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Age-associated memory impairment: diagnostic and treatment issues

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DEDICATION

To Pam, Lucy and Adam for helping me to find my truth, and to Mum and Dad for teaching me to appreciate the beauty of stars.

Where is man's truth to be found?

Truth is not that which can be demonstrated by the air of logic. If in this bit of ground, and not in another, orange-trees grow sturdy and are rich in fruit, then this bit of ground is truth for orange-trees.

If a particular religion, or culture, or scale of values, if one form of activity rather than another brings self-fulfillment to a man and releases the prince within, then this scale of values, this culture, this form of activity constitutes his truth.

Antoine de Saint-Exupery, from "Terre des hommes" (1939).

We are all in the gutter, but some of us are looking at the stars.

Oscar Wilde, from "Lady Windermere's Fan" (1891).
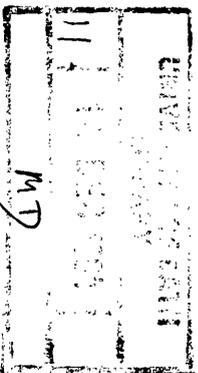
AGE-ASSOCIATED MEMORY IMPAIRMENT:
DIAGNOSTIC AND TREATMENT ISSUES

submitted by Dr Andrew Barker

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ABBREVIATIONS

AACD	Ageing-Associated Cognitive Decline
AAMI	Age-Associated Memory Impairment
AAMI1	Age-Associated Memory Impairment according to diagnostic criteria of Crook *et al* (1986)
AAMI2	Age-Associated Memory Impairment according to diagnostic criteria of Crook (1989)
ACMI	Age-Consistent Memory Impairment
ASRT	Anomalous Sentences Repetition Test
BSF	Benign Senescent Forgetfulness
BVRT	Benton Visual Retention Test (revised)
CT	Computerized Tomography
CVA	Cerebrovascular Accident
DISTRESS	Distress as a result of memory decline
DSM III-R	Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association) (current version)
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association) (version shortly to be released)
EDUCN	Years of full time education
GDS	Geriatric Depression Scale
GDSS	Geriatric Depression Scale (short version)
GP	General Practitioner
GPMC	General Practitioner-referral Memory Clinic
HAM-D	Hamilton Depression Rating Scale

IQ	Intelligence Quotient
LFTs	Liver Function Tests
LLF	Late Life Forgetfulness
LOG MEM	Logical Memory subtest of the Wechsler Memory Scale
MACQ	Memory Assessment Clinics Questionnaire (memory complaint questionnaire)
MMSE	Mini-Mental State Examination
NART	National Adult Reading Test
NARTIQ	NART estimated IQ
NIMH	National Institute of Mental Health, USA
RICE	Research Institute for the Care of the Elderly, Bath
SD	Standard Deviation
SRMC	Self-Referral Memory Clinic
STAI-S	State-Trait Anxiety Inventory - State
STAI-T	State-Trait Anxiety Inventory - Trait
VOCABIQ	IQ estimated from the Vocabulary subtest of the WAIS
WAIS	Wechsler Adult Intelligence Scale
WAIS-R	Wechsler Adult Intelligence Scale (revised)
WAIS Vocab	Vocabulary subtest of the WAIS
WALT	Associate Learning subtest of the Wechsler Memory Scale
WALT (hard)	Hard score on the WALT

ABSTRACT

Reports of deteriorating memory are common with increasing age. In a minority of cases these may be the recognition of the first signs of dementia. In most people however, they relate to non-disease ageing-related changes in cognition.

The term Age-Associated Memory Impairment (AAMI) was proposed, with diagnostic criteria, by a Work Group of the United States National Institute of Mental Health to describe people suffering from an ageing-related decline in memory (Crook *et al*, 1986). No prevalence study has yet been performed with the full set of diagnostic criteria and little work has been carried out to assess the validity of these. Despite these criticisms, pharmacological treatment trials have already been reported, and AAMI is likely to appear in some form in DSM-IV, the forthcoming updated version of DSM III-R (American Psychiatric Association, 1987), an internationally used classification of mental disorders.

In this thesis a prevalence study of AAMI is described. Prevalence rates are reported, but these vary dramatically with minor alterations to the diagnostic criteria. Several individual criteria are critically examined and suggestions for improvements are made.

Three further studies are described which investigated factors involved in the presentation of memory complaint to a self-referral memory clinic by people with mild cognitive impairment. Memory complaint in particular

was chosen for additional investigation because it is with this symptom that people with AAMI will present to doctors, and also because a poor correlation had been shown between memory complaint and test performance in the prevalence study, despite this symptom being an essential part of diagnosis in AAMI.

Memory complaint in attenders at a self-referral memory clinic appears to be more closely related to affective and personality factors than memory performance. Controversial issues regarding the concept and treatment of AAMI are discussed.

DECLARATION

Except where specified, the content of this thesis is purely my own work. All references quoted were personally consulted by me.

PRESENTATIONS AND PUBLICATIONS

The following presentations and publications have arisen directly out of work undertaken towards this thesis.

Presentations

POSTER PRESENTATIONS

"The relationship between memory and depression in memory clinic attenders."
Cardiff psychogeriatric symposium V, 1992.

ORAL PRESENTATIONS

"Memory performance, self-reported memory loss and depressive symptoms in attenders at a GP-referral and a self-referral memory clinic."
Mental Illness in Old Age conference, Liverpool, 1993.

"The relationship between memory and depression in memory clinic attenders."
Bath University postgraduate medical meeting, 1992.

"A community prevalence study of memory impairments in a population of over fifty year-olds registered with a Bath health centre."
Bath University annual postgraduate medical research meeting, 1993.

ORAL PRESENTATIONS (CONTINUED)

"Age-associated memory impairment."

Two local meetings of Bath and Bristol psychiatrists, 1992.

Publications

Barker, A. and Jones, R. (1993) Age-associated memory impairment: diagnostic and treatment issues. *International Journal of Geriatric Psychiatry* **8**, 305-310.

Barker, A. and Jones, R. (1993) Age-associated memory impairment. *International Journal of Geriatric Psychiatry* **8**, 780-781.

Barker, A., Carter, C. and Jones, R. (1994) Memory performance, self-reported memory loss and depressive symptoms in attenders at a GP-referral and a self-referral memory clinic. (Accepted for publication Oct 1993, *International Journal of Geriatric Psychiatry*).

CONTENTS

x

CHAPTER 4 : SELF-REPORTED MEMORY LOSS, MEMORY PERFORMANCE AND DEPRESSIVE SYMPTOMS IN ATTENDERS AT A GP-REFERRAL AND A SELF-REFFERAL MEMORY CLINIC

FOREWORD

The purpose of this thesis is to examine the concept, diagnostic criteria and prevalence of Age-Associated Memory Impairment (AAMI), a term proposed by a Work Group of the United States National Institute of Mental Health to describe people suffering from an ageing-related decline in memory (Crook *et al*, 1986). The concept of AAMI is based on the premise that such ageing-related changes exist, and that they are the psychological manifestations of underlying neurobiological changes in the central nervous system.

Chapter 1 is a general introduction to the area. Current psychological models of memory are presented and methodological problems of ageing-related research are examined. The evidence for ageing-related changes in memory and neurobiology is reviewed, and the significance of such changes discussed. A section on Benign Senescent Forgetfulness (BSF) is included since this term is already commonly used to describe elderly people with ageing-related changes in memory, and is the description that AAMI aimed to improve upon. The final section introduces the concept and diagnostic criteria of AAMI.

Chapter 2 describes the main project of the thesis; a prevalence study of AAMI with examination of some of the more important of the diagnostic criteria proposed.

Many argue for the future pharmacological treatment of AAMI. The self-referral memory clinic at the Research Institute for the Care of the Elderly (RICE) attracts many older people requesting medical help because of memory dysfunction. It is therefore an ideal setting to examine factors involved in self-presentation of memory complaint.

Chapter 3 describes characteristics of the first 100 people who attended the self-referral memory clinic. Chapters 4 and 5 describe two studies which examine the significance of memory complaint in people presenting to the self-referral memory clinic.

The final chapter is a general discussion of the findings and conclusions of the research performed for this thesis. Controversial issues regarding the concept and treatment of AAMI are discussed.

CHAPTER 1

INTRODUCTION

Age-Associated Memory Impairment, the subject of this thesis, refers to an ageing-related change in secondary memory. The reader may not be familiar with terms used in psychological models of normal memory functioning, so the first section of this chapter aims to give a brief introduction to the area.

Methodological problems of research into ageing-related phenomena will be examined before describing the evidence for changes in memory and neurobiology with ageing, since these will limit the conclusions which can be drawn from such evidence. The chapter concludes with sections on BSF and AAMI.

1.1   Normal memory functioning

The term memory describes the registration, retention and retrieval of information. It is one of a number of cognitive functions carried out in the brain which include language, praxis, visuospatial and perceptual function and conceptualization (Rabins, 1992).

1.1.1 THE MULTISTORE MODEL OF MEMORY

The multistore model of memory was proposed in its original form by Broadbent (1958), some thiry five years ago. He described a model where memory functioning was divided into three discrete parts: a

sensory store, a short term store and a long term store. Other researchers have subsequently produced amended and amplified versions, but the basic structure remains the same.

Sensory memory is that which enables us to make use of stimuli entering our nervous system. It allows the holding of information at a subconscious level long enough to be able to recognise patterns and select the relevant or important information that needs to be transferred into short term memory (Greene and Hicks, 1984; Duchek, 1991).

Short term memory is used for cognitive task processing such as remembering the first half of a sentence while reading the second half, remembering a phone number in order to dial or for mental calculation. It has also been called "primary", "immediate", or "working" memory (see Baddeley below).

Long term memory is for more permanent storage of memory that will be needed for future retrieval. It is also known as "secondary" memory, although some researchers refer to secondary memory as "recent" memory and add "tertiary" memory to refer to remote, distant, memory (Crook *et al* 1986).

1.1.2 WORKING MEMORY

Baddeley (1986) developed the concept of short term memory as "working memory", which concerns temporary storage used in a wide variety of information processing skills. It overlaps conceptually with the short term memory store in the multistore model of memory, but uses a more functional approach. Working memory in Baddeley's model

consists of a collection of temporary storage subsystems coordinated by a "central executive". The two subsystems so far described are the visuospatial scratch pad (or sketch pad) and the articulatory loop. The visuospatial scratch pad is probably used for the temporary retention of spatial or patterned visual information. The function of the articulatory loop is for the temporary retention of short streams of words, for example in silent reading, necessary for fluent reading ability.

The central executive carries out all functions not performed by other subsystems, but in the main has a supervisory role in attention control. Baddeley thinks of the central executive as a system that cuts in when the routine automatic "schemata" processing of information cannot continue undisturbed, either because of conflicting demands, or because a high degree of attention is required because of risk or particular importance.

The central executive and the two subsystems which have so far been elucidated are capacity limited. Tasks that require simultaneous retrieval, selection and storage will therefore place the greatest demands on the central executive. Although Baddeley's working memory theory is set within the multistore model of memory, he sees these systems as important in a variety of other cognitive tasks which rely heavily on information processing.

1.1.3 THE MEMORY TRACE

Broadbent believed that effective transfer of a memory to the long term store involved the laying down of a "memory trace"; a record of processing that has occurred. This idea was elaborated by Craik and

5

Lockhart with "levels of processing" theory (see Parkin, 1987). The "deeper" or more elaborate and extensive the processing, the more durable the memory trace was felt to be. Orthographical (visual) processing was the most superficial, phonological (auditory) next, and semantic (meaning) the deepest and hence the most durable. The theory of levels of processing led to improved memory training based on elaboration and semantic coding of information, rather than pure rehearsal. Its popularity declined however, probably because of the lack of testable hypotheses generated (Parkin, 1987).

1.1.4 PROCEDURAL, PROPOSITIONAL, EPISODIC AND SEMANTIC MEMORY

Tulving (1983) developed the concept of the long term memory store, dividing it into procedural and propositional memory. These refer to the learning of skills and factual knowledge respectively. Propositional memory could be divided into episodic and semantic memory. Episodic memory refers to personally experienced events, whereas semantic refers to knowledge of the world that is independent of a person's identity and past, and generally consists of words and concepts. He differentiated the two types on the basis of the sorts of information processed by them, characteristics of their operations, and their applications in real life.

Episodic memory is experiential and is coded temporally. Retrieval of episodic memory makes it more likely to be remembered at a later time but tends to modify the memory. Semantic information is normally received in symbol form (usually language), and is conceptually coded. Semantic memories tend to be overlearned rather than single episodes of experience. They are usually added into a person's pre-existing

6

conceptual structure, so are less likely to be changed, modified or lost. Retrieval of semantic memory, may make later access quicker. Tulving (1983) demonstrated that information that has been semantically rather than episodically coded is subsequently more accurately retrieved.

1.1.5 FLUID AND CRYSTALLIZED INTELLIGENCE

A further distinction that is made by many psychologists is between "fluid" and "crystallized" intelligence (Belsky, 1984; Rabbitt 1992). Fluid intelligence is the ability to devise a solution to a newly presented problem, and can be seen as the efficiency of rapid information processing. Performance IQ tests measure this construct. Crystallized intelligence includes the systems involved in long term retrieval from a person's accumulated store of factual knowledge. Verbal intelligence tests are often used to assess this factor for estimation of premorbid IQ in the elderly, since scores tend to be stable over time from adulthood onwards (Crawford, 1992) and in a variety of clinical conditions associated with old age (Crawford *et al*, 1988).

1.2 Methodological problems of ageing-related research in memory and neurobiology

Before reviewing the evidence for ageing-related changes in memory and neurobiology, it is important to recognise the methodological limitations of research attempting to measure changes across the lifespan. These include the cohort effect, the effects of physical and functional mental illness and the problems of defining, diagnosing and excluding cognitive illness (Rabins, 1992). It is pertinent at this point to highlight the

difference between age-related and ageing-related changes. Many things change with increased age, both internally and in the external environment: some of these are caused by the ageing process itself and many others are due to factors independently associated with a person's chronological age. Age is a state and ageing a process.

1.2.1 THE COHORT EFFECT

Most studies examining ageing-related changes in memory and cognition are cross-sectional: they compare groups of young and old subjects and analyze psychometric data for differences between them. The alternative, following up large groups of people for several decades, is extremely demanding both practically and financially. By the time results are obtained, they are automatically several decades out of date. There are methodological problems, however, in treating cohorts of people of differing ages as though they are distinguished solely by their chronological age (Belsky, 1984). Two longitudinal studies demonstrate how the cohort effect can affect conclusions drawn from cross-sectional studies.

Schaie and Labouvie (1974) assessed randomised community subjects from the ages of 21 to 84 years in seven-year cohorts cross-sectionally and then longitudinally over 14 years. All ten cognitive measurement variables on cross-sectional comparison showed age-related decrements in function, often starting in the 20's or 30's. However, only five of these showed progressive changes over the follow-up period, and these were far smaller than predicted by the cross-sectional comparison.

These findings were backed up by a prospective study (Arenberg, 1990) over 12 years of 400 men from the ages of 20 to 70+ using the Benton Visual Retention Test (a measure of secondary memory). Test scores at baseline showed a progressive decline across 10 year age bands, but over the follow-up period only the older groups (50's and above) showed a deterioration in scores.

1.2.2 EXPLAINING THE COHORT EFFECT

People of different ages may have previously had, and may currently have, different psychological, social and physical experiences which might affect their performance on psychometric tests as well as their underlying neurobiology. Any variation seen between two differently aged cohorts may actually represent these differing past and current experiences rather than a change due to ageing itself.

It is argued (Perlmutter *et al*, 1987) that differences in past educational experience will affect the use of mnemonic techniques and test-taking ability as well as a person's attitude towards continuing education and intellectually challenging leisure activities. Perlmutter *et al* also drew attention to the role of common stereotypes of ageing on social conditions and internal and external expectations of an elderly person, all of which may directly affect memory performance.

Rabbitt (1992) demonstrated how highly practised memory skills can give improvements in specific areas of memory performance. Age-related memory differences may be affected by which particular skills have been gained during life and also by which skills are currently relevant to a person's social demands and so are practised. Some attempts have been

made to improve the relevance, or "ecological validity" of cognitive tests for the elderly, for example by matching names to faces on video screens (Crook *et al*, 1990[A]). No standardized testing has yet been developed for use in the home on everyday household tasks, though the process abilities component of the Assessment of Motor and Process Skills assessment tool (Doble, 1991; Fisher, 1993) may be of value in the future.

Past or present lifestyle influences such as nutrition and exercise may also change with age and make interpretation of cross-sectional differences in neurobiology difficult (Prendergast and Armbrecht, 1990; Morris and McManus, 1991).

Finally, the older the study cohort becomes, the more and more selective becomes the group studied. A cross-sectional study of "normal" ageing from the age of 80 to 100 would include a majority of dead subjects. In longitudinal studies, loss of "at-risk" subjects makes the remaining group likely to have been supernormal at baseline rather than average.

1.2.3 THE EFFECTS OF PHYSICAL AND MENTAL ILLNESS

Elderly people suffer from more physical and functional mental illnesses than young people and as a result tend to be receiving more medications. A variety of drugs and medical conditions are known to affect sensory, primary and secondary memory, and may practically interfere with test taking. In these circumstances it is difficult to separate the effects of ageing on memory from these age-associated physical factors. The exclusion of people with particular medical problems and medications is

one way around this, but again at the risk of only including "supernormal" individuals.

There are a number of methodological problems regarding cognitive illness in research investigating ageing-related memory changes. These include the difficulty of diagnosing mild dementia and, more broadly, in defining dementia and distinguishing it from normality.

1.2.4 THE EFFECT OF DEMENTIA

Dementia is an umbrella term used to describe a syndrome of multiple higher cognitive deficits in which there is commonly a decline in intellect, personality and behaviour. It is normally chronic and progressive. The prevalence increases with age in an exponential fashion, approximately doubling in magnitude every five years from the age of 60 onwards (Jorm, *et al* 1987; Hofman *et al*, 1991). It can be caused by a variety of brain diseases (WHO, 1992) and most commonly Alzheimer's disease and multi-infarct dementia (Jorm *et al* 1987; Brayne and Calloway, 1989) although the prevalence of senile dementia of Lewy body type has probably been underestimated (Perry *et al*, 1990).

In studies of ageing-related changes in memory, people with dementia are usually excluded, since dementia is seen as an age-related disease rather than an ageing-related process. It could be argued that age-related differences demonstrated in cognition or neurobiology are due to the greater number of people with dementia with increasing age. Attempts are generally made to exclude these subjects, but first, a diagnosis has to be made.

11

1.2.5 THE DIFFICULTY OF DIAGNOSING MILD DEMENTIA

Dementia, and particularly Alzheimer's disease, often has an insidious onset and patients are extremely difficult to identify. Some attempts have been made to predict decline in people with mild cognitive changes (Boller *et al*, 1991; Burns *et al*, 1991; Flicker *et al*, 1991), but as yet there is no generally applicable psychological or biochemical diagnostic marker for Alzheimer's disease. Genetic techniques are unlikely to provide all the answers (Whalley, 1991). Definitive diagnosis of Alzheimer's disease can only currently be made by examination of brain tissue for histological analysis. This is normally only obtained post mortem or rarely by brain biopsy, so for research purposes the exclusion of people with Alzheimer's disease is based on clinical assessment.

Unfortunately, a variety of factors can affect cognitive performance with resulting misdiagnosis of mild dementia. These include low IQ and poor educational background, low social class, and medical and psychiatric factors (Henderson and Huppert, 1984; Burvill, 1993). Rosenman (1991) followed a group of 75 elderly people over 3 years and used progression of cognitive impairment to validate an initial diagnosis of mild dementia. He found poor agreement between five operational diagnostic methods for subjects who had validated mild dementia. These methods showed no more accurate prediction of dementia than clinical judgement alone or a simple 23/24 cutoff on the Mini-Mental State Examination, a short screening test for dementia (Folstein *et al*, 1975).

Because of the uncertainty of the significance of mild memory problems, many different terms are in existence which describe mild memory impairment in the elderly not sufficiently severe to merit the diagnosis of

dementia (Dawe *et al*, 1992). Widely used terms include "subcases" of dementia in the Geriatric Mental State (see Copeland *et al*, 1992), "Limited cognitive disturbance" in the Comprehensive Assessment and Referral Evaluation (CARE) (Gurland *et al*, 1982), "Questionable dementia", CDR 0.5 in the Clinical Dementia Rating scale (Hughes *et al*, 1982), "Minimal dementia" in the Cambridge Mental Disorders in the Elderly Examination (CAMDEX) (Roth *et al*, 1986), "Mild Organic Psychosyndrome" (see Hindmarch *et al*, 1991), "Very mild cognitive decline" from the Global Deterioration Scale (GDS 2, the "phase of forgetfulness") (Reisberg *et al*, 1982), "Benign Senescent Forgetfulness" (Kral, 1958) and "Age-Associated Memory Impairment" (Crook *et al*, 1986).

The purpose of some of these diagnostic labels is unclear, whether to identify people who are likely to be in the early stages of a dementing process, those with a non-progressive cognitive impairment, those with ageing-related changes or a group of people not otherwise classifiable in prevalence studies of cognitive impairment. Follow-up studies are not always available. Dawe *et al* (1992) reviewing some of the studies in which these terms had been used, reported an annual incidence of dementia varying between 1 and 25%. O'Brien and Levy (1993) note that longitudinal studies on categories of mild memory impairment generally show little progression to dementia when primarily based on subjective memory complaint, but more when based on objective deficits.

In order to improve the clinical diagnosis of Alzheimer's disease, operational criteria have been produced (McKhann *et al*, 1984; American Psychiatric Association, 1987) which improve diagnostic reliability of

established disease (Tierney *et al*, 1988). Similar criteria have also been proposed for diagnosing multi-infarct dementia (Roman *et al*, 1993).

Diagnosis is further complicated by disagreements over classification, even for Alzheimer's disease. Some propose that young onset disease should be distinguished from that of later onset, and base the distinction on neurochemical, pathological and genetic evidence (Gottfries, 1985). Certainly, the genetic factors that look convincing in early onset disease appear different from later onset cases (Harrison, 1993; Poirier *et al*, 1993; Scott, 1993), and the distinction between ageing related changes and dementia is harder in the elderly where many interacting causes of cognitive impairment coexist (Wilcock, 1988; Barker, 1992; Murphy, 1992). This area is particularly challenging for diagnosis, and there is a lack of widely accepted diagnostic criteria for mild dementia.

