterioration occurred in the CT measures investigated (lateral ventricular size, third ventricular size and cortical atrophy) in 63 of the patients over one year. There was a wide variation in the size of the changes observed, 14 out of 63 patients showing no significant change while six showed a marked increase in ventricular size. However, neither group differed from the others in any demographic, cognitive or other CT variables which suggested, at least on the CT measures used in this study, that no clearly identifiable subgroups of SDAT were present. Changes in CT indices were not related to initial severity of disease. An increase in ventricular size was associated with cognitive deterioration.
CHAPTER 8
NEUROLOGICAL SIGNS

8.1 RESULTS

Table 8.1 shows the frequency with which each neurological sign was present. The number of subjects varies slightly as a small number were resistive to physical examination and it was not possible to examine them fully. There was no difference in the frequency of neurological signs in those with "possible" or "probable" AD (with the exception of an abnormal plantar response) and the results were essentially the same when the groups were analysed separately. Thus, for the sake of convenience, the findings are presented for the group as a whole.

Patients with a grasp reflex had a younger age of onset (69.7 cf. 75.1 years, p<0.01) and longer duration of illness (101.3 cf. 61.8 months, p<0.05) than those without this reflex. Subjects with increased tone had a longer duration of illness (86.5 cf. 62.2 months p<0.03) and a tendency towards a younger age of onset (71.6 cf. 75.2 years p=0.058) than those with normal tone. Similarly, subjects with myoclonus had a tendency towards a younger age of onset (70.4 cf. 75.4 years, p=0.064, all above statistics, students 't' test).

Table 8.2 shows the scores on cognitive function for those with and without neurological signs. There was no difference in scores for subjects with and without abnormal reflexes, extensor plantars, snout reflex, palmomental reflex, tremor or epileptic fits. A grasp reflex, increased tone and myoclonus were found to be significantly more common in the CDR III category (severe dementia, Chi square test, p<0.0005, p<0.003 and p<0.03)
TABLE 8.1

FREQUENCY OF NEUROLOGICAL SIGNS IN SDAT

<table>
<thead>
<tr>
<th>Sign</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unequal Reflexes (N = 165)</td>
<td>7</td>
<td>4.2</td>
</tr>
<tr>
<td>Extensor Plantars (N = 161)*</td>
<td>6</td>
<td>3.7</td>
</tr>
<tr>
<td>Snout Reflex (N = 159)</td>
<td>65</td>
<td>40.9</td>
</tr>
<tr>
<td>Palmo-Mental Reflex (N = 160)</td>
<td>4</td>
<td>2.5</td>
</tr>
<tr>
<td>Grasp Reflex (N = 161)</td>
<td>13</td>
<td>7.3</td>
</tr>
<tr>
<td>Any Primitive Reflexes (N = 158)</td>
<td>73</td>
<td>46.2</td>
</tr>
<tr>
<td>Tremor (N = 165)</td>
<td>9</td>
<td>5.5</td>
</tr>
<tr>
<td>Increased Tone (N = 163)</td>
<td>17</td>
<td>10.4</td>
</tr>
<tr>
<td>Myoclonus (N = 173)</td>
<td>8</td>
<td>4.6</td>
</tr>
<tr>
<td>Epileptic Fits (N = 176)</td>
<td>5</td>
<td>2.8</td>
</tr>
<tr>
<td>Extrapyramidal Signs (N = 162)</td>
<td>19</td>
<td>11.7</td>
</tr>
<tr>
<td>Drug Induced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal Signs (N = 162)</td>
<td>4</td>
<td>2.5</td>
</tr>
</tbody>
</table>

* More common in subjects with 'possible' Alzheimer's Disease
(p<0.02, Chi-square test with Yates Correction)
TABLE 8.2
COGNITIVE FUNCTION IN SUBJECTS WITH NEUROLOGICAL SIGNS

<table>
<thead>
<tr>
<th></th>
<th>Mini-Mental State examination (MAX = 30) Mean ± SD</th>
<th>CAMCOG (MAX = 107) Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grasp Reflex:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present (N = 13)</td>
<td>0.1 ± 0.3</td>
<td>0.3 ± 1.1</td>
</tr>
<tr>
<td>Absent (N = 148)</td>
<td>9.1 ± 6.5 ***</td>
<td>30.4 ± 21.7 ***</td>
</tr>
<tr>
<td>Increased Tone:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present (N = 17)</td>
<td>1.7 ± 3.1</td>
<td>7.0 ± 11.6</td>
</tr>
<tr>
<td>Absent (N = 146)</td>
<td>9.0 ± 6.6 ***</td>
<td>29.9 ± 22.2 ***</td>
</tr>
<tr>
<td>Myoclonus:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present (N = 8)</td>
<td>2.2 ± 3.4</td>
<td>5.9 ± 8.6</td>
</tr>
<tr>
<td>Absent (N = 165)</td>
<td>8.3 ± 6.7 *</td>
<td>27.8 ± 22.5 ***</td>
</tr>
<tr>
<td>Extrapyramidal Signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present (N = 19)</td>
<td>4.1 ± 5.6</td>
<td>15.7 ± 19.1</td>
</tr>
<tr>
<td>Absent (N = 143)</td>
<td>8.8 ± 6.6 **</td>
<td>29.2 ± 22.4 *</td>
</tr>
<tr>
<td>Drug Induced Extrapyramidal Signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present (N = 4)</td>
<td>1.8 ± 2.2</td>
<td>6.0 ± 6.4</td>
</tr>
<tr>
<td>Absent (N = 158)</td>
<td>8.4 ± 6.7 *</td>
<td>28.2 ± 22.4 *</td>
</tr>
</tbody>
</table>

KEY: SD - Standard deviation statistics, students' 't' test. Difference in cognitive function between those with and without physical signs, *p<0.05; ** p<0.01; *** p<0.001.
respectively). Thus, there was a strong association between these signs and advanced dementia. A grasp reflex and increased tone were more common in patients who died within the three-year follow up (Chi square test, p < 0.02, p < 0.007 respectively). There was no sex difference in patients with and without neurological signs.

Table 8.3 shows the relationship with CT scan changes. Extrapyramidal signs were associated with increased third ventricular size and calcification of the right globus pallidus, a grasp reflex was more common in those with frontal lobe atrophy and those with a history of epileptic fits had more atrophy in the left sylvian fissure region.

Table 8.4 shows the incidence of new signs during the first 12 month follow-up. The number at risk is smaller than the total number due to exclusion of those exhibiting the sign initially and due to attrition of the sample (because of death during follow-up or poor co-operation with physical examination). There was no difference in the numbers developing signs in subjects with "possible" or "probable" AD with two exceptions - the development of an extensor plantar response and epileptic fits were more common in those with possible AD. The relationship between age, age of onset and duration of illness and the development of a grasp reflex, increased tone and myoclonus was the same as the relationship between these features at the start of the study. VBR was significantly greater in those developing a grasp reflex (19.5 cf. 15.0 p < 0.05) and an extensor plantar response (20.7 cf. 15.0, p < 0.02) and showed a tendency to be
### TABLE 8.3