1.2.6 THE DIFFICULTY OF DEFINING MILD DEMENTIA

Henderson and Huppert (1984) found estimates of the prevalence of mild dementia in elderly populations varying between 2.6% and 52.7% because of different methods of identifying subjects and diagnostic criteria used. Mowray and Burvill (1988) applied a variety of diagnostic criteria from different schedules for mild dementia in a single community population of over 70 year olds, and found prevalence rates varying between 3% and 64%. Problems experienced in applying diagnostic criteria included the interpretation of what constituted "significant" interference with work, social activities or relationships, and also the differentiation of cognitive from physical factors in limiting function.

Diagnosing and excluding people with mild dementia from studies examining ageing-related changes is therefore problematical. However, a new layer of complexity is added when the existence of dementia as distinct from normality is questioned. If normal ageing and dementia were part of a continuum, as has been suggested (Brayne and Calloway, 1988), then any attempt to describe "normal" ageing-related changes would be meaningless.

1.2.7 THE DIFFICULTY OF DISTINGUISHING DEMENTIA FROM NORMALITY AND THE CONTINUUM APPROACH

Brayne and Calloway (1988) studied the frequency distribution of scores on a modified Blessed dementia scale and the information memory concentration scale in an elderly population, since both are correlated with the cholinergic deficit and with the numbers of brain plaques and tangles seen in patients with Alzheimer's disease (Blessed *et al*, 1968; Perry *et al*, 1978). They showed that in an elderly community population the frequency distributions of these scales are highly skewed, smooth and unimodal, suggesting that normality and senile dementia of the Alzheimer's type lie on a continuum, cutoff points being arbitrary.

The paper was criticized (Hofman *et al*, 1988) because of the crude nature of the measuring instruments and the heterogeneity of the population studied. The comparison was drawn with atherosclerotic changes which increase in prevalence with age and are distributed unimodally, but would not be considered by most to be part of normal ageing because of their association with myocardial and cerebrovascular disease.

There is disagreement over what the continuum view represents. Dawe *et al* (1992) use continuum to mean that it is very difficult to distinguish between early dementia and normal ageing. This is unhelpful as it adds nothing to the clarification of factors associated with progression of cognitive impairment. Accepting the continuum view prematurely carries the danger that there might be less research directed at more accurate methods of predicting prognosis, or discovering subtypes of disease for future treatments. Conversely, accepting the binary view too readily might limit study design and hence the conclusions that could be drawn from research findings. The issue may not be resolved until longitudinal studies are performed which include neuropathological and psychometric assessment on a randomised community population with a full range of cognitive function (Brayne, 1993).

Although Brayne and Calloway's position has supporters (Crook *et al*, 1986; Anon (Editorial), 1989), the consensus at the present time amongst researchers is that Alzheimer's disease and normal ageing are distinct because of a variety of quantitative and qualitative neuropathological (Katzman, 1988; Wilcock, 1988; Muller *et al*, 1991), neurochemical (Bowen *et al*, 1979; Bartus *et al*, 1982) and psychological (Huppert and Kopelman, 1989) differences.

1.3 Subjective reports of memory changes with ageing

Reports of deteriorating memory are common with increasing age. In a large study of volunteers aged 50 to 79 all subjects felt their memory had declined in the previous thirty years (Abson and Rabbitt, 1988). Memory complaints are very common in general population samples also (Bowles

et al, 1989), older people reporting more retrieval failures than the young.

However, there are problems with taking these self reports as evidence of true decline in memory, since a number of studies have shown there is little relationship between memory complaint and objective memory performance (Popkin *et al*, 1982; Abson and Rabbitt, 1988; O'Connor *et al*, 1990).

Memory complaint is probably more closely related to depression ratings than objective test performance in both depressed and normal community dwelling adults (Popkin *et al*, 1982; Bolla *et al*, 1991). Elderly people expect their memory capacity to deteriorate and tend to be more upset by memory problems than the young (Perlmutter *et al*, 1987). Therefore more objective evidence is required to prove the existence of true ageing-related changes in memory.

1.4   Objective measures of memory changes with ageing

Reviews of ageing-related memory performance generally agree that sensory memory, primary (short term) memory, and tertiary (remote) memory decline little with age, but that tests of secondary (recent) memory show marked differences between young and old subjects (Craik 1977; Poon, 1985; Crook *et al*, 1986; Cunningham and Brookbank, 1988; Rabbitt, 1992). In particular, the retrieval process in secondary memory appears to be affected (Bowles *et al*, 1989). These changes are present even after cohort effects are taken into consideration (Schaie and Labouvie, 1974; Arenberg, 1990).

A variety of memory tests have been used in ageing-related research, often concentrating on a particular area or domain of secondary memory. However, performance on different domain-specific tests varies both within and between individuals. This can be so for a variety of reasons: people have natural strengths and weaknesses, some practise particular skills more than others and some people have a higher general ability than others in terms of performance IQ/fluid intelligence. It is not surprising therefore, that age is more closely correlated with a measure of performance IQ such as the AH4 test (Heim, 1970) which assesses a variety of information processing skills, than it is with individual tests (Abson and Rabbitt, 1988). Current memory functioning is also more closely correlated with performance IQ than with age (Winthorpe and Rabbitt, 1988). After controlling for AH4 score, little age-related change exists in individual test scores (Rabbitt, 1988; Cockburn and Smith, 1991). Therefore, although memory declines with age, performance IQ does also, and after the age-related change in IQ is taken into account, little residual variance in individual test performance remains.

1.4.1 SLOWED INFORMATION PROCESSING AS THE MEDIATING FACTOR IN AGEING-RELATED MEMORY DECLINE

The reduced performance IQ associated with ageing appears to be related to a slower information processing rate (Stine *et al*, 1989). Slower information processing predicts less "deep" processing and also allows less rehearsal in working memory, functionally reducing working memory capacity. Light and Burke, pre-eminent in this field, believe that age-related changes in both language and memory are due to a decrease in working memory capacity (Light and Burke, 1988).

Slowed information processing is also identified by Rabbitt as the most sensitive index of general cognitive change in old age (Rabbitt, 1992). This would suggest that not just memory, but all cognitive systems may be affected to some extent by ageing, and indeed Baddeley (1986) showed that a number of non-memory tasks that rely on the central executive are worse in the elderly, such as reaction time, visual search and comprehension. Thus ageing-related changes in cognition will affect a wide range of everyday skills (Crook *et al*, 1986; Rabins, 1992).

Since working memory is a primary memory function, one may ask why no reliable changes in primary memory are found with increasing age. Most research of primary memory has used simple tests, for example the digit span. Baddeley's working memory model predicts that age-related differences would be more evident when the central executive is under greater demand. This is in fact the case, as demonstrated when increased speed of processing is required (Cunningham and Brookbank, 1988; Meyer and Rice, 1989).

1.4.2 INTER-INDIVIDUAL VARIABILITY IN DECLINE

Even though mean secondary memory test performance has been shown to decline with age, this could signify the whole population's performance gradually deteriorating or only a proportion declining rapidly while the performance of others remains stable. In fact, in cross-sectional studies, as the mean performance decreases with age, the variance increases, suggesting great variability between individuals in the rate of decline (Rabbitt, 1992). Some studies of elderly people show individuals performing as well as young controls (Bushke and Grober, 1986; Arenberg, 1990).

19

This variablility was also shown in a 7 year prospective study of healthy elderly people (Schaie, 1990). Using a variety of cognitive tests, Schaie showed that for some tests there was a decline in mean scores for people in their 50's, and for all tests in 60 to 70 year olds. If significant deterioration was defined as being a decline of 1 SD from baseline scores, then by age 81, incidence of deterioration on particular tests was between 30% and 40%. Conversely, between 60-85% of people remained stable or improved on specific abilities, and very few people had global decline in all areas.

1.4.3 THE IMPACT OF AGEING-RELATED MEMORY CHANGES
ON EVERYDAY LIFE

Although there may be changes in secondary and primary memory with ageing, there is evidence that poor retrieval tends to relate to routine rather than important information (Niederehe and Yoder, 1989). This is perhaps why although reported memory decline is very common in community residing elderly people, only a minority regard the memory change as a nuisance (Sunderland *et al*, 1986).

Semantic memory appears to be relatively well preserved (Cunningham and Brookbank, 1988; Bowles *et al*, 1989), which will help elderly people when in familiar surroundings and may help compensate for losses in other cognitive areas. Craik reports several studies demonstrating that elderly people use the context of information to be retained to a far greater extent than young people and that if this context is given in testing situations, ageing related differences are greatly reduced (Craik, 1990). The older person has wider life experience, and has had a greater chance to learn information and skills relevant to their lifestyle. Since

some of the changes in memory may relate to lack of practice induced by limited social demands, it is of interest that age related effects in inductive reasoning and verbal meaning demonstrated by Schaie between middle aged and elderly cohorts were no greater than that which can be achieved by educational intervention, ie training (Schaie, 1990).

Therefore, although primary and secondary memory does decline with age in parallel with other cognitive functions, the changes are not universal and do not necessarily affect a person globally. Ageing-related changes are not as great in magnitude as those which occur through interpersonal variation in IQ or in training. Often, people simply restructure their environments and lifestyles to accommodate to these changes, and other cognitive factors related to ageing may help compensate for losses in memory performance. Many elderly people accept the changes associated with becoming old as natural. In a study of human ageing, Perlin and Butler (1980) found that all subjects had experienced an identity crisis in terms of sensing themselves as old, but reported that "..finding oneself old has been a normative crisis, not an affliction, for most if not all of our subjects".

However, it has been noted that the effects of a decline in memory may be profound for some people, particularly those in employment or with intellectually demanding leisure activities (Crook et al, 1986).

1.5   Neurobiology of normal ageing

Ageing affects most if not all of the major physiological systems in the body (Brocklehurst, 1973). Typical ageing-related changes in these

systems have been described as a decreased ability to maintain homeostasis under conditions of physiological stress (Davies, 1990).

In animal nervous tissue, histological changes associated with ageing have been reliably reported at the subcellular level, and are similar across a wide range of species (Bellamy, 1985). The difficulty of assessing the neurobiological changes of normal ageing in the human central nervous system is that the tissue for analysis is not easily available. Brain tissue can only be obtained at post mortem, or rarely at biopsy, both of which are unusual in healthy elderly people. Accurate information is therefore sparse, but a synopsis of some of the main and reliably found changes will be presented.

1.5.1 MACROSCOPIC CHANGES

Brain weight decreases with age, particularly from the age of sixty onwards (Cole, 1985). Cortical atrophy is maximal in the frontal and temporal association cortex (Morris and McManus, 1991). This atrophy can be seen as ventricular dilatation and sulcal widening using magnetic resonance imaging and computerized tomography (CT), with a shift in the electroencephalogram pattern to lower frequency activity in healthy elderly adults (Obrist, 1980). There is increasing variability in brain size with age (Jernigan, 1987; Morris and McManus, 1991), and one-off CT-derived measurements of brain structures are unhelpful for differentiating normal and demented groups of people (Bird *et al*, 1986). Medial temporal lobe thickness, assessed by CT, declines exponentially with age in people with no evidence of cognitive dysfunction (Jobst *et al*, 1992).

1.5.2 MICROSCOPIC CHANGES

At the cellular level, the cortical atrophy seen in the frontal and temporal association cortex appears to be due in the most part to reduced size of neuronal cells rather than reduced numbers (Morris and McManus, 1991). There are modest age-related losses in specific cell populations in the cortex and neuroglia numbers increase in these areas (Brody, 1987). Most subcortical nuclei show no reduction in number of neurones, except catecholaminergic nuclei containing melanin (locus ceruleus and substantia nigra). Cellular abnormalities such as neuritic plaques, neurofibrillary tangles, Lewy bodies, lipofuscin and amyloid are often seen in the brains of cognitively normal elderly people, though their exact relationship to disease states remains unclear. Alzheimer-type changes are certainly common in non-demented elderly people, and are more common than could be expected if they were early manifestations of Alzheimer's disease (Ulrich, 1985).

Cellular changes in the nucleus basalis of Meynert (nbM) are of particular interest because of the nucleus' cholinergic output and the dramatic loss of cells seen here in Alzheimer's Disease (Bartus *et al*, 1982). In a group of neurologically intact and pathologically normal patients (De Lacalle *et al*, 1991) it was estimated that compared to young adults, 26% of nbM neurones are lost by the age of 60 and 50% by the age of 100. This decrease in cell number was found to be accompanied by increased cell size up to the age of 60, after which cell size also decreased. The authors suggested that neuronal plasticity was lost at around the age of 60, and benign memory impairment is seen because the brain can no longer compensate for the ageing-related cell loss.

1.5.3 BIOCHEMICAL CHANGES

Of all of the neurotransmitter and neuromodulator systems, the cholinergic system has received the most research attention because of its importance in memory dysfunction and Alzheimer's disease in particular (Bartus *et al*, 1982). Little or no change is found in the activity of choline acetyltransferase with normal ageing. However, there is reduced acetylcholine release on laboratory induced stimulation, and postsynaptic muscarinic receptors are probably reduced in number and less plastic (ie they cannot up- or down-regulate so efficiently) (Muller *et al*, 1991).

Age-related cholinergic dysfunction will of course interact with age-related changes in other neurotransmitter systems which are starting to be described (Decker and McGaugh, 1991). Neuronal cells become less sensitive to acetylcholine but not to glutamic acid, arguing against a generalized decrease in neurotransmitter system activity with ageing. Levels of gama-aminobutyric acid are significantly reduced, but little change in somatostatin is seen (Roth, 1986). 5-hydroxytryptamine (5-HT) turnover is probably increased, and numbers of 5-HT receptors are reduced (McEntee and Crook, 1991). The concentrations of noradrenaline and dopamine are reduced, and there may be impaired regulation of adrenergic receptors (McEntee and Crook, 1990). Metabolites produced from turnover of the monoamines are not reduced however, suggesting that increased turnover compensates for the decreased total neurotransmitter pool (Gottfries, 1992). There appears to be a slight decrease in brain lipid, carbohydrate, protein and mineral content with ageing (Samorajski and Persson, 1985).

Although a direct link between the described changes in neurobiology with normal ageing and the cognitive changes described by AAMI cannot yet be proven, it would not seem unreasonable to assume that they are connected.

1.6 Benign senescent forgetfulness

Before examining the concept and diagnostic criteria for AAMI, the condition Benign Senescent Forgetfulness (BSF) will be described in some detail. This term is already widely used in the UK to describe elderly people with poor memories who are not suffering from dementia, and BSF was the direct forerunner to AAMI. There are differences in the groups as described however, which need to be explored.

1.6.1 STUDIES BY KRAL

Kral (1958) first suggested the terms "benign" and "malignant" senescent forgetfulness to differentiate a relatively stable "mild" type of memory impairment from an "amnestic" type which had a definite and sometimes rapid progress. He initially performed psychiatric and neurological examinations on all 162 residents (mean age 79.4 yrs) of the Hebrew Old People's and Sheltering Home in Montreal (Kral, 1958). 43.2% of the population had neurological signs of cerebrovascular or degenerative disease, and 35.2% had signs of hemiparesis. It is unclear what formal cognitive testing was used as part of the assessment procedure.

Kral divided the residents into 5 groups on the basis of their mental state: Group A were well preserved intellectually with no signs of functional illness; group B were felt to have "mild" memory impairment, which was intermittent with no clinically ascertainable memory defect; group C included residents without memory defect but with a past or present history of functional mental illness; group D he described as having an amnestic syndrome, with defects in at least recent memory, orientation and remote memory; group E resembled group D but psychotic signs were also present.

Kral (1962) followed up a subgroup of 94 of this population 4 years later, though it is unclear how this group related to the original subjects. He demonstrated a significantly higher mortality rate in people with an amnestic type of memory impairment, but no significant difference between the "normal" group and the group with "mild" memory impairment (which he now labelled as benign senescent forgetfulness). He later reported that in this follow-up period only one of 20 BSF patients developed the amnestic syndrome (Kral, 1978).

Kral performed a second study, in the geriatric service of a mental hospital (Kral *et al*, 1964). 695 patients were seen who had a total of 1290 assessments between them during a three year observation period. Four diagnostic groupings were considered: senile psychosis, arteriosclerotic psychosis, schizophrenia, and manic-depressive psychosis. The average length of stay for schizophrenic patients was 31.2 years and for people with manic depression 14.0 years. The "functional" groups (schizophrenia and manic-depressive psychosis) were considered to have no memory problem or the benign type of memory impairment. Death rates were higher for the "organic" groups (56%)

compared to the "functional" groups (19%). The organic group's functional ratings mostly declined with time whereas the functional group's ratings generally improved, perhaps because of sustained therapeutic involvement. He reassessed these patients 5 years later, and found the death rate still to be significantly higher in the amnestic group (Kral, 1978).

1.6.2 THE CLINICAL DESCRIPTIONS OF BENIGN AND MALIGNANT SENESCENT FORGETFULNESS

Benign senescent forgetfulness, as described by Kral, is characterized by an intermittent difficulty in recalling specific facts. There is no distinction between recent and remote memories in the difficulty of recall, but personal experiences seem to be recalled better than facts with less personal meaning. Subjects tend to remember an experience itself but forget relatively unimportant detail. Kral felt that the prime defect was in recall, although he acknowledged that a variety of factors could be responsible for this. These included the time lapse since the event or the last recall of the event, modifications of the retained information during retention, and dynamic factors operative at the time of recall. The memory impairment is not accompanied by confabulation or disorientation and remains relatively stable in both character and severity.

In contrast, Kral characterised the malignant form as an impairment particularly of recent memory, including personal experiences. Disorientation is present, especially of time, and confabulation is found early on in the disorder. This type of memory impairment is progressive, often rapidly. In time, Kral's concept of malignant senescent

forgetfulness developed into the amnestic type of memory impairment and he subsequently incorporated it into Alzheimer's dementia.

1.6.3 CRITICISMS OF THE CONCEPT OF BENIGN SENESCENT FORGETFULNESS

Kral's senescent forgetfulness groups were defined by comparison with an unimpaired "normal" peer group. The proposition of BSF therefore suggests that a non-dementia memory disorder exists in a subset of the elderly population distinct from normal ageing. Although he identified a "normal" group he did not produce objective criteria to distinguish BSF from normality, and additionally described BSF as an expression of a "senium naturale" (Kral, 1978). He also did not rule out the possibility that BSF was part of the same neuropathological process as Alzheimer's disease, possibly differing in severity or location of the disease process.

The populations Kral studied were plainly not representative of the general population. Many healthy elderly people have transient memory retrieval problems, but these people were not examined. Nursing home residents and chronic psychiatric hospital patients are likely to have had other physical and mental health problems which could have caused memory impairment. It is difficult to extrapolate from these to the elderly population at large. No distinction was made between people with chronic problems and problems of recent onset, though if the impairment described is distinct from both normality and dementia, and non-progressive, the question must be raised as to how the deficit came about. It is possible that many of these patients had long standing cognitive impairment from a variety of causes that often result in misdiagnosis of dementia (Spear Basset and Folstein, 1991).

1.6.4 RECENT WORK

Despite the methodological limitations of some of Kral's research, more recent work has added weight to Kral's proposition of a mild memory disorder distinct from normality and dementia.

Larrabee *et al* (1986) carried out a series of cognitive tests on a population of healthy elderly people. Cluster analysis revealed a subgroup of subjects, who, despite globally intact intellectual ability, had reduced verbal and visual memory performance. These differences were particularly pronounced on retrieval tasks and indicated, in keeping with Kral's view, an intermittent rather than a consistent long term retrieval problem. On reassessment one year later there was no differential change in test scores for the control and senescent forgetfulness groups. However the numbers in the study were small and there was only a short follow-up period. Larrabee and Crook (1989) also used cluster analysis, on age-residualised scores from computerized cognitive tests on a larger group of normal elderly volunteers, to reveal a forgetful group that tended to be older.

O'Brien *et al* (1992) followed up 68 patients who originally had given a history of memory difficulties suggestive of Kral's BSF at a memory clinic, where cognitive testing revealed normality or benign age-related memory changes. No subjects who were felt to be suffering from early dementia or other psychiatric disorder were included. After a mean follow-up period of 3.1 years 64 patients were traced and 55 returned for follow-up. Telephone and/or GP contact did not reveal any of the non-attenders to be suffering from dementia. There were 6 new cases of

dementia, which, although more than double the expected number, was not significantly raised statistically.

The Global Deterioration Scale (Reisberg *et al*, 1982) is a clinical instrument reflecting the continuum of clinical presentations between normal ageing and severe dementia. It is divided into 7 stages from stage 1 (no cognitive decline - clinical phase normal) through stages 4 (moderate cognitive decline - clinical phase late confusional) and 5 (moderately severe cognitive decline - early dementia) to phase 7 (very severe cognitive decline - clinical phase late dementia). GDS 2, the phase of forgetfulness, is characterized by subjective but not objective cognitive deficits and GDS 3 is an early confusional stage with mild deficits evident on careful clinical testing. GDS 2 and 3 probably describe subjects who would have been classified by Kral as suffering from BSF.

Reisberg *et al* (1983; 1986) studied 106 community residing elderly people over a mean of 3.6 years, 72 of whom were in the GDS 2 or GDS 3 stages. All 40 of GDS 2 subjects were still community residing at follow-up, and only 2 had declined more than 1 GDS stage. Of 32 subjects originally in GDS 3, 1 had died, 1 was institutionalised and amongst the other 30, 3 had clinically improved and 3 deteriorated. There was a divide then, with subjects in GDS 4 having a worse prognosis; of 22 subjects, 6 were dead, 6 institutionalised, and of the remaining 10 community residing subjects, 4 were more than 1 stage worse. This suggests that the majority of people with subjective and mild objective memory impairment have relatively little deterioration compared to a more impaired group who are probably in the very early stages of Alzheimer's disease.

1.7 Age-associated memory impairment

1.7.1 THE ORIGINAL PAPER BY THE NIMH WORK GROUP

The term "age-associated memory impairment" (AAMI) was proposed, with diagnostic criteria, in 1986 by a Work Group of the National Institute of Mental Health in the United States, "to describe the memory loss that may occur in healthy, elderly individuals in the later decades of life" (Crook *et al*, 1986). The authors' stated aim was to distinguish the sufferers from those who experience no such loss and from those whose impairment is associated with other "specific" disease states. Although the work group included NIMH representatives and researchers in the fields of medicine and psychology, almost half of the 46 members were affiliated to various pharmaceutical companies.

The work group (Crook *et al*, 1986) felt that the term Benign Senescent Forgetfulness was imprecisely defined, with little psychometric assessment as part of its definition, and described a particular subset of older people with memory impairment. They queried the use of "benign" to describe what to some people is distressing and disabling and felt that the lack both of agreement on terminology and of specific diagnostic criteria made research and scientific communication difficult.

The work group's paper reviewed research into ageing-related changes in memory, and concluded that memory does decline, in parallel with other cognitive functions that make up fluid intelligence. It is notable though, that memory, rather than other cognitive loss, is focussed on in both the diagnostic criteria and the term AAMI itself. The authors felt that many healthy elderly people are distressed by an ageing-related decline in

31

memory and are not reassured by doctors telling them that they are not suffering from dementia, or that it is a normal part of ageing. The work group thought that this advice is partly given out because of the lack of effective treatment for the disorder and suggested that "..it would seem appropriate to recognize the distress that frequently lies behind complaints of memory loss in the elderly and recognize the importance of developing effective treatments."

Evidence for ageing-related memory loss in other mammals and ageing-related changes in human neurobiology was reviewed. The work group considered that the ageing-related neuropathological and neurochemical changes that exist are probably quantitatively rather than qualitatively different from Alzheimer's disease. They therefore considered that compounds that reverse the relevant neurochemical deficits may be of therapeutic value in both AAMI and dementing disorders.

AAMI was proposed by the group "..to describe memory decline with age". It is to be characterized by complaints of everyday memory impairment with evidence of impairment on psychometric tests. Although the diagnosis is limited to people over the age of 50 it was not thought to be necessarily any different from that found in younger adults. AAMI can progress, but marked progression would exclude subjects from the diagnosis.

Proposed diagnostic criteria were then listed in the paper "for selecting research participants", and a copy of these may be found in Appendix 1. The criteria include memory complaint as "subjective evidence" of decline, backed up with memory test performance worse than 1 standard deviation below the mean for young adults as objective evidence. Other

diagnostic criteria require adequate intellectual ability and absence of other possible specific medical and psychiatric causes of memory impairment. The working group did not intend the diagnostic terminology and criteria to be definitive, and expected alterations as further research was carried out.

1.7.2 RECENT WORK

McEntee and Crook (1990) suggest that AAMI may be present in most people over the age of fifty. Most of the published work on AAMI has been on highly selected samples of people of above average intelligence and educational background (Crook *et al*, 1990[A]; Crook *et al*, 1990[B]; Crook and Larrabee, 1991). Based on data generated from these studies, Crook and Larrabee (1991) estimated that 70% of 50-59 yr olds, and 91% of 70 yr olds would satisfy the memory performance inclusion criteria on one test of secondary memory.

No prevalence studies using the originally suggested diagnostic criteria have been reported, though there are three studies from which the prevalence can be estimated. Reinikainen *et al* (1990) used some of the inclusion criteria in a group of 67-77 year olds and found 56% to satisfy these criteria. Smith *et al* (1991) used most of the diagnostic criteria but had previously screened their over 55 year-olds for memory complaint and relevant medical conditions. 49% satisfied their criteria. Lane and Snowdon (1989) used most of the inclusion diagnostic criteria but performed no physical assessments or investigations on their over 65-year-old subjects. They estimated a prevalence of 35% in this population.

1.7.3 CRITICISMS OF THE CONCEPT AND DIAGNOSTIC CRITERIA OF
   AAMI

Although the attempt to recognize the problem of ageing-related memory change and to operationalize the diagnosis has been welcomed (Dawe *et al*, 1992) much of the published response to the NIMH work group's paper has been critical (Bamford and Caine, 1988; Rosen, 1990; O'Brien and Levy, 1992; Barker and Jones, 1993[A]).

The original description of AAMI is confused both in the text and in the proposed diagnostic criteria. The confusion is compounded by the lack of any discussion as to why these particular criteria were chosen. It is not entirely clear whether AAMI aims to define the subgroup of elderly people with memory changes that are commonly seen in normal ageing, the subgroup who are distressed by these changes, or "to describe memory decline with age" (Crook *et al*, 1986). The question as to the relationship to dementia is unresolved since it is to be distinguished from Alzheimer's disease but the similarity in neurobiology between the disorders has been stressed (Crook *et al*, 1986; Crook, 1989).

Smith *et al* (1991) have rightly commented that since AAMI is supposed to be describing normality, then the use of "impairment" in the diagnostic label is misleading and perhaps "decline" would be more appropriate. Rosen has suggested using the term "definitional" rather than "diagnostic" criteria to avoid any implication that AAMI is a disease state (Rosen, 1990).

Other criticisms have extended from the concept of diagnosing and suggesting drug treatment for what is essentially normality, to details of

the individual criteria used. Criticisms of the concept and diagnostic criteria of AAMI will be expanded upon in Chapters 2 and 6.

Despite critical reviews, it seems likely that AAMI will appear in some form in DSM-IV, perhaps under the name Ageing-Associated Cognitive Decline (AACD) (Caine, 1993). Pharmacological treatment trials are underway for AAMI despite the untested validity of the disorder, and a few have been reported (Crook and Lakin, 1991; Crook *et al*, 1991; McEntee *et al*, 1991). This is of concern to some physicians (O'Brien and Levy, 1992; Barker and Jones, 1993[B]).

1.8 Summary

In this chapter methodological problems in carrying out research into ageing-related phenomena have been described. Despite these, evidence suggests that ageing-related changes do exist in memory and cognition, and in central nervous system neuropathology and neurochemistry, though their relationship to dementia has not yet been fully elucidated.

AAMI has been proposed to describe the condition of ageing-related memory impairment. There have been criticisms of the concept of diagnosing normality and of the criteria suggested to identify subjects. No prevalence study has yet been performed using all of the diagnostic criteria. Despite criticisms, some pharmacological treatment trials have already been reported, and AAMI is likely to appear in some form in the forthcoming version of DSM-IV.

35

1.9　Aims of thesis

The aims of this research project were three-fold:

1. To perform a prevalence study of AAMI.

2. To examine the concept and diagnostic criteria of AAMI.

3. To assess factors affecting the presentation of people with memory complaint to a self-referral memory clinic.

CHAPTER 2

A PREVALENCE STUDY OF AGE-ASSOCIATED MEMORY IMPAIRMENT

2.1 Introduction

In Chapter 1, evidence from psychological and neurobiological assessment was presented, which, despite the methodological problems discussed, suggests that ageing-related changes in memory do exist and that they are likely to be related to underlying neurobiological changes.

Classification of ageing-related memory decline was discussed with particular reference to Age-Associated Memory Impairment (AAMI) (Crook *et al*, 1986). No prevalence study of AAMI has yet been performed using all of the proposed diagnostic criteria (which can be found in Appendix 1). Despite criticisms of the concept and diagnostic criteria chosen, pharmacological treatment trials for AAMI are underway and some have reported positive results (Crook and Lakin, 1991; Crook *et al*, 1991; McEntee *et al*, 1991). AAMI is likely to appear in some form in the forthcoming version of DSM-IV (Caine, 1993).

It is therefore vital to carry out a prevalence study of AAMI in the general population and to critically examine the proposed diagnostic criteria. Of particular interest are factors involved in memory complaint, since these will affect not only diagnosis but also the decision of patients to present to clinicians for help.

Although the inclusion criteria for a diagnosis of AAMI require memory complaint, it is not clear whether the work group really meant "complaint" or "report". Memory complaint which is distressing enough to motivate a person to seek medical help is clearly different from a report elicited in response to a questionnaire in a prevalence study. The Memory Assessment Clinics Questionnaire (MACQ) (Larrabee *et al*, 1992) is the only memory complaint questionnaire designed for AAMI, but this purely asks subjects to report any changes in memory noted (see Methods, section 2.2). Memory complaint should surely include both recognition of memory impairment and some expression of dissatisfaction or distress. Therefore, in the present study an additional question was added to enquire how distressing this change was felt to be. Hereafter, when the term memory complaint is used, it should be interpreted to mean a combination of report and distress, ie distress expressed because of a perceived memory impairment.

Limitations in the use of self-report questionnaires when studying cognitive ageing have been noted elsewhere (Rabbitt and Abson, 1990). These include the problems of assessing people with varied insight, the difficulty of validating reports of memory decline, and the effect of an individual's personality and affective state on memory complaint. There is some evidence that self-reports of memory dysfunction are poorly correlated with objective test performance, and more closely related to psychiatric symptomatology (Bassett and Folstein, 1993) and in particular depression (Popkin *et al*, 1982; O'Connor *et al*, 1990; Bolla *et al*, 1991). To examine this further, measures of depression and anxiety were included in the current study's methodology.

The only other test used in the methodology which requires explanation is the National Adult Reading Test (NART) (Nelson,1982). The Vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1955) is suggested in the original diagnostic criteria to measure intellectual function. Both tests measure verbal intelligence. However, the NART is more resistant to a variety of clinical conditions associated with increased age (Crawford *et al*, 1988), and is generally preferred amongst UK workers (Crawford, 1992). It is used in addition to the WAIS Vocabulary subtest in the present study.

The rest of this chapter describes a pilot study and then the main prevalence study of AAMI using the diagnostic criteria as suggested by the NIMH work group. Several of the individual diagnostic criteria are critically examined. Further discussion of conceptual and treatment issues in AAMI will be found in Chapter 6.

2.2   Methods for the pilot study

The methodology was tested in a pilot study on a sample of 10 subjects over a two week period in May 1992. Following this, the main study recruitment took place and was completed by June 1993. All methodology was passed by the Bath District Health Authority Ethics Committee.

A copy of the AAMI diagnostic criteria used with cutoff scores for the relevant cognitive tests can be found in Appendix 1. Copies of the introductory letters, consent form, questionnaire and interview schedules can be found in Appendices 2 to 7.

2.2.1 SUBJECT SELECTION

General Practitioners from the Combe Down surgery, The Avenue, Combe Down, Bath, provided the names and addresses of all patients registered with them who were fifty years old and above. The subjects were divided by sex and then grouped into nine, 5-year age bands (50-54, 55-59 etc) up to 90-94. This age band was chosen as the upper limit, since for the main study, 20 subjects were to be chosen from each age band, and there were fewer than 20 patients over the age of 94 registered with the practice. For the pilot study a group of 10 subjects was chosen which consisted of the first two names in alphabetical order from alternate age bands (i.e. including subjects from the youngest and oldest age groups).

2.2.2 SUBJECT RECRUITMENT

Subjects were initially contacted by letter with a covering note of introduction signed by all four of the Practice's General Practitioners. Then direct contact was made, either by telephone or if necessary by calling at the home, to inform subjects about the study and to ask for their participation. Those consenting to take part were sent a confirmatory letter of the agreed appointment time and a questionnaire which the participants were requested to complete prior to the interview. Any reason given for not participating was recorded, as were the age and sex of non-participants, in order to check for respondent bias.

2.2.3   QUESTIONNAIRE DETAILS

The questionnaire included demographic details, past and present health, and contained measures of memory complaint, depression and anxiety. Subjects were requested to complete the questionnaire just before the interview if possible and were asked to try to be as honest as possible. The time taken by subjects to complete the questionnaire varied between around twenty minutes to an hour.

2.2.3.1   Memory complaint questionnaire

The memory complaint questionnaire was based on the MACQ (Larrabee *et al*, 1992), devised for quantifying memory complaint in clinical trials for AAMI. It asks subjects to rate how their memory has changed since their secondary school or college days on 7 everyday memory tasks. Possible scores range from 7 to 35, with a score of 21 representing no change, and higher scores indicating more decline. A score of 25 or above is considered to represent significant memory complaint and this level is used for inclusion into clinical trials. An additional question was added (the distress scale) which enquired how distressing the change was felt to be (rated 1 - not at all, to 5 - very much).

2.2.3.2   Geriatric Depression Scale

Subjects then completed the Geriatric Depression Scale (GDS) (Yesavage & Brink, 1983), a simple Yes/No self-report questionnaire designed specifically for use in elderly people which has been found to be valid in medically ill and cognitively impaired individuals (Koenig *et al*, 1988; O'Riordan *et al*, 1990). Possible scores range from 0 to 30 with higher

scores indicating more depression. A cutoff score of 11 has been suggested to indicate possible depression (Brink *et al*, 1982), though scores may be higher when self-administered rather than staff-administered (O'Neill *et al*, 1992[A]).

2.2.3.3 State-Trait Anxiety Inventory

The Spielberger State-Trait Anxiety Inventory (Spielberger *et al*, 1983) was included in the questionnaire because it is a very widely used instrument for the assessment of current and trait anxiety and has been validated for use in elderly people (Patterson *et al*, 1980). Subjects are first instructed to rate on a four point scale how closely 20 statements regarding feelings about oneself relate to their own feelings at the time of completing the test (state anxiety, STAI-S). A second set of statements follows (some the same, some different) with the instruction to rate how much the statements relate to how they generally feel (trait anxiety, STAI-T).

Trait anxiety is equivalent to the personality dimension described by the terms neuroticism and negative affectivity (Jorm, 1989). Neuroticism may be important in the presentation of unexplained physical symptoms (Costa and McCrae, 1987; Goldberg and Bridges, 1988). Since memory complaint in previous work had been shown to be poorly correlated with memory performance (i.e. symptoms of memory impairment were not explained by objective assessment), it was felt a measure of trait anxiety would provide a valuable insight into the nature of memory complaint.

The Spielberger measure of trait anxiety presumes to measure a relatively stable construct. However, the Trait scale measures the tendency to

perceive stimuli as threatening and thereby producing state anxiety symptoms. The state-trait model of anxiety therefore predicts closer correlations between the two in social-evaluative situations (Spielberger *et al*, 1983) and when self esteem is threatened (Spielberger, 1972). Test-retest correlations are closer for the Trait scale than for the State scale however (Thompson, 1989), and the Trait scale shows good correlation with other trait anxiety, neuroticism and negative affectivity scales (Jorm, 1989).

2.2.4 INTERVIEW DETAILS

At the interview, written consent was obtained and any difficulties in completion of the questionnaire were attended to. Several cognitive tests were then performed according to procedural instructions provided with manuals wherever these were in existence. Training had been received in the administration of these tests from experienced practitioners.

2.2.4.1   The Mini-Mental State Examination

All participating subjects first underwent the Mini-Mental State Examination (MMSE) (Folstein *et al*, 1975), a widely used cognitive test designed to screen for the presence of dementia, with scores less than 24 out of 30 suggested to indicate probable dementia. People scoring below 24 are excluded by the AAMI criteria, though the suggestion to raise this cutoff for exclusion to 26 or less (Crook, 1989) is examined in the results section. If it was clearly evident that a subject was suffering from dementia, they were not asked to proceed further, and subjects

(and carers where appropriate) were advised that they could withdraw their consent at any point in the interview without pressure to continue.

2.2.4.2   Measures of verbal intelligence

The Vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1955) and the National Adult Reading Test (NART) (Nelson, 1982) were then administered. The WAIS, although recommended in the original AAMI criteria (Crook *et al*, 1986), was not referenced. In a later publication reference is made to the 1955 version of the test (Wechsler, 1955) rather than the revised version (Wechsler, 1981), so in the present study the 1955 version was used.

The Vocabulary subtest of the WAIS (WAIS Vocab) consists of a list of 40 words which are read out loud while being shown to the subject. The subject is asked for the meaning of the word and their responses are rated against a set of scoring criteria and examples given in the manual. The rater can prompt in a neutral way if they are uncertain whether the subject knows the meaning of the word. A "raw" score is produced that can be converted to a "scaled" score, which compares the raw score to the mean performance of a reference group of 20-34 year olds. Scaled scores vary between 0 and 19 with a mean of 10 and a standard deviation of 3. Estimated fullscale IQ (VOCABIQ) can be computed using Nelson and McKenna's (1975) regression equation.

The inclusion criteria for AAMI suggest a cutoff raw score and scaled score. However, the raw and scaled scores suggested do not equate in either the 1955 or the 1981 version of the WAIS across the age range proposed, and it is unclear whether one or both scores should be met for

inclusion. For the present study the diagnostic criterion of a scaled score of at least 9 was used.

The NART consists of a list of 50 words to be slowly read out loud by the subject. These pronunciations are marked as correct or incorrect, and the total error score converted to estimated full scale IQ (NARTIQ) using Nelson's (1982) tables.

2.2.4.3   Memory tests

All three tests of secondary memory suggested in the AAMI criteria were used (Benton Visual Retention Test-(revised), administration A (BVRT) (Benton, 1963); Logical Memory subtest of the Wechsler Memory Scale (LOG MEM) (Wechsler and Stone, 1983); Associate Learning subtest of the Wechsler Memory Scale (WALT) (Wechsler and Stone, 1983). For the prevalence data, the cutoff score for at least one of these tests had to be satisfied.

The BVRT consists of a series of ten cards on which one or more geometric figures are displayed. The subject is shown a card for 10 seconds. The card is then removed and the subject requested to draw a diagram as much as possible like the one they saw. This procedure is repeated for each card. The drawings are marked as correct or incorrect against a set of scoring criteria and examples given in the manual. Possible scores range from 0 to 10).

The logical memory test consists of two short stories of three sentences each. The first story is read out loud and then the subject is requested to tell the rater everything that they remember from the tale. This is then

repeated for the second story. The responses are recorded verbatim and marked for accuracy against the originals. This is done by the stories having each been divided into more than twenty sections and the scoring procedure rates differently for exact replication or partial recollection of each section. Possible scores range from 0 to 23).

The WALT consists of a list of 10 pairs of words. These are slowly read out to the subject. The first word of each pair is then read out and the subject is requested to produce the word that was paired with it. Some of the pairings are easy to remember (North - South) and others are hard (Cabbage - Pen). The subject is informed whether they were correct or not after each response, and if incorrect, the correct answer is repeated by the assessor. This sequence is repeated for the same pairs of words two more times with the order changed on each occasion. The score at the end is the sum of the total correct "hard" responses (WALT hard) plus half of the total correct easy responses. Possible scores range from 0 to 21).

2.2.5 FOLLOW-UP INTERVIEW FOR PHYSICAL AND PSYCHIATRIC ASSESSMENT

If, after completion of these tests, subjects were found to be suffering from possible AAMI as defined by scores on the MACQ and cognitive tests, or were thought to be possibly suffering from dementia, a second interview was organised for physical and psychiatric assessment. At this follow-up assessment, a close friend or relative was interviewed wherever possible.

A semi-structured interview was completed which had been designed to have particular emphasis on symptoms and signs necessary for clinical diagnoses of major depressive episode or dementia according to DSM III-R criteria (American Psychiatric Association, 1987), as well as covering possible medical exclusion factors for the diagnosis of AAMI. At the end of the psychiatric assessment a score on the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1967) was recorded as this is required by the AAMI exclusion criteria. The HAM-D is an interviewer-based rating scale designed for use by clinicians with training in psychopathology in order to rate the severity of illness in people suffering from depression. It includes 17 symptoms and signs of depressive illness, each of which is rated according to clinical guidelines (Hamilton, 1980).

A physical examination was performed and a score on the Hachinski Ischaemia Score (Rosen *et al*, 1980) recorded. This score is produced by assessing the presence or absence of a series of symptoms and signs thought to be associated with multi-infarct rather than primary degenerative dementia (Alzheimer's disease), and is a modified version of the ischaemia score originally described by Hachinski *et al* (1975). Blood samples were taken for urea and electrolytes, blood sugar, liver function tests (LFTs), thyroid stimulating hormone, full blood count, vitamin B12, folate, Treponema pallidum Haemagglutination Assay (TPHA) test and Venereal Disease Research Laboratories test (VDRL). All laboratory tests were carried out at the Royal United Hospital Bath and were requested through the normal channels.

A letter was sent to the relevant GP for all subjects who had the physical and psychiatric assessment, with results of the various tests and suggestions for future management if appropriate.

2.2.6 DIAGNOSIS

Dementia was diagnosed according to the DSM III-R classification of mental disorders of the American Psychiatric Association (American Psychiatric Association, 1987).

Two versions of the diagnostic criteria for AAMI have been published. The first set were the original criteria produced by the NIMH work group (see Appendix 1). AAMI diagnosed by these criteria will be referred to as AAMI1. This is the principal diagnosis under study. The second set differed slightly in the cutoffs used for the tests of secondary memory, and were described by Crook (1989). The cutoff for the BVRT was raised to 7 or less and the WALT (hard) score was suggested rather than the WALT total score, with a cutoff set at 6 or less . AAMI diagnosed by the latter set of criteria will be referred to as AAMI2.

2.3   Results of the pilot study and subsequent
modifications to the methodology for the main study

Of the 10 subjects whose names had been selected from the practice list for the pilot study, 1 had died, and one was not contactable over the two week period chosen. Six of the remaining 8 subjects agreed to be seen. Two were found to be suffering from both AAMI1 and AAMI2, and none from dementia. The methodology was found to be generally satisfactory, but was amended in a number of ways. These amendments are incorporated into the description of the main study methodology which follows.

2.3.1 SUBJECT SELECTION

A new, up to date practice listing was obtained just prior to the commencement of the main study to make the list as accurate as possible and to minimise the effect of delay between age band classification and interview. To try and avoid the potential embarrassment of trying to contact people who had recently died, medical notes of selected patients were consulted just prior to contact being made.

A random age-stratified sample of 180 people was required; 20 subjects from each of the nine age bands. The list of subjects was divided by sex. To ensure an equivalent sex distribution in the sample compared to the study population the proportion of men and women in each age band in the practice population was multiplied by 20 and the nearest round number used. Subjects were selected by taking every 'n'th name where n = number of practice population in age band divided by the number required in sample. The number of males and females selected from each age band was is shown in Table 1.

2.3.2 SUBJECT RECRUITMENT

Patients were contacted in small batches rotating through the age bands, so that any delay between selection and recruitment would have minimal differential effect on the bands' mean age.

Sometimes several telephone and personal calls had to be made at varying times of day on different days of the week over several weeks in order to make contact.

Table 1

Age band and sex distribution of study sample

Age band	Male	Female
50-54	10	10
55-59	10	10
60-64	10	10
65-69	9	11
70-74	8	12
75-79	7	13
80-84	7	13
85-89	6	14
90-94	2	18
Total	69	111

2.3.3 INTERVIEW DETAILS

Patients generally found the time taken for testing to be acceptable, but to control for the differential effect of fatigue on tests performed earlier or later in the interview, the order of pre-existing IQ and secondary memory measures was reversed in the second half of the sample seen.

The cognitive testing interview and the interview for physical and psychiatric assessment were scheduled to fit in with the subject's and the investigator's commitments; a number of these were carried out in the evening or at the weekend because many of the younger subjects were working.