**NEUROLOGICAL SIGNS IN SDAT - SUMMARY OF CT FINDINGS**

<table>
<thead>
<tr>
<th>EXTRAPYRAMIDAL SIGNS</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N = 13) (N = 116)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size of third ventricle</td>
<td>2.3 ± 0.73</td>
<td>1.9 ± 0.58</td>
</tr>
<tr>
<td>(cm², Mean ± SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcification in right globus pallidus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Absent</td>
<td>9</td>
<td>109</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GRASP REFLEX</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FRONTAL LOBE ATROPHY</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1</td>
<td>33</td>
</tr>
<tr>
<td>Mild</td>
<td>3</td>
<td>72</td>
</tr>
<tr>
<td>Moderate</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HISTORY OF FITS:</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N = 3) (N = 134)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size of left sylvian fissure area</td>
<td>12.2 ± 2.7</td>
<td>8.3 ± 2.9</td>
</tr>
<tr>
<td>(cm², Mean ± SD)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**KEY:**  
- a - students' 't' test, p<0.02  
- b - chi-square test, p<0.005  
- c - chi-square test, p<0.03  
- d - students' 't' test, p<0.03
<table>
<thead>
<tr>
<th>Sign</th>
<th>Proportion Developing the sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unequal Reflexes (N = 119)</td>
<td>10, 8.4</td>
</tr>
<tr>
<td>Extensor Plantars (N = 113)*</td>
<td>6, 5.3</td>
</tr>
<tr>
<td>Snout Reflex (N = 68)</td>
<td>17, 25.0</td>
</tr>
<tr>
<td>Palmo-Mental Reflex (N = 114)</td>
<td>3, 2.6</td>
</tr>
<tr>
<td>Grasp Reflex (N = 114)</td>
<td>8, 7.0</td>
</tr>
<tr>
<td>Tremor (N = 116)</td>
<td>5, 4.3</td>
</tr>
<tr>
<td>Increased Tone (N = 114)</td>
<td>11, 9.6</td>
</tr>
<tr>
<td>Myoclonus (N = 122)</td>
<td>7, 5.7</td>
</tr>
<tr>
<td>Epileptic Fits (N = 127*)</td>
<td>4, 3.1</td>
</tr>
<tr>
<td>Extrapyramidal Signs (N = 109)</td>
<td>4, 3.6</td>
</tr>
<tr>
<td>Drug Induced</td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal Signs (N = 119)</td>
<td>3, 2.5</td>
</tr>
</tbody>
</table>

* More common in subjects with 'possible' Alzheimer's Disease (p<0.02, Chi-square test with Yates Correction)
greater in subjects developing myoclonus (19.3 cf. 14.9 p=0.64, all above statistics students 't' test). The development of a snout reflex and extrapyramidal signs was associated with an increased death rate during the follow-up period (p < 0.02, p < 0.005 respectively, Chi square test).

8.2 DISCUSSION

The main findings were:
1) a snout reflex and extrapyramidal signs were the commonest neurological features in patients with SDAT;
2) a grasp reflex, increased tone and myoclonus were associated with younger age of onset, longer duration of the illness and more severe dementia;
3) some neurological signs had anatomical correlates as assessed by CT scan and
4) the incidence of neurological signs was surprisingly high and their occurrence was associated with an increased death rate and increased VBR.

The prevalence of neurological signs in DAT has been documented previously. Mayeux et al (1985b) studied 121 patients and found extrapyramidal signs in 28%, drug induced extrapyramidal signs in 10% and myoclonus in 10%. The population from which the sample was drawn was not stated in the paper but the report emanated from a department of neurology. In a later paper, the same group used a subsample of the first population (Stern et al, 1987) and found that subjects with extrapyramidal signs deteriorated more quickly (both functionally and cognitively) than those without. The proportion with myoclonus
in the present sample was lower than that described previously (Mayeux et al, 1985b; Hauser et al, 1986). One reason for this may be that previous authors have depended on observations by others in addition to, or instead of, direct examination of the patient. Therefore, I may have under-estimated the number with myoclonus by limiting my assessment to the period of direct observation (which lasted on average 90 minutes). Subjects with extrapyramidal signs were less commonly seen in the present sample than that from the Department of Neurology sample previously described (Mayeux et al, 1985b). It is possible that subjects referred to such a department may have extrapyramidal pathology overrepresented compared to the present catchment area sample of predominantly elderly psychiatric referrals.

Koller et al (1982) studied 52 subjects with DAT and found a snout reflex in 28 (54%) and a grasp reflex in only one subject. They found that the reflex was present in an equal proportion of normal (ie non-demented) elderly subjects and demonstrated a significant association between a snout reflex and increasing age in both groups. Tweedy et al (1982) found a snout reflex in 19%, a grasp reflex in 17% and a palmomental reflex in 47% of 32 patients with DAT. Huff and Growdon (1986), reporting on 165 patients, found these three reflexes in 18%, 10% and 10% respectively. Paulson and Gottlieb (1968) described a snout reflex in 52%, a palmomental reflex in 21% and a grasp reflex in 18% of 85 patients with senile and pre-senile dementia. The proportion with a snout reflex in the present study (41%) was greater than that described previously but the patients were on average ten years older than those in previous studies and an
association between the snout reflex (but not other primitive reflexes) and age has been demonstrated (Koller et al, 1982). The number with a grasp reflex was similar to those in other studies (Huff and Growdon, 1986; Tweedy et al, 1982; Paulson and Gottlieb, 1968). The lower number with a palmomental reflex may be due to the fact that other samples have been drawn from neurological sources where one might reasonably expect there to be an increased number of neurological abnormalities than those from a psychiatrically based population where behaviour disturbance and self neglect were the prominent reasons for referral. However, the significance of primitive reflexes is not certain and their presence has been demonstrated in subjects with non-organic psychiatric conditions (Keshevan et al, 1979).

The association between neurological signs and other features of dementia has been examined. Stern et al (1987) found that extrapyramidal signs and myoclonus were associated with greater cognitive impairment. Mayeux et al (1985b) found that subjects with myoclonus had a younger age of onset than those without. Kaye et al (1988,a) found a younger age of onset and more severe cognitive impairment in their subgroup of DAT patients with myoclonus. As these authors suggested (and confirmed partially with neurochemical analysis) this may imply that the presence of myoclonus represents a subgroup of SDAT patients. The possible diagnostic confusion between myoclonic SDAT and Creutzfeld-Jakob disease has been discussed (Jacob, 1970; Fadden and Townsend, 1976). The observations that myoclonus is associated with a younger age of onset and more severe
dementia has been replicated by the present study. The association between the presence of a grasp reflex and more severe cognitive impairment has been reported previously (Huff and Growdon, 1986; Tweedy et al, 1982) and the present study confirms this finding.

Two studies (Tweedy et al, 1982; Koller et al, 1982) have failed to find an association between a snout reflex and cortical atrophy as assessed by CT scan. However, the former group did find increased lateral ventricular size in DAT patients with the reflex. The present study has shown the association between extrapyramidal signs and basal ganglia abnormalities (as shown by increased third ventricular size and calcification in the right globus pallidus). Interestingly, patients with drug induced extrapyramidal signs did not show evidence of basal ganglia damage. Kaye et al (1988,b) found increased CSF volume in patients with extrapyramidal signs but did not differentiate between cortical and subcortical atrophy. The association shown in the current study between a grasp reflex and frontal lobe atrophy replicates a well known finding (Paulson, 1971). The association between epileptic fits and left sylvian fissure area atrophy may suggest that shrinkage or scarring of the left temporal lobe predisposes to epileptic fits. However, the numbers involved in these last two observations were small and the associations require replication.

The finding of an increased VBR in patients developing neurological signs (grasp reflex, myoclonus and extensor plantar response) may suggest that subcortical damage is the immediate precursor to their development, as has been shown with the snout
reflex (Tweedy et al, 1982). The lack of correlation between these neurological signs at entry to the study and VBR may be due to the different and often lengthy period between the development of the sign (which may have been some time prior to the beginning of the study) and the CT scan which would have masked such an association.

The incidence of neurological signs was surprisingly high and requires explanation. The proportion with signs traditionally associated with vascular disease (extensor plantar response and unequal reflexes) was very low at the beginning of the study because of their specific exclusion by the NINCDS/ADRDA criteria. Such patients may well have developed these signs in the follow up period as a manifestation of previously unrecognised vascular disease. Also, as these signs were generally associated with advanced disease, it is not surprising that they should develop them in the course of such a study. The high incidence in relation to the relatively low prevalence confirms the increase in mortality seen in patients with these signs.

8.3 SUMMARY

A snout reflex was present in 41%, extrapyramidal signs in 12%, drug induced extrapyramidal signs in 3%, myoclonus in 5% and a history of epileptic fits in 3% of the patients. A grasp reflex and extrapyramidal signs were associated with severe cognitive impairment. Extrapyramidal signs were associated with increased third ventricular size and basal ganglia calcification. Patients with a grasp reflex had more frontal lobe atrophy and a
history of epilepsy was related to left temporal lobe atrophy. Lateral ventricular size was greater in patients developing a grasp reflex during the 12 month follow up period. Extrapyramidal signs and primitive reflexes were associated with a higher subsequent mortality.
CHAPTER 9
SURVIVAL

9.1 RESULTS

Of the 178 patients in the study, 84 (47%) had died at the 36 month follow-up. Their characteristics and the differences between survivors and non-survivors are shown in Table 9.1. There were incomplete data on four subjects and so the final analysis was confined to 174 patients. CT scans were available on 136 subjects. Comparing mortality with the general population, the cohort had an increased mortality compared to rates for the Camberwell Health Authority. The Standard Mortality Ratio (SMR) for men was 2.825 (95% confidence interval (CI) 1.615, 4.587) and for women 3.676 (95% CI 2.584, 4.734). There was no statistical evidence for a difference between SMR's for men and women (P=0.34) and the overall SMR for the whole sample was 3.457 (95% CI 2.761, 4.329). There was a suggestion that younger subjects had a higher SMR than the older patients (Table 9.2). However, the heterogeneity test for an interaction with age was not statistically significant (Day and Breslow, 1987, p=0.25).

Factors affecting survival

Each of the factors was examined in turn to estimate the effect on survival using the proportional hazards model of Cox. The results are presented in Table 9.3. Subjects with higher scores on the MMSE survived longer and older subjects died sooner. Those with the highest cortical atrophy scores on CT scan and those with longer duration of illness died sooner. Subjects with misidentification syndromes survived for longer while whose with depressive symptomatology died more quickly. It
TABLE 9.1

<table>
<thead>
<tr>
<th>Groups</th>
<th>Male: Female</th>
<th>Differences Between</th>
<th>Significance of the Survival</th>
<th>Non-Survivors</th>
<th>Survivors</th>
<th>Mean: SD</th>
<th>Mean: SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d≤0.05p</td>
<td>19</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d≤0.05α</td>
<td>25</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d≤0.034</td>
<td>20</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d≤0.02p</td>
<td>13</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>d≤0.01p</td>
<td>47</td>
<td>41</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d≤0.003p</td>
<td>45.92</td>
<td>32.62</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d≤0.001p</td>
<td>6.7</td>
<td>6.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d≤0.000p</td>
<td>6.4</td>
<td>6.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d≤0.000p</td>
<td>6.4</td>
<td>6.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d≤0.000p</td>
<td>12.2</td>
<td>7.0</td>
<td>23.9</td>
<td>7.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d≤0.000p</td>
<td>47.3</td>
<td>71.0</td>
<td>56.7</td>
<td>36.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d≤0.000p</td>
<td>71.2</td>
<td>71.5</td>
<td>74.1</td>
<td>7.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d≤0.000p</td>
<td>6.2</td>
<td>6.1</td>
<td>78.7</td>
<td>6.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

KEY: SD = Standard deviation

A - Chi-square test; b - Student's t test

NS = non-significant at p<0.05

MAX = 30

MINIMUM STATE EXAMINATION

FOLLOW UP PERIOD (MONTHS)

DURATION OF ILLNESS (MONTHS)

AGE (YEARS)

SEX: FEMALE

SEX: MALE

NOTE: P-parenthetical
### TABLE 9.2

**STANDARD MORTALITY RATIOS (SMR's) BY AGE GROUP**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Observed</th>
<th>Expected</th>
<th>SMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-74 years</td>
<td>6</td>
<td>1.2</td>
<td>5.00</td>
</tr>
<tr>
<td>75-84 years</td>
<td>44</td>
<td>10.8</td>
<td>4.07</td>
</tr>
<tr>
<td>85+ years</td>
<td>30</td>
<td>10.7</td>
<td>2.80</td>
</tr>
</tbody>
</table>

84 of the original 178 patients died. There were 80 deaths in the 174 cases in whom complete data were available.
### TABLE 9.3

**UNIVARIATE MODELS FOR THE EFFECT OF VARIOUS FACTORS ON SURVIVAL IN ALZHEIMER'S DISEASE**

<table>
<thead>
<tr>
<th>VARIABLES COMPARISON</th>
<th>HAZARD RATIO</th>
<th>SIGNIFICANCE (p VALUE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in age by one year</td>
<td>1.06</td>
<td>0.002</td>
</tr>
<tr>
<td>Female vs male</td>
<td>0.76</td>
<td>0.32</td>
</tr>
<tr>
<td>Increase in duration of illness by one month</td>
<td>1.005</td>
<td>0.06</td>
</tr>
<tr>
<td>Incident vs prevalent cases</td>
<td>0.82</td>
<td>0.38</td>
</tr>
<tr>
<td>Probable vs possible AD</td>
<td>0.80</td>
<td>0.41</td>
</tr>
<tr>
<td>Hallucinations: present vs absent</td>
<td>1.47</td>
<td>0.17</td>
</tr>
<tr>
<td>Thought disorder: present vs absent</td>
<td>0.94</td>
<td>0.80</td>
</tr>
<tr>
<td>Misidentification: present vs absent</td>
<td>0.55</td>
<td>0.02</td>
</tr>
<tr>
<td>Depression: present vs absent</td>
<td>1.70</td>
<td>0.04</td>
</tr>
<tr>
<td>Family history: present vs absent</td>
<td>0.64</td>
<td>0.08</td>
</tr>
<tr>
<td>Increase in MMSE Score by one point</td>
<td>0.95</td>
<td>0.001</td>
</tr>
<tr>
<td>Increase in CAMDEX praxis score by one point</td>
<td>0.90</td>
<td>0.001</td>
</tr>
<tr>
<td>Increase in CAMDEX language score by one point</td>
<td>0.96</td>
<td>0.005</td>
</tr>
<tr>
<td>Increase in CAMDEX memory score by one point</td>
<td>0.93</td>
<td>0.03</td>
</tr>
<tr>
<td>Increase in VBR by 1*</td>
<td>0.91</td>
<td>0.58</td>
</tr>
<tr>
<td>Cortical atrophy (1) vs 0*</td>
<td>0.72</td>
<td>0.36</td>
</tr>
<tr>
<td>Marked cortical atrophy (2) vs 0*</td>
<td>1.98</td>
<td>0.03</td>
</tr>
</tbody>
</table>

A hazard ratio of $> 1$ means that the first normal variable causes more rapid death and $< 1$ means the variable causes less rapid death, on comparison with the baseline.

* scores for VBR and cortical atrophy in the text
is noteworthy that in these univariate analyses, the reduced rate in women compared to men was not statistically significant. Furthermore, although the incident cases had a longer survival as one would expect, this was not significantly different from the survival of the prevalent cases. The individual scores on the CAMCOG subscales were all significantly associated with survival. Each of these scales was highly related to the MMSE and to each other. Further analysis of these is presented below.

**Multivariate modelling**

In order to adjust for possible confounding relationships between the factors examined above, the proportional hazards model was used in a multivariate manner. The whole sample was used so the CT scan data were excluded from this analysis. The final model is given in Table 9.4. The first point to note is that the effect of age of onset does not appear. This is because age and duration are associated and age of onset adds little to predicting survival once age and duration are included. Being female emerges as a factor prolonging survival. No particular confounder was identified here although other variables in the final model appeared to contribute to unmasking the effect of sex. The "probable" category also appears to be important in the final model. The importance of the "probable"/"possible" distinction was obscured by the association between the "probables" and higher MMSE. The "possible" group had more physical illness and this presumably led to poorer survival.