Arranging two visits for cognitive and physical/psychiatric assessment was found to be very time consuming, and so it was decided wherever possible to combine the visits.

2.3.4 ANALYSIS

Years of education (EDUCN), MMSE, DISTRESS as a result of perceived memory decline and AGE were not normally distributed, therefore non-parametric techniques were used for these variables. For the remaining variables parametric statistical calculations were performed.

All other statistical procedures are described in the results section, and were carried out with the aid of the statistical software package SPSS-PC. A level of $p < 0.05$ was set for statistical significance and all p values quoted are based on a two-tailed test of significance.

2.4   Results of the main study

2.4.1 PRACTICE DEMOGRAPHICS

The breakdown of the practice population by sex and age is shown in Table 2. For comparison, data is given from the Office of Population Censuses and Surveys for England and Wales 1991 (OPCS, 1993[A]). 41% of the total practice population are aged 50 and over compared to 31% of the general population. 26% of the practice population are over retirement age compared with 19% of the general population. From the County Monitor of the same year (OPCS, 1993[B]) the practice population appears to be representative of the population of Bath, though Avon as a

whole is similar in age structure to England and Wales (Bath 23.4% of pensionable age or over, vs 19.4% of Avon) (data not shown).

The sex distribution of the over 50's is similar in the practice population and the general population (practice population 43% male, general population England and Wales 45% male).

Table 2

Patient numbers by sex in five year age bands at Combe Down surgery (22/5/93) compared with 1991 Census data for England and Wales

Age band	Practice population			England and Wales (thousands)		
	Male	Female	Total	Male	Female	Total
50-54	211	203	414	1359.3	1357.3	2716.6
55-59	204	217	421	1280.0	1296.2	2576.2
60-64	215	234	449	1237.2	1321.9	2559.1
65-69	203	225	428	1150.4	1331.3	2481.7
70-74	178	252	430	879.5	1154.4	2033.9
75-79	134	239	373	653.2	1013.7	1667.0
80-84	92	154	246	377.6	741.6	1119.2
85-89	38	98	136	164.6	419.1	583.8
90-94	5	38	43	-	-	-
50+	1281	1672	2953	7147.5	8817.6	15965.3
90+	6	50	56	45.7	182.1	227.8
95+	1	12	13	-	-	-
All ages	3540	3679	7219	24891.5	26063.3	50954.8

2.4.2 DESCRIPTION OF THE STUDY SAMPLE

Of the 180 names obtained from the practice list, 16 could not be approached for the study; they were effectively "missing" from the sample. One subject's date of birth was wrong so she was in fact too young to be considered for the study, and for one subject the address given was a UK address for somebody living abroad. 3 subjects were deceased and one was too ill to be seen and died in hospital shortly after. 7 had moved out of the area (4 into a nursing home) and 2 were not registered any longer but it was unclear whether they had moved or were deceased. One person was uncontactable; he did not have a telephone, and 8 visits on different days including weekends and at different times of the day including early morning and evening over the course of 6 weeks did not locate him. He did not respond to a second letter sent to him.

Of the remaining 164 subjects, 23 (14%) refused to help at all. Of these 23, the most common reason given was that the person was too busy (8). Other common reasons given included suspicion of my intentions; the belief that taking memory tests would be worrying; and ill health, either physical or emotional. Of the 141 people who agreed to help, 7 would only do so by answering questions over the phone or by completing the questionnaire part of the study. Common reasons given for agreeing to help with the questionnaire but not with cognitive tests included being too busy and feeling threatened by testing. The feelings of threat sometimes related to the fear of detection of early dementia, and sometimes to discomfort at being put on the spot and embarrassed at their performance. Since the group who agreed to help but not to be interviewed was so small, little useful data can be gleaned from them.

Therefore they will be combined with the refusers in subsequent analysis. 134 subjects were therefore seen out of 164 subjects in the sample (consent rate of 82%).

2.4.3 COMPARISON OF SUBJECTS "MISSING", "REFUSED" AND SEEN

The distribution of subjects not contactable "missing", subjects who refused, and subjects who were seen is shown in Table 3.

Table 3
Age band distribution of subjects not contactable (missing), subjects who refused and subjects who were seen, by age band

Age band	Missing	Refused	Seen
50-54	5	-	13
55-59	-	4	16
60-64	2	5	13
65-69	2	3	17
70-74	-	4	16
75-79	1	2	14
80-84	1	4	17
85-89	2	5	13
90-94	3	3	15
Total (%)	16(8.9)	30(16.7)	134(74.4)

Chi-Square 18.4 p=0.3

The reason the row totals do not all add up to 20 is due to slippage in age bands because the age of the subjects when seen was used for analysis rather than age at randomisation (up to one year previously). There is no significant difference in age band distribution between the

groups (Chi-square test) or in the mean age of the three groups (Table 4) with the non-parametric Kruskal-Wallis test. There was still no significant difference in age band distribution or mean age between the three groups after combining the "missing" and "refused" groups into one "not seen" group (Age band by seen/not seen Chi-square = 3.4 p=0.9; mean age seen vs not seen = 73.1 (SD 13.9) vs 72.8 (SD 12.6) Mann-Whitney Test z= -0.19 p=0.9).

Table 4

Comparison of "missing" subjects, subjects who refused and subjects seen by age

	Mean	SD	Cases
Missing - not contactable	70.0	16.8	16
Refused to be seen	74.7	12.0	30
Seen	72.8	12.6	134
For Entire Population	72.9	12.9	180

Kruskal-Wallis test 1 way anova, Chi-Square 1.4 p=0.5

Sex distribution between the three groups is shown in Table 5. No statistically significant difference is seen. There was still no significant difference in sex distribution after combining the "missing" and "refused" groups into one "not seen" group (Chi-square = 2.7 p=0.1).

In conclusion, these analyses indicate that the subjects who were not seen did not bias the sample of those actually studied in terms of age and sex.

Table 5
Comparison of "missing" subjects, "refused" and subjects seen by sex

	Missing	Refused	Seen	Total(%)
Female	10(9)	23(21)	78(70)	111(100)
Male	6(9)	7(10)	56(81)	69(100)

Chi-Square 3.5   p=0.17

2.4.4 STUDY WITHDRAWALS

Of the 134 people agreeing to be seen, 3 could not complete all of the tests due to fatigue and 6 due to physical handicaps (poor sight, hearing, or weakness following stroke). None of these 9 subjects were believed to be suffering from a dementing illness. Three could not be coded for the diagnosis of AAMI due to missing test data. Of the other 6, only one satisfied the original AAMI criteria and five did not. These nine subjects will not be considered further, and the rest of the data relates to the remaining 125 subjects.

2.4.5 PREVALENCE OF DEMENTIA

11 subjects were found to be suffering from dementia. All were over 80; 2 in the 80-85 group, 4 in the 85-90 group, and 5 in the 90-94 group. 6 were classified according to DSM III-R criteria as suffering from primary degenerative dementia of the Alzheimer type, 2 from multi-infarct dementia, and 3 from senile dementia not otherwise specified.

To check that these numbers were close to that expected, population prevalence rates based on these findings were calculated. Proportions of cases with dementia in each 5 year age band were multiplied by

population numbers of the same age band in the Census data of 1991 for England and Wales (OPCS, 1993[A]). The resulting figures were added together for cross age-band prevalence rates, with the denominator the sum of total population numbers of the same age bands in the Census data of 1991 for England and Wales (OPCS, 1993[A]). Population numbers for over 90's were used for the 90-94 group multiplier because no data on the 90-94 age group is given in the Census. The numbers are so small in this age group that little significant difference would be made by this manoeuvre. Prevalence rates for England and Wales based on this calculation were estimated as 5.8% of over 65's and 24.5% of over 80's. These are close to previously estimated prevalence rates and lend support to the adequate exclusion of dementia from the study sample.

2.4.6 PREVALENCE OF AAMI

Cases of AAMI were identified using the originally published diagnostic criteria (AAMI1)(Crook *et al*, 1986) and the later modified criteria (AAMI2)(Crook, 1989). There was no sex difference in prevalence of AAMI with either definition (AAMI1 M:F = 10/55:12/70, Chi-square 0.02 p=0.9; AAMI2 M:F 13/55:16/70 Chi-square 0.01 p=0.9). Therefore no differential computation was performed for total prevalence rates by sex.

Distribution of cases of AAMI1 and AAMI2 by age band are shown in Table 6. Estimated prevalence rates based on these figures were calculated using the same methodology as used for the dementia rates described above. Prevalence rates were calculated for three, fifteen-year age bands, for over 50's and for the total population and are shown in Table 7. Fifteen-year age bands were chosen to limit the effect of random variation in the numbers of actual cases in individual age bands.

Prevalence rates are shown to vary by a factor of 40% for 50-94 year olds, or 50% for 50-64 year olds depending on which set of criteria are used. Increased frequency of exclusion factors mainly accounts for the lower prevalence of AAMI seen in older age groups.

Table 6
Distribution of AAMI1 and AAMI2 cases by age band

Age band	AAMI1		AAMI2	
	No	Yes	No	Yes
50-54	8	5	7	6
55-59	16	–	16	–
60-64	12	1	10	3
65-69	11	6	9	8
70-74	14	1	13	2
75-79	10	4	10	4
80-84	12	1	11	2
85-89	9	2	9	2
90-94	11	2	11	2
Total	103(82.4)	22(17.6)	96(76.8)	29(23.2)

Table 7
Estimated prevalence rates of AAMI1 and AAMI2

Age band	AAMI1	AAMI2
50-64	15.8%	23.5%
65-79	24.1%	31.0%
80-94	11.8%	16.2%
50-94	18.5%	25.5%
All ages	5.8%	8.0%

2.4.7 PSYCHOMETRIC DESCRIPTION OF STUDY SUBJECTS NOT SUFFERING FROM DEMENTIA

Before examining individual inclusion criteria, the subjects with dementia were removed since full data was not available for these. This left 114 subjects. Descriptive statistics of psychometric variables necessary for diagnosis of AAMI in these subjects are shown in Table 8.

Table 8

Descriptive statistics for psychometric variables of study subjects not suffering from dementia

Variable	Mean	SD	Minimum	Maximum
MACQ	24.3	4.5	7	35
BVRT	5.6	2.3	0	10
LOG MEM	6.5	2.9	1.5	13.5
WALT Total	12.2	4.1	4	21
WALT hard	4.5	3.3	0	12
Scaled score of WAIS Vocab	12.4	2.9	7	19
MMSE	27.7	2.1	21	30

2.4.8 SUBJECTS SATISFYING INDIVIDUAL AAMI INCLUSION CRITERIA

The proportions of subjects satisfying various inclusion and exclusion criteria are shown in Table 9. A score of 25 on the MACQ is the suggested cutoff to indicate significant memory complaint, and 22 indicates at least some reported overall decline. The significance of scoring below the cutoff score on different numbers of tests is unclear.

The original criteria propose using a cutoff score 23/24 on the MMSE, although others have suggested using 26/27 (Crook, 1989).

Table 9

Subjects satisfying individual AAMI diagnostic criteria

```
MACQ        55/114 (48%) scored 25 or more.

            81/114 (71%) scored 22 or more.

AAMI1 MEMORY TEST CRITERIA:

BVRT        65/114 (57%) scored 6 or less.

LOG MEM     53/114 (46%) scored 6 or less.

WALT Total  69/114 (61%) scored 13 or less.


86/114 (75%) satisfied criteria for at least 1 test.

19/114 (17%) satisfied criteria for only 1 test.

33/114 (29%) satisfied criteria for 2 tests.

34/114 (30%) satisfied criteria for all 3 tests.

AAMI2 MEMORY TEST CRITERIA:

BVRT        90/114 (79%) scored 7 or less.

LOG MEM     53/114 (46%) scored 6 or less.

WALT hard   81/114 (71%) scored 6 or less.


101/114 (89%) satisfied criteria for at least 1 test.

 22/114 (19%) satisfied criteria for only 1 test.

 35/114 (31%) satisfied criteria for 2 tests.

 44/114 (39%) satisfied criteria for all 3 tests.

WAIS Vocab  102/114 (89%) scaled score of 9 or more.

MMSE   5/114 non-demented subjects scored less than 24.

       26/114 non-demented subjects scored less than 27.
```

2.4.9 EXCLUSION CRITERIA

Of 125 subjects with full data, 31 had memory complaint and memory test performance compatible with a diagnosis of AAMI1: 9 of these had medical or psychiatric factors that excluded the diagnosis (30%). These are listed in Table 10. 11 out of 40 (28%) potential AAMI2 candidates were excluded because of medical/psychiatric factors.

Table 10

Subjects excluded because of medical factors

1	Transient ischaemic attack 5 and 15 years ago.
2	Heavy alcoholic intake in past and most likely in present - unexplained high mean cell volume. DSM III-R major depressive episode. HAM-D > 12.
3	Untreated hypothyroidism detected on laboratory screen.
4	Severe angina. Currently taking diazepam and propranolol.
5	Taking amitriptyline and diazepam. HAM-D > 12.
6	Diabetes, severe arteriopath - bilateral amputee. Taking temazepam and DSM III-R major depressive episode. HAM-D > 12.
7	Cerebrovascular accident (CVA). DSM III-R major depression, on antidepressants. Hachinski > 3. HAM-D> 12.
8	CVA. Diabetic and hypertensive. Hachinski > 3.
9	Liver failure under treatment. History of haematemesis, blackouts, anaemic and abnormal LFTs on laboratory analysis.

All subjects had brief medical histories taken including current medication. However, only those subjects with possible AAMI or dementia had further physical and psychiatric assessment. 39/125 subjects had known medical exclusion factors including current or past medical illness, concurrent medication, Hachinski scores higher than 3, Hamilton depression rating scores of 13 or higher or psychiatric illness which may cause cognitive impairment. Those not already listed above are shown in Appendix 8.

Five people had Hachinski scores greater than 3 and all of these would have been excluded by medical factors in their past medical history. Four subjects had a DSM III-R diagnosis of major depressive episode - all of these and one other subject had a HAM-D score of greater than 12. Only one of the people with a DSM III-R diagnosis of major depressive episode and/or a HAM-D score of greater than 12 was not excluded for other reasons (physical illness, psychotropic medication).

2.4.10   MODIFYING THE AAMI INCLUSION CRITERIA

The MACQ was used to quantify self-reported memory decline and a level of 25 used to indicate significant decline. The AAMI criteria make no such quantification. If any reported decline whatsoever was considered to be significant, approximately 50% more subjects would have been classified as AAMI sufferers (52% for AAMI1 and 49% for AAMI2).

If, as has been suggested, the score on the MMSE for inclusion was raised from 24 to 27, approximately 26% fewer AAMI1 and 20% fewer AAMI2 cases would have been identified.

2.4.11 REPORTED MEMORY DECLINE AND MEMORY TEST PERFORMANCE IN SUBJECTS WITH AND WITHOUT EXCLUSION FACTORS

T-tests were performed (Table 11) for interval inclusion/exclusion variables between people with and without exclusion factors for AAMI (with the exception of the MMSE for which the non-parametric Mann-Whitney test was used). Reported memory loss was no different between the two groups. The BVRT and the MMSE were significantly lower for people with medical exclusion factors, there was a trend for the WALT score to be lower and there was no significant difference in logical memory score. Appendix 9 gives raw data listings for the mean score and SD for the variables MACQ, DISTRESS, BVRT, LOG MEM, WALT, MMSE, NARTIQ, and VOCABIQ in all non-demented subjects and all healthy subjects.

Table 11

Reported memory decline and memory test performance in subjects with and without exclusion factors

	Exclusion factors Mean (SD)	No exclusion factors Mean (SD)	Statistic	p value
MACQ	24.9(4.1)	24.0(4.6)	t= 0.9^A	0.4
BVRT	4.2(2.5)	6.1(2.0)	t= 4.0^A	0.0001
LOG MEM	5.7(3.1)	6.7(2.8)	t= 1.7^A	0.10
WALT	11.1(4.1)	12.6(4.1)	t= 1.7^A	0.09
MMSE	26.9(2.2)	28.0(1.9)	z= 4.7^B	<0.00001

^{A} T-test
^{B} Mann-Whitney test (exact p value not computed by SPSS-PC)

2.4.12 PSYCHOMETRIC MEASURES IN SUBJECTS WITH POSSIBLE AGEING-RELATED DECLINE IN COGNITION

Subjects with exclusion factors according to the AAMI criteria were removed before examining relationships of psychometric measures in those for whom any cognitive decline present might reasonably be attributed to ageing. This left 86 subjects with data for analysis, whose age and sex distribution is shown in Table 12.

Table 12

Subjects with no exclusion factors according to AAMI criteria

Age band	Female	Male	Total(%)
50-54	3	8	11(12.8)
55-59	6	7	13(15.1)
60-64	6	5	11(12.8)
65-69	9	7	16(18.6)
70-74	6	5	11(12.8)
75-79	5	3	8(9.3)
80-84	4	2	6(7.0)
85-89	3	2	5(5.8)
90-94	4	1	5(5.8)
Total(%)	46(53.5)	40(46.5)	86(100.0)

Since years of education (EDUCN), MMSE, DISTRESS as a result of perceived memory decline and AGE were not normally distributed, non-parametric Spearman rank correlations were used in the correlation analyses described. For the remaining variables parametric Pearson product moment correlations were performed.

2.4.12.1 The relationships between cognitive test performance, education and age

The correlation table of cognitive test performance and age with education, memory test performance and IQ is shown in Table 13. Unfortunately exact p values are not computed by SPSS-PC if less than 0.001, so these appear as $p < 0.001$.

Table 13

Correlation coefficients of cognitive test performance and age with education, memory test performance and IQ

	EDUCN	BVRT	LOG MEM	WALT	NARTIQ	VOCABIQ
BVRT	.24 $p<0.001$					
LOG MEM	.41 $p<0.001$	.50 $p<0.001$				
WALT	.42 $p<0.001$	.51 $p<0.001$	.59 $p<0.001$			
NARTIQ	.67 $p<0.001$	.24 $p=0.03$	.37 $p=0.001$	.50 $p<0.001$		
VOCABIQ	.62 $p<0.001$	.34 $p=0.001$	.42 $p<0.001$	.56 $p<0.001$	.81 $p<0.001$	
MMSE	.36 $p=0.001$	.47 $p<0.001$	.47 $p<0.001$	.67 $p<0.001$	.41 $p<0.001$	.34 $p=0.002$
AGE	-.19 $p=0.076$	-.64 $p<0.001$	-.34 $p=0.001$	-.29 $p=0.006$	-.16 $p=0.2$	-.08 $p=0.4$

Strong and highly significant correlations can be seen between all of the memory tests with age. Verbal IQ, as estimated by the NART or by the Vocabulary subtest of the WAIS, is closely correlated with all of the memory tests and the MMSE but no significant correlation is seen

between age and verbal IQ. Length of time in education is significantly correlated with all of the cognitive tests, and there is a trend for older people to have had fewer years of education.

2.4.12.2 The relationship of cognitive test performance, age and education with memory complaint

No statistically significant correlations are seen between reported memory decline or related distress with any of the memory tests or MMSE (Table 14).

Table 14

Correlation coefficients of cognitive tests and education with memory complaint

	MACQ	DISTRESS
BVRT	.07 p=0.5	.02 p=0.9
LOG MEM	-.07 p=0.5	-.10 p=0.4
WALT	.06 p=0.6	.06 p=0.6
MMSE	.04 p=0.7	-.01 p=0.9
NART IQ	.24 p=0.02	.26 p=0.01
VOCAB IQ	.22 p=0.04	.15 p=0.2
AGE	-.02 p=0.9	.00 p=1.0
EDUCN	.21 p=.049	.15 p=0.17

Significant positive correlations are demonstrated for NART estimated IQ with both reported decline and distress and between WAIS Vocabulary estimated IQ and education with reported decline. Reported memory decline and distress experienced as a result of this decline were strongly correlated (Spearman rank correlation coefficient = 0.64, p<0.001).

2.4.12.3 Relationship between memory complaint and estimated decline in memory

Memory complaint may be poorly related to cognitive test performance because absolute values bear no relation to decline. One way of estimating decline is to use the NART or WAIS Vocabulary generated IQ score as an estimate of original performance (Christensen, 1991). The NART estimated IQ is preferred in the UK as being a more reliable measure of pre-existing IQ (Crawford, 1992).

z scores were therefore computed for each of the short term memory tests and NARTIQ and differences in z scores used as an estimate of present versus past performance (NART z score - Test z score). Table 15 shows correlation coefficients for memory complaint with z score differences between NARTIQ and memory test scores (BVRT ZDIFF, LOG MEM ZDIFF and WALT ZDIFF.

A statistically significant correlation is seen between both reported memory decline and distress as a result of this decline with LOG ZDIFF. This means that people with a lower logical memory score relative to their estimated pre-existing IQ have higher memory complaint. No significant relationship is seen for the WALT or BVRT.

Table 15

Correlation coefficients of memory test performance relative to NART score with reported memory decline and distress experienced at this decline

	MACQ	DISTRESS
BVRT ZDIFF	.14 p=0.2	.19 p=0.08
LOG MEM ZDIFF	.28 p=0.009	.28 p=0.009
WALT ZDIFF	.18 p=0.1	.15 p=0.2

2.4.12.4 Relationship between memory complaint and affective symptoms

In contrast to the weak relationship between memory complaint and objective memory test performance, self-reported memory loss and distress are both significantly correlated with measures of depression and state and trait anxiety (Table 16). The strongest correlation is between trait anxiety and distress as a result of perceived memory decline.

Table 16

Correlation coefficients for reported memory decline and distress as a result of this decline, with affective symptoms

	MACQ	DISTRESS
GDS	.24 p=0.03	.31 p=0.004
STAI-S	.31 p=0.004	.24 p=0.02
STAI-T	.33 p=0.002	.48 p<0.001

2.4.12.5 Relationship between cognitive test performance and IQ with affective symptoms

There is no statistically significant correlation between state and trait anxiety with memory test performance or verbal IQ, though a modest correlation is seen between depression with BVRT and logical memory scores (Table 17).

Table 17

Relationship between cognitive test performance and IQ with affective symptoms

	GDS	STAI-S	STAI-T
BVRT	-.23 p=0.04	-.11 p=0.3	-.01 p=0.9
LOG MEM	-.36 p=0.001	-.20 p=0.07	-.19 p=0.08
WALT	-.16 p=0.1	-.08 p=0.5	.05 p=0.7
MMSE	-.19 p=0.08	-.11 p=0.3	.04 p=0.7
NARTIQ	-.12 p=0.3	-.02 p=0.9	.15 p=0.2

2.4.12.6 Relationship between reported memory decline, logical memory test performance, IQ and affective symptomatology

In order to examine the relative weight of memory test performance and affective symptomatology in the prediction of reported memory decline, a stepwise multiple regression model was constructed. Reported memory decline (MACQ) was the dependent variable and LOG MEM score,

NARTIQ, LOG MEM ZDIFF, and the affective symptom rating scales (GDS, STAI-S, STAI-T) were independent (Table 18). The LOG MEM score was used since this had shown the strongest correlation with memory complaint. Pin and pout levels were set at 0.05 and 0.1 respectively (pin and pout refer to the p value of the F statistic for a variable in order to enter or subsequently remove that variable in stepwise multiple regression and the levels chosen are the ones most commonly used).

The only variable that entered the regression equation was trait anxiety, and this accounted for 11% of the variance. NARTIQ and LOG MEM ZDIFF were just excluded.

Table 18

Stepwise multiple regression analysis in the prediction of reported memory decline (MACQ = dependent variable)

Variables in regression equation	B (SE)	Beta[A]	T	Sig T
STAI-T	.22 (.07)	.33	3.3	p=0.002
(Constant)	17.5 (2.1)		8.3	p<0.0001[C]
Variables not in regression equation		Beta in[B]	T	Sig T
LOG MEM		-.01	-.07	.9
LOG MEM ZDIFF		.20	1.85	.07
GDS		.07	.55	.6
STAI-S		.18	1.43	.2
NARTIQ		.20	1.94	.06

[A]Beta = regression. coefficient
[B]Beta in = regression coefficient if variable were
      entered next into equation
[C] Exact p values are not computed by SPSS-PC below 0.0001

2.5 Discussion

2.5.1 PREVALENCE DATA

The aims of the project described in this chapter were to perform a prevalence study of AAMI and to examine some of the proposed diagnostic criteria for AAMI.

Total-population and over-50s prevalence rates of AAMI1 were estimated to be 5.8% and 18.5% respectively based on 1991 census data for England and Wales. The age and sex structure of the sample population seen was not statistically different from those not seen. Prevalence rates for dementia are very close to internationally estimated rates of around 5% and 20% for over-65 and over-80 year olds published elsewhere (Jorm *et al*, 1987; Hofman *et al*, 1991). The prevalence rates for AAMI are therefore unlikely to have been distorted by either non-participant bias or undetected cases of dementia.

Three other studies of AAMI have been published from which estimates of prevalence can be made. Reinikainen *et al* (1990) performed the MACQ, MMSE, WALT and BVRT on a community sample of 67-77 year olds, and showed the prevalence with these criteria to be 55.8%. Smith *et al* (1991) applied most of the diagnostic criteria to a group of people 55 years and over who had been previously screened for memory complaint and relevant medical conditions. AAMI was present in 49%. Lane and Snowdon (1989) used similar criteria to Smith *et al* on a group of people 65 and over, but performed no physical assessments or investigations. They found a prevalence of 35%. The current study estimate is likely to be more accurate since, with the exception of an

ECG, the criteria used were those as originally proposed by the NIMH work group, with memory complaint more accurately defined and with subjects assessed for the presence of medical and psychiatric causes of memory impairment.

2.5.2 LIMITATIONS IN STUDY METHODOLOGY

A community prevalence study such as that described in the present chapter could always benefit from a larger study population, but the intensity and the time-consuming nature of the work required from one investigator precluded more subjects being seen. The fact that the prevalence rates for dementia were so close to internationally accepted values lends support to the likely accuracy of the data for AAMI.

The prevalence rates for dementia may be underestimates since, because of the delay between subject selection and recruitment (up to a year), a relatively large number of those who could not be contacted had died or had moved into a nursing home.

It was hoped that the STAI-S could be used as an indication of the level of anxiety at the time of the cognitive testing, as well as to correlate with memory complaint, by asking subjects to complete the questionnaire just before the interview. In retrospect it would have been wise to include this instruction on the front of the questionnaire or in the letter confirming the appointment, because often people had completed the questionnaire several days before the interview. This makes it difficult to draw strong conclusions about the relationship between state anxiety and memory test performance, though the correlations with memory test scores were stronger for State than Trait anxiety.

Unfortunately, although an electrocardiogram (ECG) should have been performed as part of the medical assessment of people with possible AAMI, no portable machine was available. It is unlikely however, that in the absence of significant clinical symptoms or signs any subjects would have been excluded on the basis of an ECG alone, and there were no specific indications for an ECG in any of the subjects seen which would have altered the findings.

2.5.3 EXAMINATION OF PROPOSED INCLUSION CRITERIA

The rates of AAMI are sensitive to the precise psychometric definition used. Thus the AAMI2 set of criteria, which differ only by minor changes in cutoff scores for the secondary memory tests, affected prevalence rates for 50-94 year olds in the present study by a factor of 40%. The exact diagnostic criteria proposed therefore need to come under close scrutiny, particularly as there is little discussion on the reasons for the criteria chosen in the original document (Crook *et al*, 1986).

2.5.3.1 Age

The prevalence study presented in this chapter relates to people over the age of fifty, as proposed in the original AAMI paper (Crook *et al*, 1986) and is therefore an advance on previous prevalence studies of AAMI (Lane and Snowdon, 1989; Reinikainen *et al*, 1990; Smith *et al*, 1991). However, if the object is to describe memory decline with age, then it is not clear why the age limit for AAMI was set at fifty. The work group acknowledged that the memory impairment defined by AAMI is not

necessarily qualitatively different from that which occurs in younger adults and performance on some tests of new learning starts declining from the twenties (Salthouse, 1982). One could question whether it is reasonable to recognize a disorder only when the sufferer reaches a certain age. No upper limit was set for age, which supposes that the ageing process is similar in 50 year olds and 100 year olds. In fact the relative sparsity of reliable normative data above the age of 80 has led to the suggestion that this should be the upper age cutoff for diagnosis (Blackford and La Rue, 1989).

By design the diagnostic criteria for AAMI attempt to define the disorder by comparing elderly people with a young population, rather than with age-matched peers, in contrast to the disorder of Benign Senescent Forgetfulness (see Chapter 1). The rationale for choosing a young population for comparison is that this is the group that the elderly compare themselves to when complaining that their memory has declined (Crook, 1989). However, elderly people do not compare themselves to the young average population, but to their own previous performance at a younger age.

2.5.3.2 Memory complaint

The diagnostic criterion of memory complaint is perhaps the most contentious of those proposed, since it is undefined and not quantified in the work group paper. In the present study, the MACQ was used, which is the only memory complaint questionnaire designed for AAMI which has a suggested cutoff score (Larrabee *et al*, 1992). The cutoff score, set to define "significant" memory complaint is presumably arbitrary. If report of any decline whatsoever is used to define complaint, then in the

present study, prevalence rates are altered by a factor of approximately 50%.

Reinikainen *et al* (1990) also used the MACQ in a community study in Finland and found 79.8% of 67-77 year olds to score 25 or more on the MACQ. This is higher than the level found in the present study, and suggests that memory complaint varies considerably across different populations even when measured identically. Abson and Rabbitt (1988) report a study where all 564 community residing volunteers felt their memory had declined with age. Unless memory complaint is defined and a standardised questionnaire devised for its measurement, the diagnostic criterion of memory complaint may markedly affect diagnosis.

The issue of whether the work group really meant complaint or report has been raised earlier, though as seen in the present study reported memory decline and distress experienced as a result of this decline are closely correlated. The original paper uses memory complaint as "subjective evidence" of memory impairment. Mild memory lapses are common in all age groups and do not presumably indicate impairment. Nor does subjective evidence necessarily imply complaint. The MACQ, produced by a member of the AAMI working group and used widely as an inclusion criterion and outcome measure for clinical trials in AAMI, asks for recognition of change rather than indication of distress caused.

In medical conditions, a patient's distress or complaint may affect a patient's decision to visit a doctor and the doctor's decision to offer treatment, but it is not normally a criterion for diagnosis. If it were so, a person who complains could be diagnosed as having the condition where another with identical cognitive and neurobiological states would not.

One could question whether self reports should be used at all for diagnosis of AAMI, since there is little evidence from the present study that either reported decline or distress at a perceived decline bear any relation to actual memory test performance or decline. There were no significant correlations between MACQ score with age or memory test performance (Table 14) even though all three tests of secondary memory were significantly correlated with age even in healthy individuals (Table 13). In contrast to this, there were significant positive correlations between the MACQ with years of education and verbal IQ score and with all three of the scales of affective symptomatology (Tables 14 and 16).

The relatively weak correlation between memory complaint and test performance has been shown elsewhere (Abson and Rabbitt, 1988; Taylor *et al*, 1992), as has the stronger correlation with depression (Niederehe and Yoder, 1989; Bolla *et al*, 1991). The strong relationship to both state and trait anxiety adds to this work. The relationship of premorbid IQ with memory complaint may indicate that better educated, more intelligent people notice and are distressed by an ageing-related decline in memory since they are more likely to have intellectually demanding working environments and leisure pursuits.

Reisberg *et al* (1988) found that a group of community residing elderly people with memory complaint performed better than those without complaint on two cognitive assessments, even though neither group had objective evidence of memory impairment. This was hypothesized to be partly due to people of higher intelligence being more troubled and seeking assessment earlier.

It was of interest that the relationship between memory complaint and performance was strengthened when an estimate of premorbid ability was included (Table 15) as this has been shown previously in one small study (Christensen, 1991). The effect in the present study was strongest for the logical memory test. Story repetition has previously been reported to be better correlated with memory complaint (Sunderland *et al*, 1986) than other tests, and it may be that this test is more ecologically valid for comparison with the MACQ than the other tests used.

It may be that some people who experience a decline in logical memory test performance are distressed by it, causing them to suffer from depressive and anxiety symptoms. State-Trait anxiety theory would predict the trait component to become more state-like in testing conditions like those described in the present study, so it would not be unexpected for the memory complaint items to correlate with the trait as well as the state anxiety dimension. However, correlations for the MACQ and DISTRESS with trait anxiety were stronger than with state anxiety or with depression (Table 16). Also, it was the GDS which correlated most strongly with memory test performance rather than the anxiety dimensions (Table 13). This suggests that the relationship of memory complaint with affective symptomatology was probably related to heightened general symptom reporting due to differences in personality rather than being related to actual decline. The relationship between reported decline with memory performance relative to pre-existing IQ becomes non-significant when IQ, depression and anxiety are taken into consideration (Table 18). The logical memory test is the test most closely correlated with affective symptomatology (Table 17). It has been argued that this task relies heavily on attention and concentration

and is affected by depression since information is only presented once (Bolla *et al*, 1991). It also may be particularly demanding on the articulatory loop (see "working memory", Chapter 1).

Depressed patients do have problems remembering (Strack *et al*, 1985), but both memory complaints and objective memory performance improve with resolution of the depression (Sternberg, 1976; Frith *et al*, 1983). However, in the present study, depressed subjects had been removed prior to correlations being performed (since they were classified as having medical exclusion factors of a DSM III-R diagnosis of major depressive episode or a HAM-D score of more than 12). Significant relationships were still seen between depression with memory test performance and memory complaint, suggesting that a similar effect of depression on memory complaint and performance exists even at a sub-syndromal level.

2.5.3.3 Memory test performance

The significance of scoring below the cutoff score on different numbers of tests is unclear. If only one memory test score needs to satisfy the criteria, the chance of inclusion will increase with each test added, because of intra-individual variation over time and over different areas of memory prowess (e.g. verbal and nonverbal memory tests). In the present study 75% of subjects satisfied one test requirement, and only 30% satisied all three (Table 9).

It is not clear why memory performance more than one standard deviation below the mean for young adults should be chosen as the cutoff for inclusion. Any cutofff imposed onto a continuum risks

seeming arbitrary, and again there is no explanation of why this level was chosen. The cutoff scores may have been set not to delineate an abnormal group, but to demonstrate that memory has declined by more than the variation that can be expected with repeated assessment on brief tests such as these. This intra-individual variability over time may be one explanation of why, in a 2 year longitudinal study of people with AAMI, 7/51 (14%) had "spontaneous remission" by improving their memory test scores (Lane and Snowdon, 1989). When developing normal or reference ranges it is usual to consider values as significant if they are more than two standard deviations outside the mean for a population (Bland, 1987). If this method were applied, however, the only subjects identified would have a high probability of suffering from dementia.

2.5.3.4 Adequate intelligence

No attempt is made in the diagnostic criteria to take into account an individual's educational and intellectual background, which in the present study (Table 13) and elsewhere (Schaie, 1990) have been shown to be strongly linked to memory test performance. In order to demonstrate decline, present memory should be compared to an internal and retrospective estimate of original cognitive functioning, such as the NART or the Vocabulary subtest of the WAIS.

There is no discussion as to why adequate intellectual function is required for the diagnosis, though it may be to remove people who had always had poor memory test performance due to low IQ. However, this will mean that only people with a relatively good vocabulary will be included (and hence bias diagnosis in favour of those with better

education, from a higher socio-economic class and with English as their first language). It could be argued that people with very poor memory function to start with are at most risk from further decline.

The proposed method of indicating adequate intellectual function is by performance on the Vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1955). The lack of reference for the WAIS in the diagnostic criteria has been mentioned previously, and is important because the WAIS-R (Wechsler, 1981) has revised tables for converting raw scores to scaled scores, and has been shown to yield IQs that are around half a standard deviation lower than the WAIS (Crawford *et al*, 1990). Once again the suggested score appears to be arbitrary and, by categorising a continuous variable, an artificial boundary is imposed that has little meaning in real terms.

The Vocabulary subtest of the WAIS may have been chosen as a measure of original intellectual function because it correlates with overall intelligence, and performance on it remains relatively stable with ageing (Wechsler, 1981). The scaled score cutoff proposed for adequate intelligence is just less than the mean for young adults, and since IQ is closely related to memory test performance, a memory test score more than one standard deviation below the mean for young adults might represent a decline. However, the decline would only be recognised if intelligence started above "adequate intellectual function" and memory deteriorated to more than one standard deviation below the mean for young adults. People of lesser original intelligence could not therefore be described as suffering from the condition. Equally, those with an original level of intellectual functioning well above average, whose memory declined markedly with age but remained above the cutoff point for

memory, would not be included by the diagnostic criteria. The suggestion to limit the IQ range to between 90 and 130 (Blackford and La Rue, 1989) may miss the groups potentially most distressed by an age-related decline in cognition.

2.5.3.5   Performance on the MMSE

Performance on the MMSE should perhaps have been placed as an exclusion criterion, since it is presumably intended to aid exclusion of people who are suffering from dementia. Raising the cutoff from 24 to 27, as has been suggested (Crook, 1989), would have removed approximately a quarter of AAMI cases (section 2.4.10). Although this would give better sensitivity for the absence of dementia it would obviously reduce the specificity, excluding many more people with low intelligence, poor education and those from lower socio-economic class rather than just those with dementia (Brayne and Calloway, 1990; Christensen and Jorm, 1992).

2.5.4   EXAMINATION OF PROPOSED EXCLUSION CRITERIA

The exclusion criteria may be overly strict. For example people with diabetes or hypothyroidism are excluded even if adequately treated. Use of the Hamilton depression rating scale to aid exclusion of people with depression could be criticised since the scale was designed for assessing the severity of illness in a patient already diagnosed as being depressed, and Hamilton (1980) advised against its use as a diagnostic instrument. Because it loads heavily on somatic symptoms which are less reliable indicators of depression in the elderly, it tends not to be used in this age group.

2.5.5 AGE-CONSISTENT MEMORY IMPAIRMENT, AND LATE LIFE FORGETFULNESS

Blackford and La Rue (1989) suggested improvements to the classification of ageing-related memory change by adding two subtypes; Age-Consistent Memory Impairment (ACMI), and Late Life Forgetfulness (LLF). Their aim was not to target a group for treatment, but to reduce the heterogeneity of people defined by the AAMI criteria and so aid research into memory in the normal elderly population. They proposed that at least four different verbal and non-verbal memory tests should be used to avoid diagnosis on the basis of one idiosyncratic weakness. AAMI would be diagnosed when at least one test is 1 SD below the mean for young adults, ACMI when at least 75% of tests were within plus or minus 1 SD for their age (therefore excluding people well above average for their age), and LLF when scoring at least 50% of tests between 1 and 2 SD's below the mean for their age (consistently below average).

Smith *et al* (1991) presented prevalence data based on Blackford and La Rue's cognitive criteria from two groups of subjects; control subjects of a dementia study and volunteers. After exclusion for medical problems the prevalence rates for control subjects were 31% AAMI but scoring more than 1 SD above age-appropriate means; 52% AAMI and ACMI; 0% AAMI and LLF; 10% AAMI but performance too variable to be classified as ACMI or LLF. Prevalence rates for volunteers were 8% AAMI but scoring more than 1 SD above age-appropriate means; 30% AAMI and ACMI; 31% AAMI and LLF; 19% AAMI but performance too variable to be classified as ACMI or LLF.

The reason given for the marked difference in diagnosis of LLF was that different methods were employed for the exclusion of people with mild dementia. The condition described by LLF is considered to be closely related to BSF (Larrabee *et al*, 1991), but many LLF subjects are likely to go on to show symptoms and signs of dementia.

2.5.6 AGEING-ASSOCIATED COGNITIVE DECLINE

A discussion document was recently published (Caine, 1993) from the Cognitive Disorders Work Group of the American Psychiatric Association Task Force on DSM-IV. Despite the many criticisms of both the concept of defining a disorder on what is essentially normal ageing and of the particular diagnostic criteria chosen, it seems likely that AAMI will appear in some form in the Z codes of DSM-IV, perhaps under the name "Ageing-Associated Cognitive Decline" (AACD). The Z code is the DSM-IV equivalent to the V codes of DSM III-R; intended to include conditions not caused by mental disorder that are a focus of attention or treatment. AACD would be the lowest in a hierarchy of AACD, mild cognitive disorder and dementia.

The criteria suggested in Caine's article were for AACD to include reported cognitive decline, absence of overall functional decrement and test scores that put a person in the normal range of age- and education-matched peers. Mild cognitive impairment would include those with a history of intellectual decline, interference with higher order tasks, and one or more impaired cognitive parameters which were relatively mild and not functionally disabling enough to be considered dementia.

The paper from the Cognitive Disorders Work Group (Caine, 1993) also stated that AACD would provide ".. a descriptive label for those individuals who might benefit from memory/cognitive enhancement through behavioural or (in the future) pharmacological intervention". Clearly pharmacological treatment for cognitive symptoms of normal ageing is still on the agenda in America.

The practicalities of distinguishing AACD, mild cognitive disorder and mild dementia from each other and from normal ageing without cognitive decline are far from clear. One suspects that this will be impossible for research psychologists, let alone physicians, and that diagnosis and management decisions will be increasingly based on self-reported memory loss. It is therefore important to understand as much as possible about the presentation of memory complaint to doctors. A self-referral memory clinic described in Chapter 3 already attracts people who are distressed at a change in memory. Therefore this was thought to be an ideal setting to examine factors associated with the presentation of memory complaint in the absence of dementia. Chapters 3, 4 and 5 describe three related projects based in the self-referral memory clinic that were designed to explore these issues.

2.6   Summary

In this chapter a pilot study and prevalence study of AAMI were described. 18.5% of people between the ages of 50 and 94 suffer from AAMI as defined in the original work group document (Crook *et al*, 1986). However, prevalence rates would vary dramatically by minor alterations in the particular diagnostic criteria chosen, and this is of

concern since there has been little work performed validating the diagnostic criteria as proposed. Indeed there are many criticisms of the individual criteria, which have been examined in some detail. Of particular concern was the use of memory complaint for diagnosis, and the failure to take into account a person's original ability. Despite these concerns, AAMI will probably appear in some form in DSM-IV and pressure for pharmacological treatment is then likely to follow. People concerned about an ageing related decline in memory are already presenting to doctors for advice and treatment. It is important therefore to understand as much as possible about the presentation of memory complaint.

CHAPTER 3

REVIEW OF THE FIRST 100 ATTENDERS AT A SELF-REFERRAL
MEMORY CLINIC

3.1 Introduction

In Chapter 2, it was demonstrated that in a medically fit community-residing population subjective memory complaint is only weakly correlated with objective memory test performance. Memory complaint is important however, because distress at perceived decline is the motivating factor in leading people to seek medical help. Memory complaint is also likely to be an important factor in affecting diagnosis and management decisions by physicians since objectively measuring decline is so difficult. This will be especially relevant if drugs are licensed for mild memory impairment. For a variety of reasons then, it is important to understand more about memory complaint and in particular about the presentation of memory complaint to doctors. One way that people with mild memory impairment already present to doctors for advice and treatment is through memory clinics.

3.1.1 MEMORY CLINICS

Several memory clinics have been described in the literature (Philpot and Levy, 1987; Van der Cammen *et al*, 1987; Bayer *et al*, 1990) and offer in-depth multi-disciplinary investigation of people with possible dementia. The Research Institute for the Care of the Elderly in Bath (RICE) has been

running a memory clinic on these lines for several years. Most referrals to such clinics come from general practitioners, though some accept self-referrers to the memory clinic either directly (Bayer *et al*, 1990; Derouesne *et al*, 1989), or after telephone screening (Philpot and Levy, 1987).

3.1.2 THE SELF-REFERRAL MEMORY CLINIC AT RICE

A self-referral memory clinic was set up in parallel with the GP-referral memory clinic at RICE in 1990 in order to improve detection and diagnosis of dementia, particularly in the early stages. The nurse running the clinic screens for significant cognitive impairment, and those identified can if necessary be referred on to the GP-referral memory clinic for more intensive investigation.

Advertisements are posted in health centres, libraries, post offices and sports centres, offering a brief assessment to people with memory problems who telephone for an appointment. Attenders are asked to complete a short questionnaire which includes demographic details, past and present medical history and current medication. The nurse performs memory tests as well as checking the pulse, blood pressure and urine with labstix urinalysis.

Tests of cognitive function include the Mini-Mental State Examination (MMSE) (Folstein *et al*, 1975) and the Associate Learning subtest of the Wechsler Memory Scale (WALT) (Wechsler and Stone, 1983). The MMSE and the WALT have been described in Chapter 2.

Most attenders are given reassurance when scores on all the tests are normal, but they are informed that if their memory continues to trouble them, then they may re-attend. All self-referrals are later discussed with a doctor or senior nurse and appropriate action is decided upon. Results of the findings are sent to the patients' general practitioners with any recommendations that are made. The attender can be separately informed of the conclusions and recommendations if appropriate.