If all the other variables (excluding the CAMCOG scores and CT scan data) were added to this model, it did not significantly
Table 9.4

Multivariate model for predicting survival in Alzheimer Disease

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard ratio</th>
<th>Significance (p Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in MMSE score by 1</td>
<td>0.93 (0.90,0.97)</td>
<td>0.001</td>
</tr>
<tr>
<td>Increase in age by 1 year</td>
<td>1.06 (1.02,1.10)</td>
<td>0.008</td>
</tr>
<tr>
<td>Depression: present vs absent</td>
<td>1.80 (1.11,2.89)</td>
<td>0.02</td>
</tr>
<tr>
<td>Female vs male</td>
<td>0.55 (0.32,0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>Probable vs possible AD</td>
<td>0.56 (0.32,0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Misidentification: present vs absent</td>
<td>0.55 (0.33,1.02)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

95% Confidence Intervals in Parentheses
improve the fit of the model (Chi-square test = 2.78, 5df, p = 0.73). The final point about this model is that the distinction between incident and prevalent cases was not associated with significant difference in survival. This suggests that the pooling of incident and prevalent cases had not distorted the results.

It has been suggested that low scores of measures of visuo-spatial ability are associated with poor survival. This was tested by including the memory, language and praxis CAMCOG subscales in a single model, the results of which are given in Table 9.5. Because of the high correlation between these subscales, none of the individual coefficients is statistically significant. However, the hazard ratio estimates indicate that the praxis subscale is a more powerful predictor of poor survival than the two other subscales. The memory and language subscales have a hazard ratio estimate of 1, indicating no effect on survival when the effects of the praxis scale are taken into account.

One further model was constructed using the 136 observations in which CT scan data were available. The cortical atrophy score variable was added to a model including all the variables listed in Table 9.2 (Chi-square = 5.091, 2df, P = 0.08). The estimates for the effect of cortical atrophy score in this model were similar in pattern to those for the unadjusted effect given in Table 9.2 (1 - 0.65, 95% CI, 0.31, 1.38; 2 - 1.44, 95% CI, 0.73, 2.82). The CT scan measure for VBR was unrelated to survival in a similar model. There was a significant departure from linearity for the cortical scores (p=0.026).
Table 9.5

A MULTIVARIATE MODEL INCLUDING THE THREE CAMDEX SUBSCALES

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>Significance (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in praxis score by 1</td>
<td>0.90 (0.79,1.03)</td>
<td>0.13</td>
</tr>
<tr>
<td>Increase in language score by 1</td>
<td>1.00 (0.95,1.06)</td>
<td>0.98</td>
</tr>
<tr>
<td>Increase in Memory score by 1</td>
<td>1.00 (0.91,1.10)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

95% Confidence Intervals in Parentheses
9.2 DISCUSSION

The main findings were:

1) the mortality rate for patients with SDAT was 3.5 times higher than would be expected for a population of similar age;

2) using a multivariate model, factors found to be significant in influencing survival included age, sex, presence of physical illness, depression, cognitive function and misidentification syndromes and

3) poor cognitive function was related to poor survival but there was some evidence that apraxia was particularly associated with early death.

Mortality rates

The finding of increased mortality in elderly patients with SDAT when compared to the normal population is not surprising. Indeed, the results would have been suspect had this not been shown. The standard mortality ratio (observed divided by expected deaths) of 3.5 is similar to that described by Kay (1962) who found a mortality rate of 4.8 for patients with dementia compared to a standard population. In the current study, 47% of subjects died within the three year follow-up. This three year cumulative mortality is lower than that described in other studies. Camargo and Preston (1945) documented a three year mortality of 70%, Shah et al (1969) found that 95% of subjects died during that time and Naguib and Levy (1982b) described a mortality rate of 69%. Goldfarb (1969) found that 57% of subjects with moderate dementia and 75% of those with
severe dementia were dead after three years. The main reason for the low mortality rate in this study is most likely due to the fact that patients in a variety of settings were studied - the majority of other reports have dealt exclusively with inpatients who will usually be more advanced in their disease and will therefore have a shorter survival time and a higher mortality rate. Two other explanations for the difference may be invoked. First, that the current sample was diagnosed using rigorous clinical criteria which have a proven high success rate with finding AD pathology at post mortem. It is possible that other studies used less stringent criteria and may have included subjects with physical illness which prompted early mortality. This is supported by the subgroup in the present sample who had "possible" AD (ie the presence of physical illness such as heart disease, diabetes or hypertension). This group had a higher mortality. A second reason for the low rate in the present population may be that mortality in dementia is genuinely decreasing as has been suggested by Duckworth et al (1979) and Christie (1982). Obviously, some other unmeasured variable may be responsible.

Factors affecting survival

Age, duration of illness, and sex: increasing age was associated with a higher mortality. While it is acknowledged that younger patients have a more severe illness and deteriorate more rapidly (Seltzer and Sherwin, 1983), Kasniak et al (1978) found that age did not affect survival. Younger patients with DAT appear to spend longer in hospital in their terminal illness than older subjects (Christie and Wood, 1988).
Patients with a longer illness died sooner which confirms a previous finding (Barclay et al 1985b) and makes clinical sense. A new finding was that mortality did not differ between cases already known to the services (prevalent cases) and cases appearing over the subsequent two years (incident cases). However, significantly more of the prevalent cases died during follow up.

The protective effect of being female also confirms previous work. Camargo and Preston (1945) were the first to document the fact that elderly male patients had an increased mortality compared to females. Kay (1962) looked specifically at subjects with dementia and found survival to be one third of that expected in females and less than a quarter of that expected in males. Shah et al (1969), in a study of 38 patients with senile dementia, found only 30% of men to be alive three months after admission to hospital compared to nearly 72% of women. One obvious explanation for this is that males with dementia are looked after in their own homes longer than females and so on admission to hospital (taken as the point of entry to many survival studies), male patients are more advanced in their disease and so consequently, death is sooner. However, this would not explain the fact that sex differences are seen in community samples which measure mortality since the onset of the illness.

Physical Illness: Not surprisingly, the 'possible' group (as defined by the NINCDS/ADRDA criteria) had a higher mortality which reflects the associated physical illness in these patients.
Cognitive function: that poor cognitive function is a predictor of early death accords with clinical experience and is documented by the present study. The majority of other studies have found poor cognitive function to indicate poor survival (Heyman et al, 1977, Berg et al, 1984, Kasniak et al, 1978). An exception was Barclay et al (1985), who found that cognitive function was not a predictor of survival but that behavioural disturbance was. The association between subscales of the Stockton Behaviour Rating Scale and death in the current population has been noted in Chapter 6.

Aphasia has been specifically associated with a poor prognosis. Kasniak et al (1978) reported that in 47 hospitalised patients (with both presenile and senile dementia), an expressive language deficit was associated with mortality in the 12 months following the examination. Aphasia has been associated with dementia of more rapid progression (Knesevich et al 1985). The finding in this study of praxis as a particular factor leading to reduced survival agrees with earlier work. McDonald (1969) and Hare (1978) stressed that parietal lobe involvement was a poor prognostic sign in SDAT. Naguib and Levy (1982,b) studied 40 patients with senile dementia and followed them for between 18 months and three years. The 27 who died had lower radioattenuation density numbers in the right parietal lobe (as assessed by CT scan) compared with those who survived. Thus, radiological evidence of parietal lobe damage was a predictor of poor survival. This work has been replicated by Colgan (1985). The findings of the present study again confirm the poor prognosis in patients with apraxia.
Psychiatric symptoms: It has been suggested that depression indicates a good prognosis in SDAT (Naguib and Levy, 1982,a). In this study, observed depression was associated with an increased mortality rate. While this appears to contradict earlier work, there is one obvious explanation for this finding. The current study used the NINCDS/ADRDA criteria to diagnose DAT. Previous studies used criteria which have not been verified histologically which casts doubt on their validity. Thus, previous studies may have included patients with depressive pseudodementia who would have had a better prognosis than subjects with DAT. An alternative explanation is that the measure of depression used in the current study was that observed by a rater and not depression complained of directly by the patient. The poor prognosis in depressed DAT subjects may be a reflection of a more severe underlying histopathology (Zweig et al, 1988).