The clinic attracts many people who report distress as a result of memory decline and who request advice and treatment. It is therefore an ideal place to study self-presentation of people with memory complaint. This chapter describes the first 100 patients who attended the self-referral clinic, with predictors of outcome.

3.2   Methods

Notes were reviewed for the first 100 patients who attended the self referral clinic, and this was done with the assistance of the nurse who ran the clinic. Data abstracted included clinical information, memory test results, route of referral and outcome. A diagnosis was sought for those patients that were followed up in the GP-referral memory clinic. Statistical tests used are described in the results section. P values quoted are based on a two-tailed test of significance. Exact p values are given unless very small in which case the sign "p<" will appear.

3.3 Results

Ninety nine of the one hundred attenders completed the questionnaire, with one person refusing to give any personal details.

3.3.1 DEMOGRAPHIC DETAILS

72 attenders were female, and the group had a mean age of 70 years (SD 9, range 47-91).   58 were married, 21 were widowed and 9 divorced without remarrying, and 11 were single.   30 attenders were living alone.

3.3.2 HOW ATTENDERS HEARD OF THE CLINIC

Of those people for whom data was available (38), 9 were advised by their general practitioner to come to the clinic, 20 saw an advertisement, and the remainder heard about the clinic by word of mouth. Although officially a self-referral clinic, often the initiative for the referral comes from someone close who is concerned, and many attenders are brought. For the 91 people who could be coded for this, 25 were brought, mostly by immediate family members or more distant relatives and friends.

3.3.3 MEDICAL HISTORY

Just over half of attenders were on some form of regular medication (53); of these most were on one type.   The commonest preparations were anti-hypertensives (8), non steroidal anti-inflammatory medications (9), laxatives (7) and antiplatelet compounds (8). One of this sample was receiving an anxiolytic, 5 were on hypnotic medications, and 3 were

taking anti-depressants. Five reported a family history of Down's syndrome, and 18 a family history of dementia. 23 reported a past history of depression severe enough to require treatment and 34 considered they had been under stress in the past year. A variety of other past illnesses were reported, the commonest being cancers (4) and cerebrovascular accidents (3).

3.3.4 COGNITIVE PROFILE OF ATTENDERS

Descriptive statistics for the MMSE and the WALT are shown in Table 1. All attenders performed the MMSE, but only 84 the WALT, generally due to inability because of poor cognitive function. Of these 84, 36 people satisfied the AAMI1 criteria (ie scored at least 24 on the MMSE and thirteen or less on the WALT), and 40 subjects achieved results above these scores on both tests.

Table 1

Descriptive statistics for cognitive test scores of attenders

Variable	Mean	SD	Minimum	Maximum	Number
MMSE	26.1	5.7	2	30	100
WALT	13.2	4.3	5.5	21	84

3.3.5 OUTCOME

At the end of their visit, 61 attenders were discharged, usually with the reassurance that their performance on the memory tests was

satisfactory. 20 were referred directly to the GP-referral memory clinic, and a further 19 were asked to re-attend the self-referral memory clinic.

Of the 19 people asked to re-attend the self-referral clinic, 4 did not attend for the appointment. Of the remaining 15, 9 were discharged as there was no indication for further assessment, and 2 were referred to the GP-referral memory clinic. 4 were asked to re-attend the self-referral clinic for a third time.

Of the 22 people seen in the GP-referral memory clinic, 20 had an organic illness responsible for their memory impairment, and 15 of these had a clinical diagnosis of probable Alzheimer's disease. One person was felt to be suffering from stress and one from ageing-related changes.

3.3.6 PREDICTORS OF REFERRAL TO THE GP-REFERRAL MEMORY CLINIC AT THE FIRST VISIT

Patients were more likely to be referred on to the GP-referral memory clinic after the first visit if they were older or if they were brought to the clinic, and were less likely to if they had a past history of depression (Table 2). A trend was seen for subjects to be less likely to be referred to the clinic if they were divorced and had not remarried. There was no significant difference in reported family history of dementia and no difference in whether the subjects were living alone or not. Both cognitive tests were significantly related to referral to the GP-referral clinic, though this is to be expected since the test scores were the principal means of determining who was referred.

Table 2

Predictors of referral to the GP-referral memory clinic and the self-referral memory clinic at the first visit

	GPMC Mean(SD)	SRMC Mean(SD)	Statistic	p value
Age	78.8(5.7)	67.7(8.6)	t= 6.9	$p<0.001^A$
Brought to clinic	15/20	10/71	Chi^2= 29.1	p<0.00001
Past history depression	1/20	22/79	Chi^2= 4.7	p<0.05
Divorced	1/20	19/79	Chi^2= 3.6	p<0.1
MMSE	19.7(6.0)	27.7(4.4)	z= -6.2	$p<0.0001^B$
WALT	8.3(2.6)	14.0(4.0)	z= -4.4	$p<0.0001^B$

[A] T-test
[B] Mann-Whitney test

3.4 Discussion

The majority of attenders came to the clinic concerned about their memory but were not found to be suffering from significant cognitive impairment and were not advised to attend the GP-referral memory clinic. At least 36% satisfied the AAMI1 criteria on the MMSE and the WALT, whilst at least 40% scored too well.

Subjects thought not to require further assessment were younger, more likely to self-present rather than be brought by a friend or relative, more often had a past history of depression and were possibly more likely to be divorced. This suggests that memory complaint in many self-referrers was less related to objective impairment, and perhaps more related to

affective illness or personality associated with affective illness. Although a full psychiatric assessment was not made on these subjects, few were taking anti-depressants. One can assume therefore that if self-referrers were suffering from depressive illness, it was undiagnosed.

It was interesting to note that a quarter of all self-referrers had been advised to attend by their general practitioners. This suggests that there may be cases where doctors do not feel a full assessment is necessary at the GP-referral memory clinic, but that reassurance is required.

3.4.1 SUPPORTING EVIDENCE FOR THE ROLE OF AFFECTIVE AND PERSONALITY FACTORS IN SELF-REFERRERS

Two studies from memory clinics which accept self-referrals give supporting evidence of affective and personality factors as being important in presentation (Philpot and Levy, 1987; Derouesne *et al*, 1989).

In a large group of subjects self-referring to a memory clinic in Paris, of those able to complete self-report questionnaires and not receiving treatment for psychiatric illness, one sixth were found to be suffering from functional psychiatric illness (Derouesne *et al*, 1989).

In the memory clinic described by Philpot and Levy (1987) a quarter of attenders were found to have no evidence of cognitive impairment, and often these people had a family history of dementia, possibly therefore having heightened fear of the disease. Family history of dementia was not related to normal cognition in the present study, though it may be that the screening process referred to by Philpot and Levy preferentially

selects people with a positive family history. Of the patients they described, a half had dementia and around one tenth were found to be suffering from depression.

It would appear that affective symptoms may be very common in people presenting to a self-referral memory clinic with memory complaint but no objective decline. The link between memory complaint and depressed mood was noted in Chapter 2. Depression can cause objective and subjective memory impairment, and may affect medical help seeking behaviour. Therefore, a prospective study was initiated to investigate the possible role of depression in the presentation of memory complaint. This study is described in Chapter 4.

3.6   Summary

In this chapter, a retrospective study was described in which case notes were reviewed for the first 100 attenders at a self-referral memory clinic. The majority of attenders were not felt to be suffering from significant memory impairment and were discharged. At least 36% satisfied the AAMI1 criteria on the MMSE and the WALT, but at least 40% scored too well to be included by the criteria. Psychosocial factors and particularly depression may be important in the self-presentation of memory complaint in the absence of significant impairment.

CHAPTER 4

SELF-REPORTED MEMORY LOSS, MEMORY PERFORMANCE AND DEPRESSIVE SYMPTOMS IN ATTENDERS AT A GP-REFERRAL AND A SELF-REFERRAL MEMORY CLINIC

4.1 Introduction

Diagnosis of AAMI relies heavily on self-report of memory loss, despite evidence demonstrated in Chapter 2 that memory complaint has little relationship to memory test performance and is more closely related to affective symptoms. In previous work memory complaint has been shown to be more closely related to depression in both depressed and normal community dwelling adults (Popkin *et al*, 1982; O'Connor *et al*, 1990; Bolla *et al*, 1991), and in those attending a memory clinic (Derouesne *et al*, 1989).

The first 100 attenders at a self-referral memory clinic were described in Chapter 3. Many people who attend are distressed as a result of age-related memory decline, but most are discharged without indication for further assessment. Psychosocial factors were thought to be important in their presentation particularly because of their lack of significant memory impairment and the frequent history of depression.

Depressive disorders are well known to affect both subjective and objective memory performance (Larazus & Folkman, 1984; Strack *et al*, 1985) but even sub-syndromal depression may affect a person's

perception of their own performance (Derouesne *et al* 1989; Bolla *et al*, 1991). Memory complaint in people treated for depression is reduced as mood lifts (Popkin *et al*, 1982; Plotkin *et al*, 1985).

AAMI is likely to appear in some form in DSM-IV (Caine, 1993), and pharmacological treatment trials have already been reported (Crook *et al*, 1991; McEntee *et al*, 1991). It is therefore important to assess the significance of memory complaint in people presenting to doctors with mild or non-detectable memory impairment.

The current study compares subjective reports of memory decline and depressive symptomatology with objective measures of cognitive performance in people presenting to the self-referral clinic. Patients attending the GP-referral clinic and age- and sex-matched non-presenting community controls are used for comparison. It was hypothesized that the presentation of memory complaint to the self-referral clinic would be more closely related to depressed mood than to memory performance.

4.2   Methods

All psychometric measures used in the present study have been described in Chapter 2.

Consecutive first time attenders presenting with memory dysfunction at the self-referral and the GP-referral memory clinics between February 1992 and October 1992 were approached and asked to take part in a study examining the relationship between memory and mood. The study was explained and a written consent obtained (see Appendix 10).

4.2.1 QUESTIONNAIRE DETAILS

Study subjects (or carers where appropriate) were questioned regarding a past history of depression that had received treatment. A memory complaint questionnaire was then completed, which was based on the MACQ (Larrabee *et al*, 1992) with the distress scale added (see Chapter 2). Subjects then completed the Geriatric Depression Scale (GDS) (Yesavage & Brink, 1983).

4.2.2 INTERVIEW DETAILS

All subjects performed the Mini-Mental State Examination (MMSE) (Folstein *et al*, 1975) and the self-referral clinic subjects also completed the Associate Learning subtest of the Wechsler Memory Scale (WALT) (Wechsler & Stone, 1983). For practical reasons the cognitive testing for a number of subjects had to be carried out by a nurse involved in running the memory clinics. Inter-rater reliability was not formally assessed, but both raters underwent the same training, and discussed grey areas in administration and scoring to ensure consistency.

Since the GDS has not been validated for people scoring below 16 on the MMSE, this cutoff was used for exclusion from the study. Age- and sex-matched randomised community controls for the two groups were chosen blind from the prevalence study subjects described in Chapter 2 and their scores on the various measures obtained. 71% of the contactable prevalence study population were eligible as controls by scoring over 15 on the MMSE and having datasets that were complete for the purposes of the present study.

4.2.3 ANALYSIS

The various statistical procedures used are described in the results section. A level of p<0.05 was set for statistical significance and all p values quoted are based on a two tailed test of significance.

4.3 Results

All of the memory clinic attenders (55/55) agreed to participate. Four subjects from the GP-referral clinic and two from the self-referral clinic were excluded because of low MMSE scores. This left 20 subjects from the GP-referral clinic and 29 from the self-referral clinic. 49 control subjects were identified and a close age match was achieved (mean age difference 0.01 years SD 0.57).

4.3.1 COMPARISON OF GP-REFERRED AND SELF-REFERRED PATIENTS

The subjects in the self-referral clinic were younger than the GP-referred patients (Table 1). 29 women and 20 men were seen, with a non significant trend for a greater proportion of women to attend the self-referral clinic. The mean MMSE score of GP-referred patients was lower than that of self-referred patients after controlling for age using multiple regression. Only one of the self-referred patients included scored less than 24 on the MMSE. There was no significant difference in reported memory decline, distress as a result of this decline, or in depression score between the groups.

Table 1

Comparison of GP-referred patients with self-referred patients

	GP-referral clinic	Self-referral clinic	Statistic and significance
Age Mean (SD)	73.7 (8.9)	66.0 (7.6)	$t=3.24^A$ $p<0.01$
Sex (F:M)	9:11	19:10	$Chi^2=2.00$ NS
Past history of treated depression	3/20	13/29	$Chi^2=4.79$ $p<0.05$ NS after controlling for sex^B
MMSE Mean (SD)	24.3 (4.1)	28.3 (2.2)	T=3.02 $p<0.05$ after controlling for age^B
MACQ Mean (SD)	26.3 (4.4)	28.8 (3.8)	$z=1.80^C$ NS
Distress Mean (SD)	2.9 (1.2)	3.6 (1.9)	$z=1.95^C$ NS
GDS Mean (SD)	10.3 (5.6)	11.1 (5.0)	$z=0.62^C$ NS

[A] T test
[B] Multiple regression
[C] Mann Whitney

Self-referrers were more likely to report a past history of depression requiring treatment, but since this was sex related (with depression F:M 13:3, without past depression F:M 15:18 $Chi=^2$ 5.64 $p<0.05$), multiple regression analysis was performed to control for sex. There was no significant difference in past history of depression between the self-referral and the GP-referral subjects after controlling for sex (T = 1.86).

4.3.2 COMPARISON OF GP-REFERRED PATIENTS WITH AGE- AND SEX-MATCHED CONTROLS

The GP-referred patients had a lower mean MMSE than their controls (Table 2). Although the GP-referred patients did not report any more decline in memory, they were more distressed by the changes. There was no significant difference in reported depressive symptoms in the referred patients, and no difference between the GP-referred patients and their controls in the reporting of a past history of depression.

Table 2

Comparison of GP-referred patients with age- and sex-matched community controls

	GP-referral clinic	Community controls	Statistic and significance
MMSE Mean (SD)	24.3 (4.1)	27.6 (1.6)	$z=2.66$[A] $p<0.01$
MACQ Mean (SD)	26.3 (4.4)	25.2 (4.9)	$z=0.83$[A] NS
Distress Mean (SD)	2.9 (1.2)	1.7 (1.0)	$z=2.39$[A] $p<0.05$
GDS Mean (SD)	10.3 (5.6)	7.9 (6.7)	$z=1.35$[A] NS
Past history of treated depression	3/20	1/20	$Chi^2=1.11$ NS

[A] Wilcoxon matched-pairs signed-ranks test

4.3.3 COMPARISON OF SELF-REFERRED PATIENTS WITH AGE- AND SEX-MATCHED CONTROLS

There was no difference between the self-referred patients and their controls in either of the cognitive tests used (Table 3). However, the self referrers reported a greater decline in their memory, were more distressed by this, and had higher levels of reported depressive symptomatology. They were more likely to report a history of depression requiring treatment.

Table 3

Comparison of self-referred patients with age- and sex-matched community controls

	Self-referral clinic	Community controls	Statistic and significance
MMSE Mean (SD)	28.3 (2.2)	28.3 (1.7)	$z=0.35^A$ NS
WALT Mean (SD)	13.7 (3.0)	14.0 (4.5)	$z=0.30^A$ NS
MACQ Mean (SD)	28.8 (3.8)	24.6 (3.7)	$z=3.62^A$ p<0.001
Distress Mean (SD)	3.6 (1.1)	1.7 (0.9)	$z=4.29^A$ p<0.0001
GDS Mean (SD)	11.1 (5.0)	6.0 (3.7)	$z=3.94^A$ p<0.001
Past history of treated depression	13/29	3/29	$Chi^2=8.63$ p<0.01

A Wilcoxon matched-pairs signed-ranks test

4.3.4 PREDICTORS OF ATTENDANCE AT THE SELF-REFERRAL MEMORY CLINIC AMONGST SELF-REFERRERS AND AGE- AND SEX-MATCHED COMMUNITY CONTROLS

In order to examine which factors most accurately predicted presentation of memory complaint to the self-referral clinic, stepwise multiple regression analysis was performed on the self-referrers and their controls, with MACQ score as the dependent variable, and pin and pout values set at 0.05 and 0.10 respectively (see Chapter 2, Section 2.4.12.6). Independent variables were past history of depression and scores on the MMSE, WALT, GDS, MACQ and DISTRESS scale.

Table 4

Predictors of attendance at the self-referral memory clinic amongst self-referrers and age- and sex-matched community controls

Variables in regression equation	B (SE)	Beta[A]	T	Sig T
Distress	.24 (.04)	.63	6.7	p<0.0001
Past history of depression	.27 (.11)	.24	2.5	p<0.05
(Constant)	-.19 (.10)		-1.8	NS
Variables not in regression equation		Beta in[B]	T	Sig T
AGE		.12	1.3	NS
MMTOTAL		-.07	-.8	NS
WALTTOT		-.05	-.5	NS
GDSTOT		.11	.9	NS
MACQ		.02	.2	NS

[A]Beta = regression coefficient
[B]Beta in = regression coefficient if variable were entered next into equation

The only two variables included in the regression equation were the DISTRESS scale and past history of depression (Table 4). These jointly accounted for 53% of the variance.

4.4 Discussion

4.4.1 RESULTS FROM THIS STUDY

In this study, patients self-referring to a memory clinic had cognitive test performance similar to a community control sample, but reported a greater decline in memory and were more distressed by this. They scored higher on a self-administered depression inventory and were more likely to report a past history of depression requiring treatment. The GP-referral group were older, had lower MMSE scores and had intermediate scores on memory complaint and depression questionnaires. Amongst the group of self-referrers and their controls, two variables in a regression equation predicted attendance at the self-referral clinic:- distress as a result of perceived memory decline and past history of depression requiring treatment.

Most of the self-referrers are seen by a nurse and are not routinely followed up. It is therefore not possible to determine whether some of the self-referrers were suffering from depression, though this would seem likely given the high mean scores on the GDS, and would agree with the high levels of depression found in memory clinics which accept self-referrers (Philpot and Levy, 1987; Derouesne et al, 1989). Three of the patients with high GDS scores were in fact assessed and were felt to be

suffering from personality disorders and not depressive illness. This puts doubt on the 100% specificity for depression reported for a score of 14 or above on the GDS (Brink *et al*, 1982). Some self-referrers may also have been in the early stages of dementia. However, the high MMSE scores of the group, and the reported small proportion of people with memory complaint but no objective impairment developing dementia over three years (Reisberg *et al*, 1986; O'Brien *et al*, 1992; Flicker *et al*, 1993), suggests that few such cases were present in this sample.

4.4.2 MEMORY COMPLAINT IN PEOPLE WITH DEMENTIA

The patients referred to the memory clinic by their GP had generally been sent because of a suspicion of dementia, and it is not surprising that on average they had lower MMSE scores. The finding that these patients did not report a significantly greater decline in memory than either of the other groups is in keeping with most previous work (Kahn *et al*, 1975; McGlone and Oppenheimer, 1990; Feehan *et al*, 1991), though not all (Grut *et al*, 1993) and suggests denial or lack of insight that is common in patients with dementia, especially in later stages (O'Connor *et al*, 1990).

4.4.3 POSSIBILITY OF GENUINE DECLINE IN SELF-REFERRERS

Unfortunately, no measure of previous memory function was available, and no tests were used to estimate original IQ for comparison with current memory performance which may have improved the validity of memory complaint (see Chapter 2). It is therefore not possible to determine whether people who complained of memory loss and depressive symptoms had experienced more or less decline than average.

It may be that the self-referral group were originally very high performers, they had genuinely declined more than their controls and were distressed by this.

However, the fact that there was little difference in mean cognitive test performance between the self-referral group and age- and sex-matched community controls suggests that on average the self-referrers had not had any greater deterioration. This, with the high scores on the GDS and the increased frequency of past depression, suggests that affective state and possibly personality are likely to be more important than cognitive factors in the presentation of memory complaint in many of the self-referrers.

On the basis of this study's findings, a further study was designed to look at these issues of personality, affect and intelligence in the presentation of complaints of ageing-related memory decline. This study is described in Chapter 5.

4.5 Summary

In this chapter a study was described which compared reports of memory loss, memory performance and depressive symptoms in attenders at a GP-referral and a self-referral memory clinic, with age- and sex-matched community controls. The GP-referred patients were older, had lower MMSE scores and had levels of memory complaint and depression between the control and self-referred subjects. The self-referrers had cognitive test performance similar to community controls but complained more of memory loss, were more depressed and more frequently reported a past history of treated depression.

Self-presentation of memory complaint appears to be more closely related to affective and possibly personality factors than memory test performance.

CHAPTER 5

MEMORY COMPLAINT IN ATTENDERS AT A SELF-REFERRAL MEMORY CLINIC: THE ROLE OF COGNITIVE FACTORS, AFFECTIVE SYMPTOMS AND PERSONALITY.

5.1 Introduction

In chapter 2 it was demonstrated that in the community, self-reported memory decline and distress experienced as a result of this perceived decline are only weakly correlated with objective memory performance. This was in keeping with previous findings, though the relationship was strengthened when a measure of pre-existing IQ was included (the NART) to improve the estimate of objective decline. Memory complaint was more closely related to affective symptomatology, however. Memory complaint is an important aspect of diagnosis in AAMI (Crook et al, 1986), and will also affect a person's decision whether to seek medical intervention and a doctor's decision on how to manage them.

In Chapter 4 the role of depression in the presentation of memory complaint was examined more closely, with a prospective study assessing depressed mood and memory complaint in memory clinic attenders. Self-referrers were found to have memory test performance similar to age- and sex-matched controls, but had higher reported decline, distress as a result of this decline and higher depression rating scores. They were more likely to report a past history of depression. Some patients may have been suffering from mild dementia and some from depression, though three of the people with many depressive symptoms were in fact thought to be suffering from personality

disorders. As no measure of previous function was available, it was not possible to assess whether the self-referrers had had more decline than average and were understandably upset by this.

The role of personality has not been investigated in this group of patients, but similar work on psychological factors in the presentation of unexplained physical symptoms suggests it may be important (Costa and McCrae, 1987; Goldberg and Bridges, 1988). Of particular relevance is the personality trait described by the terms trait anxiety, neuroticism and negative affectivity (Jorm, 1989). The Spielberger State-Trait Anxiety Inventory (Spielberger et al, 1983) is the most commonly used measure of trait anxiety and has been validated for use in elderly people (Patterson et al, 1980). It is more fully described in Chapter 2.