Psychotic symptoms (delusions, hallucinations and misidentification syndromes) have been associated with a more rapid cognitive decline (Drevets and Rubin, 1989, Stern et al, 1987). Paradoxically, misidentification syndromes are associated with a reduced mortality (Drevets and Rubin, 1989), a finding confirmed by the present work. The reasons for this are unclear but explanations vary from differing underlying neuropathology to differing patterns of care being provided for such patients.

In conclusion, SDAT is associated with greatly reduced survival and several features of the disease help to predict mortality. This has implications for the care of patients and also suggests clinical heterogeneity in SDAT.
9.3 SUMMARY

The mortality rate of the sample was 3.5 times that expected of a population of similar age. The cumulative 36 month mortality was 47%. Factors shown to be associated with reduced survival included increasing age, longer duration of illness, male sex, presence of physical illness, poor cognitive function, observed depression and absence of misidentification syndromes. Apraxia was a stronger predictor of death than aphasia or amnesia.
10.1 RESULTS

Relatives were approached during the study and a request for a post mortem examination was made to all the relatives of patients, either before or immediately after death. Of the 84 subjects who had died during the three year follow up, full post mortems were obtained on 48. In the remaining cases, I was not told of the death until several weeks after the event in seven patients and consent was refused in 29.

Table 10 details the neuropathological diagnoses in the 48 cases. Thirty subjects satisfied the "probable" NINCDS/ADRDA criteria and 18 the "possible" criteria. The reasons 18 were placed in the "possible" category were - diabetes (five cases), evidence of vascular disease unrelated to the dementia syndrome (three cases), epilepsy prior to onset of dementia (two cases), episodes of delirium (two cases) and one case each of hypertension, vitamin B12 deficiency, carcinoma of lung, subacute bacterial endocarditis, temporal arteritis and lymphoma.

There were ten patients with "possible" AD in whom the diagnosis of "definite" AD was made at post mortem. Four of these had diabetes (all were on oral hypoglycaemic medication). The conditions in the other six which led to them being classified as "possible" AD were: hypertension; evidence of peripheral vascular disease and atrial fibrillation associated with dementia which had a slightly atypical presentation; vitamin B12 deficiency, epilepsy (still on medication); a previous
<table>
<thead>
<tr>
<th>CLINICAL CRITERIA VERSUS PATHOLOGICAL DIAGNOSIS</th>
<th>PROBABLE AD</th>
<th>POSSIBLE AD</th>
<th>TOTAL</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL CRITERIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROBABLE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POSSIBLE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>23</td>
<td>10</td>
<td>33</td>
<td>69%</td>
</tr>
<tr>
<td>AD/VASCULAR</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>11%</td>
</tr>
<tr>
<td>AD/CLBD</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>6%</td>
</tr>
<tr>
<td>VASCULAR</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>CLBD</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>DIAGNOSIS</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ABILITY OF CLINICAL CRITERIA PREDICT AD PATHOLOGY:</th>
<th>PROBABLE AD</th>
<th>POSSIBLE AD</th>
<th>TOTAL</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEIMER PATHOLOGY PRESENT</td>
<td>27</td>
<td>14</td>
<td>41</td>
<td>85%</td>
</tr>
<tr>
<td>HEIMER PATHOLOGY ABSENT</td>
<td>3</td>
<td>4</td>
<td>7</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCULAR PATHOLOGY ABSENT</td>
<td>28</td>
<td>13</td>
<td>41</td>
<td>85%</td>
</tr>
<tr>
<td>SCULAR PATHOLOGY PRESENT</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>15%</td>
</tr>
</tbody>
</table>

KEY: AD - Alzheimer's Disease
     CLBD - Cortical Lewy Body Disease
history of sudden confusion allegedly diagnosed as a stroke and cancer of the lung. The neuropathological findings in the eight 'possible' subjects without 'definite' AD are shown in Table 10(a). Three subjects had neuropathological changes consistent with normal ageing but no evidence of disease responsible for their dementia. Two had associated physical disease (temporal arteritis and subacute bacterial endocarditis) while the other had features of depression, in addition to being demented.

Table 10(b) breaks down the neuropathological diagnoses as to whether AD changes were present or not. The sensitivity with which the criteria were able to predict AD was 90% and 77.8% for the 'probable' and 'possible' criteria respectively. Specificity could not be assessed as the sample did not include patients who did not satisfy the NINCDS/ADRDA criteria. (However, two additional patients were assessed and found not to satisfy the NINCDS/ADRDA criteria and so were not recruited into the study. As both were inpatients in the Joint Hospital, post mortems were performed when they died and neither had AD.)

Table 10(c) shows the ability of the criteria to exclude patients with vascular disease. Only two patients who satisfied the "probable" criteria had evidence of vascular disease, both of whom also had AD changes. Two subjects had evidence of vascular disease only - one was a centenarian who developed a stroke after the onset of dementia and the other was a woman who had been in hospital for many years and who had a lymphoma diagnosed earlier in life. Both were placed in the "possible" category. The "probable" criteria were therefore correct in excluding vascular disease in 93.3% of cases, the "possible" criteria excluded such
changes in 72.2%.

10.2 DISCUSSION

The main findings of were:

1) AD can be diagnosed accurately during life by applying NINCDS/ADRDA criteria, without the need for extensive investigation and resources;

2) significant vascular disease can be almost entirely excluded by the strict use of these criteria;

3) in some patients AD can be confidently diagnosed even when accompanying physical illness such as diabetes, epilepsy or cancer is present and

4) cortical Lewy bodies are a common neuropathological finding in elderly demented patients.

There have been several studies which have evaluated the agreement between clinical and pathological findings in dementia. The rate of agreement between clinical and histological diagnoses of AD varies from about 50% (Homer et al, 1988, Alafuzoff et al, 1987) to 95% and above (Martin et al, 1987, Boller et al, 1989). Alafuzoff et al (1987) were correct in only 53% of cases. However, they examined only the frontal lobe and almost certainly underdiagnosed the condition. Homer et al (1988) did not use any standardised criteria for their clinical diagnosis which probably accounted for their success rate of only 46%. They were, however, trying to predict neuropathological findings in dementias with a variety of aetiologies whereas the present study confined itself to the clinical diagnosis of AD. Studies where agreement has been 90% or above have all employed the NINCDS/ADRDA criteria.
The current findings of three patients in whom no neuropathological diagnosis could be reached is in accord with other studies. Homer et al (1988) found one such patient out of 27, Perl et al (1984) one case out of 26 and Wade et al (1987) one out of 65. Three explanations are possible. First, the clinical diagnosis was wrong and a condition, not resulting from structural brain disease (eg physical disease in another organ or pseudodementia) was responsible for the patient's symptoms and behaviour. Second, that a metabolic disturbance in the brain, not associated with structural abnormalities, was responsible. Third, that standard neuropathological techniques may be missing cases in which changes not hitherto recognised as pathognomonic of AD (eg A4 protein deposition) are present. It can be seen from Table 10 that the NINCDS/ADRDA criteria are consistent with a successful neuropathological diagnosis of AD in 90% of cases. Ten patients were classified as having "possible" AD because of associated physical illness which may have indicated either the presence of vascular disease or another disorder which may have accounted for the dementia. Despite this, all had AD proven at post-mortem.

The paucity of significant vascular disease in this sample was expected as patients with the widely recognised features of vascular dementia (eg sudden onset, stepwise deterioration etc.) were specifically excluded. All subjects in the sample had a low Hachinski score which is in keeping with the dearth of vascular disease seen. The original Hachinski score (Hachinski et al, 1975) was developed on the basis of blood flow studies and the loadings given to each item were arbitrary. Subsequent
studies (Rosen et al, 1980, Loeb and Gandolfo, 1983) have shown that only some of the original items do in fact predict the presence of infarcts. By employing the "probable" NINCDS/ADRDA criteria in this sample, all cases in this study with pure vascular disease were excluded.

Finally, cortical Lewy body disease (CLBD) was found in five cases. Patients with CLBD have features of a Parkinson syndrome and it has been suggested that they represent a variant of AD (Hansen et al, 1990). No such distinguishing features were found in this sample. The frequency of CLBD (10.4%) was very similar to that of Perry et al (1989) and appears to constitute the second commonest neuropathological finding in neurodegenerative dementia in old age.

10.3 SUMMARY

The NINCDS/ADRDA were able to predict Alzheimer pathology at post mortem in 85% of cases. Only two patients out of 48 had pure vascular pathology, both of whom were in the "possible" AD category. Cortical Lewy body disease was found in 10.4% of cases, of which half also had sufficient Alzheimer changes for that diagnosis to be made in addition. Three subjects had cerebral changes consistent with ageing alone - no cause for their dementia syndrome was found.
CHAPTER 11
CONCLUSIONS AND FUTURE STRATEGIES

The main conclusions of this study will be summarised in relation to the hypotheses outlined in the Introduction.

**Hypothesis 1** - there is considerable clinical heterogeneity in Senile Dementia of the Alzheimer Type (SDAT) and that features of the disease will be identified which predict future cognitive decline and survival - the study has confirmed, in view of the diverse nature of psychiatric symptoms, behaviour disturbance and neurological signs found, that clinical heterogeneity does exist in SDAT. The features related to cognitive decline and mortality included age, sex, cognitive performance, hallucinations, misidentification syndromes, observed depression, behaviour disturbance, family history of dementia in parents, duration of illness of less than two years and neurological signs.

**Hypothesis 2** - specifically, apraxia and ventricular enlargement will be related to a poor outcome and depression will be associated with a good outcome - apraxia appeared to be related to reduced survival, ventricular enlargement was not and depression (observed by a rater) was associated with poor survival.

**Hypothesis 3** - the proportion of patients with specific psychiatric symptoms and behaviour disturbance will be lower than other studies because of the representative nature of the population under investigation - generally speaking, this has been found, particularly for the psychiatric symptoms.
Hypothesis 4 - specific psychiatric symptoms and behaviours will have structural correlates as assessed by Computed Tomography (CT) scan - this has been shown in the case of depression, some types of delusion, mania, wandering behaviour, hyperorality and aggression.

Hypothesis 5 - subgroups will be identified by longitudinal changes in cognition and CT scans - longitudinal changes in both measures were disappointing in elucidating subtypes but, apart from the obvious conclusion that subtypes assessed on these measures did not exist, this may be due to inherent problems in longitudinal investigations.

Hypothesis 6 - by the use of appropriate clinical criteria, it will be possible to predict during life which patients will have Alzheimer's disease changes at post mortem - it has been shown, by applying the NINCDS/ADRDA criteria, that histopathological changes of Alzheimer's disease at post mortem can be predicted with nearly 90% accuracy.

The major problem surrounding clinical heterogeneity in SDAT is one of definition, both of the clinical syndrome and of the method of establishing heterogeneity. The syndrome consists of two parts - a clinical picture (defined as dementia) and a histopathological pattern (defined in terms of plaques and tangles in the neocortex and hippocampus). While there is overwhelming evidence that the two are causally linked and are distinct from the changes which occur during normal ageing, much is unknown. The aetiology of the condition is unknown, the pathogenesis unclear, specific diagnostic tests unavailable and
no effective treatment is possible. Also, neither the clinical features nor the neuropathological findings are specific to SDAT. Given these uncertainties, the finding of clinical heterogeneity in SDAT is not surprising.

Another problem when discussing heterogeneity is the definition of subtypes (or subgroups). So far, no definite criteria have been developed though suggestions have been proposed along the lines of qualitative and quantitative subtypes (Jorm, 1985). These categories remain theoretical and depend on the elucidation of causal factors. The latter depends on the discovery of the responsible gene or genes and the identification of environmental agents modifying the genotype. The uncertainties surrounding the nosological status of SDAT should provoke a more cautious approach to the elucidation of subtypes.

There are four reasons why clinical heterogeneity may be discovered in SDAT. First, it may be due to erroneous diagnosis ie patients with conditions other than SDAT may have been studied. Second, true subtypes of the disorder may be present as is the case in Duchenne and Becker muscular dystrophy (ie qualitative subtypes). Third, there may be differential expression of the same underlying disorder, perhaps with different genetic or environmental causes (eg a single or double dose of a responsible gene as is the case in Thalassaemia minor and major). Fourth, clinical heterogeneity may be due to differences in severity of the same underlying condition ie that all patients will develop the same symptoms if they have the disease for a sufficient length of time.

A review of the literature shows that there are clinically
distinct groups of patients who have dementia (and senile dementia) of the Alzheimer Type. These groups have been variously defined in terms of familial aggregation, age of onset, neuropsychological profile, clinical symptomatology, survival and neurochemical and neuropathological features. A weak point in existing studies is that the populations under study consist of unrepresentative groups of patients who, with the exception of neuropathological studies, lack precise diagnostic criteria. The patients studied in the present work were from a defined catchment area of Health District and all satisfied stringent criteria for the clinical diagnosis of Alzheimer's disease.

Another important factor in the work presented in this thesis is that all the patients examined were elderly and the vast majority had been referred to psychiatrists. It is likely that elderly subjects presenting to their General Practitioners (from whom most of the patients in the study were originally referred) would require more severe (and/or additional) symptoms to merit referral to a specialist than would younger patients. It is probable that, in many elderly patients, early symptoms of dementia are put down to "normal ageing" and so referral for specialist investigation is not made until a relatively later stage of the disease. Also, the reason for referring a particular patient to a psychiatrist rather than to a neurologist may be influenced by factors such as symptomatology and age but also may be entirely arbitrary. Common sense dictates that patients with troublesome behavioural disturbance or prominent psychiatric symptomatology should be referred to psychiatrists.
It is possible that any differences in clinical heterogeneity between this and other studies may be, in part, explained by the selection process of the sample, particularly in the case of neurological signs, psychiatric symptoms and behavioural disturbance.

As all the patients were 65 years or over on admission to the study, age and age of onset of the disease were not important variables. However, some associations were found. Subjects with misidentification syndromes and myoclonus were younger than those without these features. The presence of misidentification and young age was associated with increased survival suggesting that, within the elderly group, relative youth predicts longer survival. The most likely explanation for this was that, as age increased, its deleterious effect on survival outweighed the effect of a more severe illness said to occur in early onset cases.

Family history of dementia is notoriously difficult to evaluate and is particularly so in the relatives of elderly subjects. The only positive finding in relation to family history was that deterioration in cognitive function was greater in those with a positive history in parents. It would be tempting to conclude that this finding indicates a genetic contribution to a more severe disease. However, no other evidence emerged to support this conclusion. With this exception, there was no indication in the study that a family history of dementia bore any relationship to other features. One may conclude that genetic factors play a less important role in dementia in the elderly than in younger patients and subtypes,
Based on this, do not exist.

Although relatively neglected as symptoms of DAT, non-cognitive abnormalities (psychiatric symptoms and behavioural disturbance) are important - they are usually apparent, potentially treatable, may shed light on the pathophysiology of the functional psychoses and, most importantly, their presence or absence may indicate subtypes. The presence of possible subtypes based on these symptoms was suggested by the association of misidentification syndromes, younger age of onset of disease and prolonged survival. Depressive symptoms were associated with a milder form of the disease (as indicated by less severe cognitive and CT scan changes) but this might simply reflect those less severely impaired being unable to express depressive ideation which required relatively intact cerebral function. A trend emerged for those with a previous history of depression to have a less rapid progression of the disease but, similar to the reverse finding with regard to family history of the illness, the significance of this solitary finding is debatable. A somewhat surprising finding was that subjects who appeared depressed had a significantly shorter survival time. Previous neuropathological studies have suggested a different neuropathology in depressed compared to non-depressed subjects and this, although untested in the present study, may be reflected in the clinical picture. Other psychiatric symptoms such as hallucinations, were associated with more rapid cognitive decline over the follow-up period which did suggest some subgrouping.