The study described in this chapter was designed to examine some of the issues raised by the previous study in Chapter 4, and in particular the role of pre-existing original IQ and trait anxiety in the presentation of memory complaint. It was hypothesized that the presentation of memory complaint in people with mild cognitive impairment would be more closely related to measures of depression and trait anxiety than to objective memory performance or estimated decline.

5.2 Methods

Consecutive first time attenders over the age of fifty presenting with memory complaint to the self-referral memory clinic were approached and asked if they would be willing to participate in a research study looking at the interaction of memory problems and mood. The study was

described and if agreeable, written consent was obtained. Recruitment took place from November 1992 until August 1993.

The methodology used was essentially the same as that used in Chapter 4. As before, a questionnaire assessed past history of treated depression, antidepressant medication, and memory complaint using the MACQ and the Distress scale. A shortened form of the Geriatric Depression Scale (GDSS) was used (possible score 0-15) which has been shown to be similarly valid and reliable as a screening device for depression (Sheikh and Yesavage, 1986). The Trait anxiety scale of the State-Trait Anxiety Inventory (STAI-T) was also incorporated into the questionnaire. The cognitive tests used included the MMSE and the WALT. The National Adult Reading Test (Nelson, 1982) was also administered as a measure of pre-existing IQ. The MACQ, DISTRESS scale, STAI-T, MMSE, WALT and NART are described in Chapter 2. For practical reasons a number of subjects had their cognitive testing performed by the nurse involved in running the clinic. Inter-rater reliability was not formally assessed, but both raters underwent the same training, and discussed grey areas in administration and scoring to ensure consistency.

In order to provide an estimate of current memory test performance relative to original level of functioning, a new variable WALT ZDIFF was calculated (WALT ZDIFF = NART z score - WALT z score) (see Chapter 2). Subjects were excluded if they scored less than 24 on the MMSE in order to reduce the chance of including people suffering from mild dementia. Age- and sex-matched controls were selected blind from the randomised community sample seen as part of the AAMI prevalence study described in Chapter 2, and scores obtained from their records.

Only controls with full relevant data and scoring above 23 on the MMSE were included.

The various statistical procedures used are described in the results section. A level of $p < 0.05$ was set for statistical significance and all p values quoted are based on a two tailed test of significance.

5.3 Results

In the time period specified, 30 new attenders were seen at the self-referral memory clinic. All consented to take part. Six subjects were not included in subsequent analysis: three had MMSE scores less than 24, one had poor eyesight and a married couple attending together had their forms removed after they started arguing over their responses. The remaining 24 subjects (5 men, 19 women) had closely matched controls (mean age difference 0.06 years, SD 0.44). Eight of the 24 controls were the same as in chapter 4. Although ideally, controls that had previously been used would have been excluded, this produced some pairs with unacceptably loose age-matching.

5.3.1 COMPARISON OF PSYCHOMETRIC VARIABLES BETWEEN SELF-REFERRAL SUBJECTS AND CONTROLS

Self-referrers had a higher NART-estimated IQ (Table 1). MMSE scores were similar for both groups, but there was a non-significant trend $(p < 0.1)$ for the self-referrers to have a higher WALT score. There was no significant difference in WALT ZDIFF between the groups. Self-referrers reported greater memory decline and were more distressed by

this. Past history of depression was more common in self-referred subjects, and levels of current depression and trait anxiety were also higher. Only one of the subjects, a control, was taking an antidepressant at the time of interview. Overall, females were more likely to report a past history of depression (12/38 females vs 0/10 males, Chi-square 4.21 Fisher's Exact Test p<0.05).

Table 1

Comparison of psychometric variables between self-referral clinic subjects and controls

	Self-referral clinic Mean(SD)	Community controls Mean(SD)	Statistic	p value
NARTIQ	117.5(7.7)	110.5(10.8)	z= -2.09	p<0.05[A]
MMSE	28.7(1.6)	28.3(1.6)	z= -1.02	NSA
WALT	14.1(3.6)	12.2(4.7)	z= -1.83	NSA
WALT ZDIFF	0.1(1.1)	-0.1(1.1)	z= 1.2	NSA
MACQ	29.2(3.5)	24.3(3.4)	z= -3.45	p<0.001[A]
DISTRESS	3.4(1.1)	1.5(0.7)	z= -3.98	p<0.001[A]
GDSS	4.4 (3.3)	2.1(1.8)	z= -2.62	p<0.01[A]
STAI-T	43.1 (11.7)	31.5(8.5)	z= -3.57	p<0.001[A]
Past history of depression	9/24	3/24	Chi2= 4.00	p<0.05

[A] Wilcoxon Matched-pairs Signed-ranks Test

5.3.2 PREDICTORS OF ATTENDANCE AT THE SELF-REFERRAL MEMORY CLINIC

In order to examine which factors predicted presentation of memory complaint to the self-referral clinic most accurately, stepwise multiple

regression analysis was performed on the combined group of 48 subjects, with pin and pout values set at 0.05 and 0.10 respectively (see Chapter 4). Independent variables were age, past history of depression, NART estimated IQ, scores on the MMSE, WALT, GDSS, STAI-T, MACQ and Distress, as well as the WALT ZDIFF score. The only two variables entered in the regression equation were the Distress and WALT score (Table 2). These jointly accounted for 31% of the variance (26% due to distress scale).

Table 2

Predictors of attendance at the self-referral memory clinic

Variables in regression equation	B (SE)	Beta[A]	T	Sig T
Distress	.27 (.04)	.72	7.2	p<0.0001
WALT	.03 (.01)	.22	2.2	p<0.05
(Constant)	-2.50(.10)		-13.5	p<0.0001
Variables not in regression equation		Beta in[B]	T	Sig T
AGE		.04	-.3	NS
MMSE		-.06	.4	NS
NARTIQ		.06	-.5	NS
WALT ZDIFF		.07	-.5	NS
PAST HIST DEP		-.00	.0	NS
GDSS		.12	-1.1	NS
STAI-T		.17	-1.5	NS
MACQ		.12	-0.8	NS

[A]Beta = regression coefficient
[B]Beta in = regression coefficient if variable were entered next into equation

5.4 Discussion

In this study it was shown that self-referring subjects on average have higher pre-existing IQs than age- and sex-matched controls, with a trend for higher WALT scores and no evidence of greater decline in WALT score relative to pre-existing IQ. They report a greater decline and are more distressed by the perceived deterioration. Self-referrers more commonly report a past history of depression, and score higher on current measures of trait anxiety and depression. The major predictor of being an attender at the self-referral clinic produced by a regression equation was distress at a perceived decline in memory with the WALT score also contributing.

A better educational background and higher intelligence has previously been described in self-referrers to a memory clinic (Derouesne et al, 1989) and in non-demented attenders at a GP-referral memory clinic (O'Brien et al, 1992). This is in keeping with the view that people with high intelligence are likely to be most disturbed by ageing related memory decline and the most likely to seek help for it (Crook et al, 1986; Reisberg et al, 1988).

Although one community study of elderly people described self-reported memory decline as universal, less than a quarter of subjects felt the memory difficulties even a slight nuisance (Sunderland et al, 1986). People who find the changes more distressing and seek medical help may do so because of factors to do with intelligence, affective state or personality.

Some self-referrers may report more depression and memory decline as part of a generalised increase of symptom reporting seen in people with more neurotic personality traits. Neuroticism is significantly related to most DSM III-R personality disorders and may also be associated with a past history of depression in the elderly (Abrams, 1991).

5.4.1 BECK'S COGNITIVE THEORY OF DEPRESSION

Beck's cognitive approach to depression may give an additional understanding of these people (Beck, 1967). He believed that dysfunctional assumptions laid down in childhood predispose a person to negative automatic thoughts and cognitive distortions which lead to the regarding of self, current experience and future negatively. These factors make a person vulnerable to depression. Previous studies have noted that non-demented attenders at a memory clinic are often concerned about the possibility of dementia (Philpot and Levy, 1987), and high levels of depression have been seen in the self-referrers described in this chapter and Chapter 4. Self-referrers view their own memory as poor, are particularly distressed by this (even though objectively their memory performance is no worse than their non-presenting peers) and more often report a history of depression severe enough to require treatment.

5.4.2 THE COMPARISON WITH UNEXPLAINED MEDICAL SYMPTOMS

A comparison can also be made between self-referrers' reports of memory decline and the phenomena of unexplained medical symptoms (Goldberg & Bridges, 1988). Self-reported poor general health is related to memory complaint in community residing elders (Cutler and Grams, 1988). In a General Practice surgery, high levels of memory complaint

could be predicted in people presenting with what the general practitioner felt were psychological or mixed psychological/somatic motives (Derouesne et al, 1993).

Somatosensory amplification is one way in which unexplained medical symptoms may arise. The term describes heightened awareness of, and concentration on, relatively weak sensations with cognitions that intensify them and make them more disturbing. Measures of amplification are correlated with depression and anxiety (Barsky et al 1990). Memory lapses are common in all age groups, and particularly in the later decades of life. Some people, for example those with high trait anxiety/neuroticism, may be more aware of them, attribute increased significance to their presence, and seek medical help for them. A psychological treatment based on a cognitive-behavioural model for functional somatic symptoms has been described (Sharpe et al, 1992) and it would be interesting to attempt a similar intervention in people with complaints of memory loss but no objective evidence of impairment.

Memory complaint may be a cause, a result, or independent of any impairment found. If drugs are licensed for treating cognitive impairment, the objective demonstration of decline, and then understanding the relationship of memory complaint to this decline, will be vital, to ensure the most appropriate pharmacological or psychological therapy is given.

5.5 Summary

In this Chapter, a study was described of cognitive and affective measures in non-dementing subjects self-referring to a memory clinic in

comparison with non-presenting age- and sex-matched community controls. The particular aims were to assess the role of pre-existing IQ and trait anxiety in the presentation of memory complaint. Self-referrers had a higher original IQ, but no evidence of greater decline despite having more memory complaint. Personality factors were demonstrated to be important alongside affective symptoms in the presentation of memory complaint in non-demented subjects, and several possible ways of understanding the interaction between these factors were discussed.

CHAPTER 6

GENERAL DISCUSSION

6.1   The reasons why this research project was necessary

This research project was planned some 5 years after the NIMH work group had published the proposed diagnostic criteria for AAMI. Responses to the concept and criteria proposed had been published, and much in these was critical.   No accurate prevalence data were available and at the time of submission of this thesis no major international journal has published a prevalence study of AAMI using the original diagnostic criteria. It was and still is of concern, therefore, that this newly defined disorder with apparently little proven scientific validity is likely to appear shortly in DSM IV, and it is surprising that treatment trials were commenced so soon.   The present study was therefore necessary to provide a better idea of how common the disorder is in the community, while at the same time allowing examination of the diagnostic criteria chosen.

6.2   A summary of the main conclusions of the thesis

The main study in this thesis (Chapter 2) provides what appear to be reliable estimates of prevalence of AAMI for various age groups. Prevalence rates for the total population and for the over 50s were estimated to be 5.8% and 18.5% respectively. These rates are less than other researchers had estimated, and this is likely to be due to the more

rigorous methodology applied in the present study. In particular, an objective measure of memory complaint was used which was designed for assessing significant reported decline in people with AAMI, and the psychiatric and medical assessment of people with possible AAMI was more extensive. Prevalence rates were shown to be dramatically affected by minor alterations to individual criteria, however. This turned the focus to the diagnostic criteria themselves. A number of the inclusion and exclusion criteria were examined and weaknesses and inconsistencies demonstrated. Of particular concern was the use of memory complaint as a diagnostic criterion and the lack of attention paid to a person's educational and intellectual background.

Memory complaint was shown to be poorly correlated with memory test performance, even though it is an essential part of diagnosis in the original AAMI criteria and is also likely to be important in DSM IV. Memory complaint is likely to be the driving factor in motivating people to seek medical attention if, as has been suggested, drugs were licensed for the treatment of AAMI. Since the psychometric complexities of demonstrating memory decline will elude most practising physicians, memory complaint is likely to be relied upon to make a diagnosis and will influence management decisions by clinicians.

It was fortunate that a self-referral memory clinic was located at the institute in which the author was based, since this provided a ready-made opportunity to study self-presentation of people with memory complaint. Three studies carried out in parallel with the prevalence study investigated factors involved in the presentation of memory complaint by people with mild or non-detectable memory impairment. These highlighted the role of psychosocial factors in the presentation of

memory complaint and most particularly high intelligence, depression and trait anxiety. Actual memory decline or impairment was thought to be of less significance.

6.3   The purpose of the diagnostic criteria for AAMI

When dissecting the diagnostic criteria and critically examining the psychometric properties of individual tests, it is possible to lose sight of the purpose of the criteria. This is a particular problem because AAMI is such a nebulous concept and the original paper by the NIMH work group had little explanation of the reasons for the specific criteria chosen, or even what population they were intending to define. This confusion has been noted by others (Bamford and Caine, 1988; Allain *et al*, 1990; Barker and Jones, 1993).

The stated purpose of defining AAMI was to aid research and scientific communication, to note the distress experienced by some elderly people and to recognise the importance of developing treatments. The justification for inclusion in DSM IV is to reassure elderly people that they are not suffering from Alzheimer's disease and to identify people who might benefit from behavioural or pharmacological intervention.

6.4   The argument for drug treatment of AAMI

The argument for treatment of AAMI is that some people probably have ageing-related reductions in cognitive test performance of up to 50% of their original function (Crook and Ferris, 1992). If this degree of impairment were seen in the young, then there would probably be little

argument over the use of drug treatments for these people. Elderly people with "normal" failing eyesight are given glasses to improve their visual acuity and this practice is not challenged. If people are distressed by a decline in memory, would it be ethical to deny them access to pharmacological treatment if this were shown to be the treatment which brought about the greatest improvement?

The real stumbling blocks in getting AAMI accepted by doctors are firstly the concept of "diagnosis" of normality and then the suggestion of using pharmacological treatment for this condition.

6.5 Criticisms of the concept of AAMI and arguments against its pharmacological treatment

6.5.1 GENERAL PRINCIPLES OF DIAGNOSIS AND TREATMENT

Doctors diagnose and treat diseases; in the medical world the term "diagnosis" is inextricably linked to disease. The definition of disease is not simple, though. A disease may be defined at a number of levels: purely as a syndrome of concurrent symptoms and signs, functionally, anatomically, or aetiologically. It is first recognised syndromally (Campbell, 1977): then, as knowledge progresses, the defining process moves up a level. Implicit in its definition though, is a distinction from health.

Although diagnosis and treatment of AAMI is frequently mentioned in the work group's paper (Crook *et al*, 1986), it is never referred to as a disease, and psychometric scores distinguishing AAMI from "pathologic"

memory loss have since been published (Crook, 1989), supporting the impression that AAMI was not intended to describe pathology.

In some medical conditions, such as diabetes and hypertension, where the clinical signs are part of a continuum in the general population, often the only basis for diagnosis and treatment is the presence of a significant deviation from the population norm, where this has been shown to be associated with increased risk of morbidity. The extreme case is easily identified, but in cases of lesser severity there is greater overlap with normality, and the balance between probable treatment success and the risk of deleterious side effects is finer.

In certain conditions, doctors already intervene in distressing changes that may be seen as part of normal ageing: maintenance of function is a well recognized and important goal of geriatric medicine. Diagnosis precedes treatment, but is not the only determining factor in the decision to treat: for example, the usage of oral hypoglycaemic drugs in elderly people with diabetes will vary with a doctor's concept of what blood sugar level constitutes disease in this age group, as well as what the most appropriate therapeutic target should be (e.g. lowering the blood sugar to a predetermined level or purely symptomatic treatment). It will also vary with the patients' demands in terms of their expressed distress and desire for specific treatments.

The doctor's role is clearly not just to treat a diagnosis, but is directed at relieving distress and promoting health. The controversy over the suggestion to treat AAMI comes not from the idea of helping people who are distressed by an ageing-related deterioration in function, but from the proposed use of drugs for this.

6.5.2 TREATMENT ISSUES IN AAMI

There has been a little work examining the effectiveness of psychological treatments for ageing-related memory decline and it appears encouraging. Willis (1989) describes a study where the level of performance of 40% of elderly subjects could be shown to return to, or to improve upon, their own performance 14 years previously on certain cognitive tasks. Willis describes several other studies where improvements in memory after psychological treatment are in the order of 0.5 - 1.0 standard deviations compared with pretreatment levels. Larrabee *et al* (1992) report a study in which training to improve memory for names and faces raised test scores from baseline by a factor of 73-111%. This improvement was shown to be maintained at six months follow up. These results are certainly better than the early drug treatment trials so far described (Crook and Lakin, 1991; Crook *et al*, 1991; McEntee *et al*, 1991).

There are several issues that need to be taken into account in explaining the concerns specifically related to pharmacological treatment.

Firstly, before a treatment is to be considered, there has to be a consensus that an impairment or dysfunction exists which can be defined to form a relatively homogeneous patient population. This has not yet been achieved for AAMI for a variety of reasons discussed in Chapter 2. Since the criteria by design make no attempt to differentiate AAMI from normal ageing the reluctance to intervene in normality or nature has to be overcome. Leber (1992) of the USA Food and Drugs Administration, though speaking from a personal viewpoint, felt that of the hurdles that any drug would have to overcome to be licensed for treating AAMI "None would be more important than the public's negative predisposition

toward treatments that can be viewed as intended to enhance the performance of those presumed to be in a disease-free state". Anti-depressants are not used for people who are sad but for people who are depressed. Indeed, artificially raising mood with chemical euphoriants is considered as drug abuse.

If a group of people with ageing-related memory decline could be satisfactorily identified, and a drug with minimal side effects was identified that significantly improved memory, what should the target be for treatment? Should elderly people be treated to a norm appropriate for their age, appropriate for young adults, or should the aim be to reverse any deterioration up to the level of the person's original function? How could one know when that level had been reached? In theory, one could even attempt to maximize a person's performance to a level greater than their original function although this might be dangerous and runs contrary to medical opinion. This has been seen in the use of anabolic steroids by athletes.

6.5.3 SMART DRUGS

There is a clear parallel here with the use of so called "smart" drugs to improve cognition. Crook (1993) insists that proposing treatment for AAMI does not provide a rationale for giving smart drugs to young healthy people since they have no neurochemical deficit or behavioural problems. One could argue that anyone requesting smart drugs would by definition be displaying behavioural problems! The argument is flawed for other reasons though, since if the disorder to be defined is an ageing-related decline, theoretically people in their mid twenties could be eligible for treatment.

Animal studies with one putative memory enhancer showed improved learning in both old and young rodents (Barnes *et al*, 1990), and this may suggest that treatment response is not limited to neurochemistry which has been altered by an ageing process. In humans, unless a memory-disordered group was defined very carefully, any improvement seen in a treatment trial might be due to a beneficial effect in people with naturally lower cognitive abilities rather than in those with an acquired deficit.

Allain *et al* (1990) describe the potential uses of cognitive enhancers to improve normal cognition in high demand situations such as examinations or for people requiring particular vigilance. There is clearly a great risk of abuse and misuse of such drugs. For this reason licensing of drugs for AAMI should be considered with extreme caution. Rosen (1990) raises a different concern; that if drugs were available for treating ageing-related cognitive impairment, people in their 50s and 60s might come under pressure at work to take medication to improve their performance.

With the many criticisms that have been described, it would appear that proposing diagnostic criteria for AAMI and suggesting pharmacological treatment for the disorder is out of step with and distant from the needs of clinicians in elderly care.

6.6 The suspicion that the motivation for defining AAMI is coming from pharmaceutical company pressure

The NIMH paper contains a section regarding treatment of AAMI which contains a rather curious argument along the following lines:-pharmacological treatment trials in diseased humans (i.e. Alzheimer's disease) have not produced significant beneficial results despite

promising results from animal studies, because the animals used were aged but normal. Therefore trials ought to be conducted on normal aged humans. The impression this gives is that a condition is being developed to fit a treatment rather than the other way around.

The emphasis on pharmacological treatment of AAMI and the proposal to focus clinical trials on people suffering from the disorder, combined with the lack of explanation for the diagnostic criteria chosen, has encouraged the suggestion that the criteria are most concerned with identifying healthy subjects for inclusion into drug trials for age-related cognitive impairments (Bamford and Caine, 1988). There is suspicion that the need for defining the disorder was at least partly influenced by needs of drug companies for a market place for compounds that have undergone extensive and expensive testing in Alzheimer's disease without significant benefit (Dawe *et al*, 1993; Hindmarch, 1993).

It is perhaps significant that such a high proportion of the work group were affiliated to various pharmaceutical companies and it is unfortunate that several of the authors of the working group's paper are associated with commercial memory clinics and the development of computerized cognitive testing systems for clinical trials into AAMI.

6.7 Future research

6.7.1 AAMI: A RESEARCH DIAGNOSIS OR A CLINICAL DIAGNOSIS?

The final pages of a thesis would normally be expected to provide suggestions for future research. This task has proved especially

demanding because of the nature of the disorder studied. The concept of AAMI is one with few clear boundaries in either medical or philosophical terms, despite the apparent clarity portrayed by the detailed list of inclusion and exclusion criteria produced for its diagnosis.

It is unclear whether the diagnostic criteria were intended to define a population of elderly people purely for research purposes or for use in clinical diagnosis of patients. Thus it is hard to suggest how they should be developed.

If they were intended for research purposes only, the aim should be to develop the diagnostic criteria further, but the risk is that the research methodology that would be necessary becomes so demanding as to be impracticable. Blackford and La Rue's work (1989) (see chapter 2), though of great merit in shifting the emphasis onto defining a disorder by comparison with age-matched peers, may be falling into this trap. They extended the one diagnosis of AAMI into three: AAMI, ACMI and LLF. A part of the process of diagnosis requires the use of at least 4 verbal and non-verbal memory tests to demonstrate a 1 and 2 standard deviation discrepancy from age-appropriate and young population norms. They did not feel they should recommend any cutoff scores on any particular tests however, because they believed the relevant cutoffs should vary for each population under study, having to be based on age-, education- and social class-matched data. The initial aim of proposing diagnostic criteria for AAMI in order to improve research and scientific communication seems to have been lost.

If the AAMI criteria were intended for clinical use, then there are many criticisms of the concept and the individual criteria which have already

been discussed. If treatments became available, as the work group clearly intended, would it really be justifiable to "exclude" people from diagnosis and hence treatment, of whatever sort, because they also had a medical condition that could be associated with memory impairment? This would surely be like refusing to treat breathlessness caused by asthma in someone because they also had congestive cardiac failure. Therefore memory impairment which may be due to other medical causes would also have to be given a diagnostic label and be open to treatment. Once one pharmacological treatment for an ageing-related phenomenon was available, others would follow - perhaps growth hormone to restore a strong lean body (Anon, 1991). This would be likely to have wide ranging implications, not only in financial terms for an increasingly stretched National Health Service budget, but also in terms of society's values.