Most of the behaviours assessed in the study were associated
with advanced dementia and so it is reasonable to postulate that their presence results from structural brain damage. The assumption implicit in this statement is that all patients will develop these behaviours which is patently not true and so some additional factor, genetic, environmental or related to pre-morbid personality must exert some influence on these particular clinical features. The exception was binge eating which was equally common across all ranges of severity but there was no other evidence to suggest that this represented a qualitative subtype.

Neurological signs were present in a surprising number of patients and myoclonus and a grasp reflex were associated with a younger age of onset and thence may represent a subtype. However, these appeared to be present in the more advanced stages of the disorder which, as with behavioural disturbance, probably reflects structural brain damage rather than a particular subtype. Other studies have used neurological signs to describe clinical subtypes of DAT, both cross-sectionally and longitudinally. As most of these studies have come from neurological clinics consisting predominantly of younger patients, sample bias may be present.

It is difficult to make valid interpretations of results based on cross-sectional assessments of a progressive disorder such as DAT. Longitudinal changes must be measured - cognitive function and CT scans were examined in this thesis. There are many problems associated with longitudinal studies, the most outstanding in this work being the actual instruments used for analysis and the presence of "floor effects" (ie the fact that
many of the patients were moderately to severely demented at the time of entry to the study and that the scope for further deterioration was therefore limited). With regard to the first point, no instruments exist which are exclusively sensitive to changes in cognitive function and so the measures used, although not ideal, were as good as any. The assessment of longitudinal CT changes faced the inherent problem of positioning the patient in the same CT plane at both points in time when, by definition, he/she will have deteriorated and therefore may be less able to co-operate. A relatively normal distribution of change in cognitive function was found, suggesting but by no means proving, that clinical subtypes as assessed on this index were not present. Similarly, the range of changes seen on the CT measures was very wide and did not suggest discrete subtypes. One can say only that the case for clinical subtypes utilising the longitudinal measures is unproven. However, patients were examined only at two points in time and prolonged longitudinal assessment may reveal additional information.

The neuropathological findings presented may appear somewhat out of place but were included to justify the clinical criteria used in the study. As mentioned in the first paragraph, research on psychiatric disorders in general and DAT in particular, is bedevilled by problems of definition. The data presented proved (in conjunction with the review of the associated literature) that a reliable diagnosis of AD was possible during life with the careful application of appropriate clinical criteria. It will be important to continue the follow-up of the survivors in the
current work and obtain post mortems on as many as possible. Neuropathological heterogeneity was not within the remit of this thesis and so has not been addressed.

Future strategies in the investigation of subtypes of DAT in general and SDAT in particular can be divided into two broad categories. First, the definitive answer will be obtained only when the aetiology and pathogenesis of the condition are understood. This may be genetic or environmental but probably involves a combination of these two. Second, longitudinal studies with clinico-pathological correlations are essential as validation of particular clinical subtypes against longitudinal changes and neuropathological findings will help to document the presence of subtypes. Both these aims will be facilitated by more detailed and prolonged longitudinal studies investigating patients earlier in the course of the disease. Neuroimaging modalities such as Magnetic Resonance Imaging and Single Photon Emission Tomography may be used to follow patients longitudinally in parallel with neuropsychological testing. Biological markers may be developed to identify subtypes of the disorder. Correlation of clinical and histopathological features is essential and post mortems should be obtained routinely on all suitable patients.

The work here has suggested some disease characteristics which may be of help to future researchers in identifying clinical features most strongly indicative of subtypes - psychiatric symptoms, behaviour disturbance and neurological signs. Ultimately, the elucidation of subtypes will depend on finding the aetiology and pathogenesis of the condition.
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**APPENDIX 1  THE MINI-MENTAL STATE EXAMINATION** (MMSE, Folstein et al., 1975)

**ORIENTATION**

1. **What is the**  
   - Year?  
   - Season?  
   - Date?  
   - Day?  
   - Month?  
   Points  
   1  

2. **Where are we?**  
   - Country?  
   - County?  
   - Town?  
   - Hospital?  
   - Floor?  
   Points  
   1

**REGISTRATION**

3. Name three objects (Apple, Table, Penny), taking one second to say each. Then ask the patient all three after you have said them. Give one point for each correct answer. Repeat the answers until the patient learns all three.

**ATTENTION & CALCULATION**

4. Serial sevens. Give one point for each correct answer. Stop after five answers.

**RECALL**

5. Ask for names of three objects learned in Question 3. Give one point for each correct answer.

**LANGUAGE**

6. Point to a pencil and a watch. Have the patient name them as you point.

7. Have the patient repeat "No ifs, ands, or buts."

8. Have the patient follow a 3-stage command: "Take the paper in your right hand. Fold the paper in half. Put the paper on the floor."

9. Have the patient read and obey the following: "CLOSE YOUR EYES" (Write it in large letters)

10. Have the patient write a sentence of his or her own choice. (The sentence should contain a subject and an object and should make sense. Ignore spelling errors when scoring.)

11. Draw the design printed below to 1.5 cm per side and have the patient copy it. Give one point if all sides and angles are preserved and if the intersection sides form a quadrangle.

 Maximum score = 30
APPENDIX 2

ABBREVIATED MENTAL TEST SCORE (AMTS, Thompson and Blessed, 1987)

1. How old are you? (exact year) 1
2. What time is it? (to nearest hour) 1

"I would like you to remember this address:
42 Church Street"

3. What year is it? (exact year) 1
4. What is the name of this part of London? 1
5. Recognition of two persons (e.g. neighbours, relatives, name photographs in room) 1
6. What is your date of birth? 1
7. In what year did the First World War begin? 1
8. Who is on the throne at the moment? 1
9. Can you count backwards from 20 to 1? 1
10. Can you tell me the address I asked you to remember a few minutes ago?

42 Church Street 1

Maximum score = 10
EXHIBIT 3

PHYSICAL EXAMINATION

DATE:............. STUDY:.............

RHYTHM: REGULAR = 0, IRREGULAR = 1.

GUE = 0 = NORMAL; 1 = ATROPHIC

TH = 0 = OWN; 1 = FALSE;

SIGHT = GLASSES WORN = 0 = NO; 1 = YES;
VISION WITH GLASSES:
0 = NORMAL;
1 = SLIGHTLY IMPAIRED;
2 = VERY IMPAIRED

RING = HEARING AID WORN = 0 = NO; 1 = YES;
HEARING WITH AID:
0 = NORMAL;
1 = SLIGHTLY IMPAIRED;
2 = VERY IMPAIRED

ILITY:
0 = NORMAL, UNAIDED
1 = WITH WALKING AID
2 = WITH HUMAN ASSISTANCE
3 = CHAIR/Bed Bound

PIRATION:
0 = NORMAL; 1 = ABNORMAL

IL RESPONSE TO LIGHT:
0 = NORMAL; 1 = ABNORMAL

IL EQUALITY:
0 = NORMAL; 1 = ABNORMAL

MOVEMENTS:
0 = NORMAL; 1 = ABNORMAL

M SYMMETRY:
0 = NORMAL; 1 = ABNORMAL

NGTH:
0 = NORMAL; 1 = ABNORMAL OR ASYMMETRICAL

F TENDON REFLEXES:
0 = NORMAL; 1 = ABNORMAL OR ASYMMETRICAL

ATION:
0 = NORMAL; 1 = ABNORMAL OR ASYMMETRICAL

:
0 = NORMAL; 1 = ABNORMAL

TARS:
0 = FLEXOR; 1 = EXTENSOR

REFLEX:
0 = ABSENT; 1 = PRESENT

REFLEX:
0 = ABSENT; 1 = PRESENT

P REFLEX:
0 = ABSENT; 1 = PRESENT

OR:
0 = ABSENT; 1 = PRESENT

EDNESS:
0 = RIGHT HANDED; 1 = LEFT HANDED

C FUNDI:
0 = NORMAL; 1 = ABNORMAL

IN LIMBS:
0 = NORMAL; 1 = ABNORMAL

LONUS:
0 = ABSENT; 1 = PRESENT
The patient will fall from his bed or chair unless protected by side rails or soft ties (day or night):
0 - never
1 - sometimes
2 - frequently