6.7.2 SUGGESTIONS FOR THE DEVELOPMENT OF AAMI

A number of suggestions to improve the diagnostic criteria and focus of AAMI have been presented in this thesis. These have arisen from the experience of interviewing healthy elderly people in their own homes, from interpretation of data that has been collected, and from reflecting on the many papers studied during the preparation of the thesis. Reference has been made to these during discussion of results. Broader issues of diagnosis and treatment have also been examined. They will be summarised here.

A proportion of people with AAMI are in the early stages of dementia, as yet undiagnosed (O'Neill et al, 1992[B]). The development of strategies to slow down or reverse the progression of Alzheimer's disease and other

forms of dementia is of major importance and such strategies are likely to be most effective in early dementia. Early detection of dementia is therefore essential in its own right, but will also assist in the delineation of non-disease ageing-related cognitive changes.

Similarly, many people, particularly those who present to doctors, are likely to be suffering from depression or other affective psychiatric illness which could potentially be easily treatable. Improving detection and treatment of these disorders should therefore be part of a broader approach to managing people presenting with mild memory problems.

In order to demonstrate cognitive decline in elderly people, the most appropriate objective comparison for current performance is an individual's previous level of function. Although ideally this would be based on sequential cognitive tests starting in early adulthood, in practice this information is unlikely to be available. The recent introduction of health screening in General Practice may be a way in the future to obtain baseline data (Barker *et al*, 1992).

Research is required to describe how memory and cognitive performance changes with age in people with varying premorbid abilities; as part of this work it is hoped that the subjects seen in the studies described in this thesis will be followed up in the years to come. When this data is available, it will be possible to estimate whether, and how much, a person's abilities have decreased. It will also be possible to estimate how much a person's memory has declined in comparison with his or her peer group. The assessment necessary will include several age and IQ standardized memory tests.

The decision to treat someone whose memory has deteriorated, whether by psychological or pharmacological means, will depend on a number of factors. These will include deciding how much deterioration represents a significant loss, the level of distress experienced, and the patient's wishes for treatment. Determining whether the distress is a cause or a result of the memory decline will need careful assessment.

I, like others (Blackford and Rue, 1989; Smith *et al*, 1991; O'Brien and Levy, 1992), am inclined to suggest that if treatments are available they should be focussed at the severe end of the spectrum of ageing-related changes, where there is greater chance of significant impairment and an increased likelihood that what is actually being seen is the early stage of a dementing process.

Finally, I am averse to the idea of pharmacological treatment being promoted for the alleviation of symptoms of ageing, as it diverts attention from understanding and accepting the inevitable facts of existence. It would be sad if, in the view of society, ageing came to be seen as a disease bringing a progressive deterioration in all faculties, to be feared and resisted at all costs, rather than as a natural process that brings many enriching experiences as life unfolds from birth to death.

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APPENDIX 1

Proposed diagnostic criteria for AAMI
(from Crook et al, 1986)

1. Inclusion criteria

   a. Males and females at least 50 years of age.

   b. Complaints of memory loss reflected in such everyday problems as difficulty remembering names of individuals following introduction, misplacing objects, difficulty remembering multiple items to be purchased or multiple tasks to be performed, problems remembering telephone numbers or zip codes, and difficulty recalling information quickly or following distraction. Onset of memory loss must be described as gradual, without sudden worsening in recent months.

   c. Memory test performance that is at least 1 SD below the mean established for young adults on a standardized test of secondary memory (recent memory) with adequate normative data. Examples of specific tests and appropriate cutoff scores are listed below, although other measures with adequate normative data are equally appropriate.

Test	Cutoff score
Benton Visual Retention Test (number correct, Administration A) (Benton, 1963)	6 or less
Logical Memory subtest of the Wechsler Memory Scale (WMS) (Wechsler and Stone, 1983)	6 or less
Associate Learning subtest (WMS)	13 or less

   d. Evidence of adequate intellectual function as determined by a scaled score of at least 9 (raw score of at least 32) on the Vocabulary subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1955).

   e. Absence of dementia as determined by a score of 24 or higher on the Mini-Mental State Examination (Folstein et al, 1975).

2. Exclusion criteria

   a. Evidence of delirium, confusion, or other disturbances of consciousness.

b. Any neurologic disorder that could produce cognitive deterioration as determined by history, clinical neurological examination, and, if indicated, neuroradiologic examination. Such disorders include AD, Parkinson's disease, stroke, intracranial haemorrhage, local brain lesions including tumors, and normal pressure hydrocephalus.

c. History of any infective or inflammatory brain disease including those of viral, fungal, or syphilitic aetiologies.

d. Evidence of significant cerebral vascular pathology as determined by a Hachinski Ischaemia Score (Rosen et al, 1980) of 4 or more, or by neuroradiologic examination.

e. History of repeated minor head injury (eg in boxing) or single injury resulting in a period of unconsciousness for 1 hr or more.

f. Current psychiatric diagnosis according to DSM-III criteria (American Psychiatric Association, 1980) of depression, mania, or any major psychiatric disorder.

g. Current diagnosis or history of alcoholism or drug dependence.

h. Evidence of depression as determined by a Hamilton Depression Rating Scale (Hamilton, 1967) score of 13 or more.

i. Any medical disorder that could produce cognitive deterioration including renal, respiratory, cardiac and hepatic disease; diabetes mellitus unless well controlled by diet or oral hypoglycaemics; endocrine, metabolic, or haematologic disturbances; and malignancy not in remission for more than 2 years. Determination should be based on complete medical history, clinical examination (including electrocardiogram) and appropriate laboratory tests.

j. Use of any psychotropic drug or any other drug that may significantly affect cognitive function during the month prior to psychometric testing.

APPENDIX 2

Text of letter of introduction from General Practitioners

Combe Down House,

Combe Down,

Bath.

BA2 5EG

Dear   ,

We are working in collaboration with Doctors from the Research Institute for the Care of the Elderly, St Martin's Hospital, who are looking at how memory changes with ageing. We would like to introduce Dr Barker who will be approaching you in the near future to see if you would be prepared to help, and enclose a letter from him. If you feel you do not want to take part, then it will not affect your treatment with us in any way. If you have any questions, please get in contact with Dr Barker directly who will be happy to deal with them.

Yours sincerely,

Dr David Carr   Dr John Turner

Dr Christina Kennaway   Dr Neil Snowise

APPENDIX 3

Text of letter enclosed with letter from GP

Dear   ,

The Doctors and Nurses at R.I.C.E. are involved in various projects investigating illness and helping to improve care for people of increasing age. It would help us greatly if we could understand more about the normal changes that occur in memory as we get older. I am therefore carrying out a community survey of people over the age of fifty who are registered with the Doctors at your Health Centre, and would be very grateful for your assistance.

If you agree to help, I would ask you to complete a short questionnaire into health and memory related issues, and would then like to meet to do some routine memory tests. This could be arranged at a time and a place convenient for you. In a minority of cases, further investigations may be suggested, but these would be voluntary and would be discussed with you.

You would of course be free to withdraw at any time, and any information given to me would be treated as confidential.

I will try to contact you personally within the next couple of weeks to see if you would be prepared to help, but if you have any questions or would like to discuss this further, please get in contact with me at the above address, or telephone number.

Thank you very much.

Yours sincerely,

Dr Andrew Barker

APPENDIX 4

Text of letter confirming appointment

Dear   ,

Thank you for agreeing to participate in the study assessing normal memory changes with increasing age. I confirm that we agreed to meet at   on

at   , and enclose the questionnaire on health and memory related issues. I would be grateful if you could try to be as honest as possible, and for the questions which give you a choice of answers try to indicate which is closest to the correct answer for you. It would be useful if you could complete the questionnaire before I see you, but if you are uncertain how to answer any of the questions, I will try and assist when we meet. I would be happy to discuss the results with you later if you wish.

I look forward to meeting you.

Yours sincerely,

Dr Andrew Barker

APPENDIX 5

Text of front sheet of prevalence study questionnaire
(rest of questionnaire was psychometric tests)

NAME ....

ADDRESS.....................................

SEX.........   DATE OF BIRTH..............

1. What has been your main lifetime occupation ?

....

2. At what age did you start school ?

....

3. At what age did you leave full time education ?

....

YOUR PAST HEALTH

4. Have you ever suffered from any of the following ?

Please tick the relevant boxes

Diabetes	☐	Parkinson's Disease	☐
Heart attack	☐	Depression	☐
Fits or blackouts	☐	Head injury for which you were hospitalized	☐
Stroke	☐	High blood pressure	☐

Are you on any regular medication ?   yes ☐ no ☐

If yes, could you please give details :-

....

....

APPENDIX 6

Prevalence study consent form

A community prevalence study of memory impairments in a population of over fifty year-olds registered with a Bath Health Centre

CONSENT FORM

I   , agree to take part in the above study which will consist of completing a questionnaire and some memory tests. I understand that in the event of my having a problem with my memory, I may be advised to have further investigations. At any stage I may withdraw from the study should I choose to do so, without having to justify my decision.

Any information obtained will be considered confidential to the study, but my general Practitioner may be informed of health related issues, after discussion with me wherever practical. There would be no disclosure of my name in any reports produced as a result of this research.

Signed   Participant

                    Investigator

APPENDIX 7

Text of interview used in prevalence study

NAME............................... ADDRESS...........................

....

DATE OF BIRTH............. TEL NO.......................

DATE G.P..........................

Scores- mac-q......gds.......stai-s.........stai-t.......

mmse.....nart.....(IQ)......(nart-r IQ).....benton......

- log mem....walt....wvocab....(scaled score)....(IQ)....
* *

MARITAL STATUS................. LIVE ALONE.............

1. WHAT HAS BEEN YOUR MAIN LIFETIME OCCUPATION ?
2. MAIN LIFETIME OCCUPATION OF PARTNER (IF FEMALE)
3. AT WHAT AGE DID YOU START SCHOOL ?
4. AT WHAT AGE DID YOU LEAVE FULL TIME EDUCATION ?

Significant past medical history

Alcohol - present units
- past Have you ever:-
C
A
G
E
Smoke - past - started stopped Average number / day
- present

Any Family History of memory problems

Systems Checklist
CVS UGS

RS THYROID

GIT CNS

Focal neurological symptoms (15) Y__N__

Presenting Memory Problems
Memory problems present...... years...... months

Age at onset:-____Between 40 And 90?   (1) Y__N__

Abrupt onset   (2) Y__N__

Insidious onset   (3) Y__N__

Progressive decline   (4) Y__N__

Stepwise progression with "patchy"
deficit distribution early in the course   (5) Y__N__

Only present during delirium ?   (6) Y__N__

Seizures or gait disturbances   (7) Y__N__
very early in illness ?

Focal neurological signs early
in course of illness   (8) Y__N__

Associated Cognitive Problems
Dyspraxia   Yes/No
Dysphasia   Yes/No
Agnosia   Yes/No

Dyspraxia, dysphasia, or agnosia present ?   (9) Y__N__

Activities of Daily Living

Significant interference with work,
social activities or relationships   (10) Y__N__

Impaired judgement ?   (11) Y__N__

Capacity For Independent Living Remains, with
adequate personal hygiene and relatively
intact judgement.   (12) __
OR
Independent living is hazardous, and some degree of
supervision is necessary.   (13) __
OR
Activities of daily living are so impaired that
continual supervision is required,
e.g. unable to maintain minimal
personal hygiene, or largely incoherent or mute   (14)__

PSYCHIATRIC EXAMINATION
Presenting problem

For DSM III-R "Major depressive episode"
A. At least 5 of following, > = 2/52 duration, a change from prev
function, including 1.or 2.
1.   Depressed mood
2.   Markedly diminished interest or pleasure
3.   Siginificant weight loss or gain when not dieting
4.   Insomnia or hypersomnia
5.   Psychomotor retardation or agitation
6.   Fatigue or loss of energy
7.   Feelings of worthlessness or innappropriate guilt
8.   Diminished ability to think or concentrate
9.   Recurrent thoughts of death, suicidal thoughts or suicide attempt
B.1. No evidence of organic initiation
  2. Not a normal bereavement reaction
C.   Delusions or hallucinations only with prominent mood symptoms
D.   Not superimposed on schizophrenia

Premorbid personality

                        Personality change   (17) Y__N__
Past psychiatric history   Y/N

Mental State Examination:

Orientation

Disturbance of consciousness   (18) Y__N__

Evidence of short term deficit (5 minutes)   (19) Y__N__

Evidence long term deficit   (20) Y__N__
      (yesterday/longer or facts of common knowledge)

Impairment in abstract thinking   (21) Y__N__
Insight

Impression/Formulation:

Non organic mental disorder responsible for memory disorder.
                                                                (22) Y__N__

Support Services at Present

CPN	_	CMHT	_
District Nurse	_	Respite care	_
Meals on Wheels	_	Day centre	_
Home Care	_	Sitting service	_
Home Aide	_	Carers course	_
Social Worker	_	Luncheon club	_
		Neighbours	_

PHYSICAL EXAMINATION

General examination :-

Thyroid   Breasts

CVS   BP   Pulse(sitting)

carotid bruits   peripheral pulses

RS

ABDOMEN

CNS
Tone   Power

Sensation   Coordination

Reflexes   BJ   TJ   BR   KJ   AJ   P

                   R
                   L

Cranial nerves

Focal neurological signs   (16) Y__N__

BLOOD TESTS
          FBC   TFTs   BIOCHEMISTRY   VDRL   B12/FOLATE

Evidence of signif cerebrovascular disease
aetiologically related to disorder   (23) Y__N__

Specific causes of the dementia excluded by history,
physical examination and laboratory tests   (24) Y__N__

Evidence of specific organic factor aetiologically
related to the disorder   (25) Y__N__

Single, severe progressive cognitive deficit
in absence of identifiable cause   (26) Y__N__

Clinical impression / Probable Diagnosis

Plan of Management/Recommendations

KEY FOR DIAGNOSIS (if in doubt consult original criteria)

DSM III-R
Dementia - 19 + 20 + (21 or 11 or 9 or 17) + 10 + 6 (No)
+ (25 or 22 (No))
Severity of dementia - Mild 12 Moderate 13 Severe 14

Alzheimer's disease - Dementia as above + 24 + 3 + 4

Multi infarct - Dementia as above + 5 + 15 + 16 + 23

NINCDS ADRDA Alzheimer's disease
Probable - Dementia as above + 1 + 4 + 18 (No) + 24
Probable unlikely- 2 or 7 or 8
Possible -(19 +20+ (21 or 11 or 9 or 17) +10 + 6(No) + 24 (25
allowed) or 26 by itself.

APPENDIX 8

Reasons for exclusion

1. Carcinoma of prostate diagnosed in past year. Severe head injury as a child.
2. CVA 3 years previously. Hachinski > 3.
3. Chronic bronchitis, with severe shortness of breath and cyanosis. Taking nitrazepam.
4. Taking diazepam.
5. Taking propranolol.
6. Dizzy spells and falls ? cause.
7. Myeloma on intermittent chemotherapy regime, taking antidepressants.
8. Two head injuries when lost consciousness and once lost vision.
9. Taking anxiolytic.
10. Memory loss beleived to be sudden and associated with falls and undiagnosed illness.
11. Taking diazepam.
12. Taking lorazepam.
13. Taking antidepressants for poor sleep.
14. CVA.
15. Was dependent on diazepam for 10 years.
16. Heavy alcohol consumption in past.
17. Lead poisoning in past and laft unable to walk. Diabetic. Myocardial infarction with loss of consciousness.
18. DSM III-R major depression. HAM-D > 12.
19. Probable schizophrenia.
20. CVA, hypertensive, dementia. Hachinski > 3.
21. Dementia. CVA.   Hachinski > 3.
22. Dementia. Low potassium.
23. Dementia.
24. Diabetes, dementia.
25. Dementia.
26. Dementia.
27. Dementia.
28. Dementia.
29. Dementia, taking antidepressants.
30. Dementia, CVA.

APPENDIX 9

Raw data listings for the mean score and SD for the variables MACQ, DISTRESS, BVRT, LOG MEM, WALT, MMSE, NARTIQ, and VOCABIQ in all non-demented subjects and all healthy subjects

MACQ

Age	All non-demented subjects			All healthy subjects		
	Mean	SD	Cases	Mean	SD	Cases
50-54	25.7	2.5	13	25.4	2.1	11
55-59	21.2	4.4	16	20.5	4.6	13
60-64	24.6	3.9	13	25.2	3.2	11
65-69	25.4	4.7	17	25.8	4.6	16
70-74	24.1	4.1	15	24.1	4.3	11
75-79	25.7	4.8	14	24.8	5.0	8
80-84	23.8	6.9	11	22.3	8.0	6
85-89	24.0	3.1	7	24.0	3.7	5
90-94	23.3	2.1	8	23.2	2.6	5
50-94	24.2	4.5	114	24.0	4.6	86

DISTRESS

Age	All non-demented subjects			All healthy subjects		
	Mean	SD	Cases	Mean	SD	Cases
50-54	2.2	1.2	13	1.9	0.9	11
55-59	1.4	0.8	16	1.2	0.4	13
60-64	1.7	0.9	13	1.7	1.0	11
65-69	1.5	0.9	17	1.6	0.9	16
70-74	1.4	0.8	15	1.3	0.5	11
75-79	1.9	1.1	14	1.8	1.2	8
80-84	2.5	1.4	11	2.0	1.0	6
85-89	1.4	0.8	7	1.4	0.9	5
90-94	1.5	0.5	8	1.4	0.5	5
50-94	1.7	1.0	114	1.6	0.8	86

BVRT

Age	All non-demented subjects			All healthy subjects		
	Mean	SD	Cases	Mean	SD	Cases
50-54	7.5	1.3	13	7.5	1.4	11
55-59	6.7	1.9	16	6.9	1.7	13
60-64	7.5	1.9	13	7.8	1.4	11
65-69	6.5	1.2	17	6.6	1.3	16
70-74	5.2	1.8	15	5.4	2.0	11
75-79	4.6	2.0	14	5.1	1.7	8
80-84	3.8	1.9	11	4.7	1.8	6
85-89	4.3	1.4	7	3.8	.8	5
90-94	2.1	1.7	8	3.0	1.4	5
50-94	5.6	2.3	114	6.1	2.0	86

LOG MEM

Age	All non-demented subjects			All healthy subjects		
	Mean	SD	Cases	Mean	SD	Cases
50-54	7.3	2.9	13	6.9	2.8	11
55-59	7.5	1.9	16	7.3	1.7	13
60-64	8.8	2.7	13	9.6	2.1	11
65-69	6.4	2.7	17	6.5	2.7	16
70-74	6.9	2.9	15	7.3	3.1	11
75-79	5.9	3.0	14	6.2	2.5	8
80-84	4.3	2.0	11	4.9	2.2	6
85-89	4.9	3.6	7	3.9	1.9	5
90-94	4.2	2.2	8	4.3	2.9	5
50-94	6.5	2.9	114	6.7	2.8	86

WALT

Age	All non-demented subjects			All healthy subjects		
	Mean	SD	Cases	Mean	SD	Cases
50-54	13.0	4.4	13	12.2	4.0	11
55-59	13.9	3.1	16	13.8	3.1	13
60-64	14.7	4.5	13	15.9	3.8	11
65-69	12.6	3.5	17	12.4	3.6	16
70-74	12.6	3.9	15	13.5	4.0	11
75-79	10.6	4.4	14	10.4	4.6	8
80-84	10.0	4.2	11	11.1	4.5	6
85-89	10.5	3.8	7	9.9	4.0	5
90-94	9.9	3.6	8	9.9	3.8	5
50-94	12.2	4.1	114	12.6	4.1	86

MMSE

	All non-demented subjects			All healthy subjects		
Age	Mean	SD	Cases	Mean	SD	Cases
50-54	28.5	1.9	13	28.3	2.1	11
55-59	28.6	1.7	16	28.9	1.2	13
60-64	28.8	1.0	13	29.0	1.0	11
65-69	27.9	2.0	17	27.9	2.1	16
70-74	28.1	1.6	15	28.5	1.7	11
75-79	26.9	1.4	14	27.3	1.4	8
80-84	26.2	2.0	11	26.9	1.6	6
85-89	27.0	2.5	7	26.2	2.5	5
90-94	26.0	3.3	8	26.6	3.4	5
50-94	27.7	2.1	114	28.0	1.9	86

NARTIQ

	All non-demented subjects			All healthy subjects		
Age	Mean	SD	Cases	Mean	SD	Cases
50-54	110.2	10.3	13	107.7	9.1	11
55-59	112.8	10.0	16	113.5	9.0	13
60-64	115.2	7.8	13	116.8	6.4	11
65-69	107.4	10.4	17	107.4	10.8	16
70-74	105.1	8.4	15	106.5	8.7	11
75-79	109.9	8.1	14	112.9	4.8	8
80-84	104.7	11.7	11	107.9	11.5	6
85-89	103.0	10.8	7	103.2	12.8	5
90-94	105.6	11.5	8	107.2	13.3	5
50-94	108.7	10.2	114	109.7	9.9	86

VOCABIQ

	All non-demented subjects			All healthy subjects		
Age	Mean	SD	Cases	Mean	SD	Cases
50-54	112.4	13.5	13	109.7	12.1	11
55-59	111.3	12.7	16	112.1	12.5	13
60-64	116.1	9.0	13	118.5	7.0	11
65-69	109.0	8.8	17	109.0	9.1	16
70-74	109.8	11.0	15	112.0	11.5	11
75-79	115.0	9.6	14	117.5	7.8	8
80-84	103.5	12.6	11	105.6	13.7	6
85-89	109.0	14.2	7	105.0	13.6	5
90-94	106.5	10.2	8	108.2	12.5	5
50-94	110.6	11.4	114	111.3	11.2	86

APPENDIX 10

Consent form for the self-referral memory clinic studies

The relationship between memory problems and mood in people attending memory clinics

Consent form

     I agree to take part in the above study which will consist of completing a questionnaire to do with my memory and how I have been feeling in general recently. This will take in the order of ten minutes. My decision whether to participate or not will not affect my treatment today or in the future in any way. Information given will be considered confidential to the Research Institute. There will be no disclosure of my name in any reports produced as a result of this research.

Signed   Participant

                                Investigator