The patient helps out on the ward (other than a regular work assignment):
0 - often helps out
1 - sometimes helps out
2 - never helps out

The patient understands what you communicate to him (you may use speaking, writing, or gesturing):
0 - understands almost everything you communicate
1 - understands some of what you communicate
2 - understands almost nothing you communicate

The patient is objectionable to other patients during the day (loud or constant talking, pilfering, soiling furniture, interfering in affairs of others):
0 - rarely or never
1 - sometimes
2 - frequently

Close supervision is necessary to protect the patient, due to feebleness, from other patients:
0 - rarely or never needs protection
1 - sometimes needs protection
2 - frequently needs protection

The patient keeps self occupied in constructive or useful activity (works, reads, play games, has hobbies, etc.):
0 - almost always occupied
1 - sometimes occupied
2 - almost never occupied

The patient communicates in any manner (by speaking, writing, or gesturing):
0 - well enough
1 - can be understood sometimes or with some difficulty
2 - can rarely or never be understood for whatever reason

The patient engages in repetitive vocal sounds (yelling, moaning, talking, etc.) which are directed to no one in particular or to everyone:
0 - never
1 - sometimes
2 - frequently

When bathing or dressing, the patient requires:
0 - no assistance
1 - some assistance
2 - maximum assistance

The patient socializes with other patients:
0 - does establish a good relationship with one or more patients
1 - has some difficulty establishing a good relationship with one or more patients
2 - has a great deal of difficulty establishing a good relationship with one or more patients.
The Patient knows his own name:
0 - almost always responds to his name
1 - sometimes responds to his name
2 - almost never responds to his name

The patient threatens to harm other patients, staff, or people outside the hospital either verbally (e.g., "I'll get him") or physically (e.g. raising of fist):
0 - never
1 - sometimes
2 - frequently

With regard to walking the patient:
0 - shows no sign of weakness
1 - walks slowly without aid, or uses cane
2 - is unable to walk, or if able to walk, needs walker, crutches, or someone by his side

The patient, without being asked, physically helps one or more patients in various situations (pushing wheel chair, helping with food tray, assisting in shower, etc.):
0 - often helps without being asked
1 - sometimes helps without being asked
2 - never helps without being asked

The patient wants to go home or leave the hospital:
0 - expresses great eagerness in leaving
1 - expresses some interest in leaving
2 - expresses almost no interest in leaving

The patient is objectionable to other patients during the night (loud or constant talking, pilfering, soiling furniture, interfering in affairs of others wandering about, getting into some other patient's bed, etc.):
0 - rarely or never
1 - sometimes
2 - frequently

The patient is incontinent of urine and/or faeces (day or night):
0 - never
1 - sometimes (once or twice per week)
2 - frequently (three times per week or more often)

The patient takes the initiative to start conversations with others (exclude side remarks not intended to open conversations):
0 - often takes the initiative
1 - sometimes takes the initiative
2 - never takes the initiative

The patient accuses others (patients, staff, or people outside the hospital) of doing him bodily harm or stealing his personal possessions (if you are sure the accusations are true, rate zero: otherwise rate one or two):
0 - never
1 - sometimes
2 - frequently

When eating, the patient requires
0 - no assistance (feeds himself)
1 - a little assistance (needs encouragement to eat, needs food cut up for him/her)
2 - considerable assistance (spoon feeding, etc.)
The patient has a regular work assignment:
0 - away from the ward
1 - on the ward
2 - no regular assignment

The patient is destructive of materials around him (breaks furniture, tears up magazines, sheets, clothes, etc.):
0 - never
1 - sometimes
2 - frequently

The patient is confused (unable to find his way around the ward, loses his possessions, etc.):
0 - almost never confused
1 - sometimes confused
2 - almost always confused

The patient knows the staff by name:
0 - knows names of more than one member of the staff
1 - knows name of only one member of the staff
2 - knows name of none of the staff

The patient engages in apparently useless repetitive movements (pacing, rocking, wringing of hands, making random movements, etc.):
1 - never
2 - sometimes
3 - frequently

The patient is in bed during the day (bed does not include couch, settee, etc.):
0 - never
1 - sometimes
2 - almost always

The patient is allowed to leave the ward
0 - whenever he/she wants.
1 - sometimes
2 - never

The patient hoards apparently meaningless items (wads of paper, string, scraps of food, etc.):
0 - never
1 - sometimes
2 - frequently

When left to his own devices, the patient's appearance (clothes and/or hair, including beard for males) is:
0 - almost never disorderly
1 - sometimes disorderly
2 - almost always disorderly

If patient were allowed the freedom of the grounds alone, he would be able to protect himself from the weather or from getting lost:
0 - would never need supervision outdoors
1 - would sometimes need supervision outdoors
2 - would always need supervision outdoors
The patient's sleep pattern at night is:
0 - almost never awake
1 - sometimes awake
2 - often awake

The patient's meals consist of:
0 - a regular solid diet, no limitations, "will eat anything"
1 - a normal diet with modification e.g. avoidance of particular food
2 - a special diet (diabetic, low salt, pureed, etc.)

The patient is willing to do things suggested to or asked of him:
0 - often goes along
1 - sometimes goes along
2 - almost never goes along

Following four factors were derived from the scale (Meer and Baker, 1966):

<table>
<thead>
<tr>
<th>Factor</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social Disability</td>
<td>1, 5, 9, 13, 17, 20, 23, 26, 29, 32.</td>
</tr>
<tr>
<td>Hy</td>
<td>2, 6, 10, 14, 18, 21, 24, 27, 30, 33.</td>
</tr>
<tr>
<td>Communication failure</td>
<td>3, 7, 11, 15.</td>
</tr>
<tr>
<td>Ally Irritating Behaviour</td>
<td>4, 8, 12, 16, 19, 22, 25, 28, 31.</td>
</tr>
</tbody>
</table>

Question about wandering behaviour was worded thus:

Patient wanders aimlessly around the ward:
rarely or never
sometimes
frequently.
APPENDIX 5

QUESTIONS RELATED TO BEHAVIOUR ASSOCIATED WITH THE 'KLUVER-BUCY SYNDROME'.

1) The patient's sexual behaviour (exposing self, obscene sex language, masturbation, propositioning others) is:
   0 - never inappropriate,
   1 - sometimes inappropriate,
   2 - often inappropriate.

2) The patient recognises well known nurses and relatives:
   0 - almost always,
   1 - sometimes,
   2 - almost never.

3) The patient goes into rages:
   0 - never or rarely,
   1 - sometimes,
   2 - frequently.

4) The patient is distractable and immediately explores things around him/her when they happen (e.g. always going up to the door when someone comes in):
   0 - never or rarely,
   1 - sometimes,
   2 - often or always.

5) The patient tends to "binge" with food (i.e. eating very quickly and stuffing food in his/her mouth):
   0 - never or rarely,
   1 - sometimes,
   2 - often or always.

6) The patient tries to put objects (other than food) in his/her mouth:
   0 - never or rarely,
   1 - sometimes,
   2 - frequently.

7) The patient seems withdrawn and apathetic:
   0 - never or rarely,
   1 - sometimes,
   2 - a lot of the time.