

Presenile Dementia
In Lothian, Scotland:
A Clinical And Genetic
Analysis.

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Summary and Guide to the Thesis.

Aim of Study.

The study aim was to identify a population of live patients in the Lothian area of Scotland, with presenile dementia of various aetiologies, and to describe the clinical profiles of each, and the patterns of decline which occur, together with any genetic characterisation possible.

Method.

Cases were identified using the Lothian Psychiatric Case Register. For the demographic data, the CAMDEX (The Cambridge Examination for Mental Disorders of the Elderly) informant interview was used. The behavioural assessment comprised of the CAPE- BRS (Clifton Assessment Procedure for the Elderly, Behavioural Rating Scale), the Cornell Depression Scale and the MOUSEPAD (Manchester and Oxford University Scale for the Psychopathological Assessment of Dementia), a new behavioural and psychopathological assessment. The subject was seen, and where possible the cognitive assessment was completed using the NART (National Adult Reading Test) and CAMCOG (cognitive assessment of the CAMDEX). A physical and neurological examination was done and the Webster scale for Parkinsonian features included. 40 mls of blood was taken at the assessment interview for the genetic analysis. After an interval of approximately one year, each case was re-assessed using these instruments.

Results.

Of 290 potential cases, 164 (57%) were excluded. Reasons: Death 50 (31%), Unsuitable 40 (24%), Refused 40 (24%), Untraced 23 (14%), Out of area 11 (7%). Of the 126 (43%) seen, 112 (89%) met the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM3R) criteria for dementia. 63 (56%) of the 112 were rated as DSM3R severe type. 80 (72%) of

the 112 fulfilled the McKhann criteria for Alzheimer's Disease. A full description of the group and the results following the second assessment are given.

The genetic testing included Apolipoprotein E (APOE), α -1 antichymotrypsin (ACT) and Very Low Density Lipoprotein Receptor (VLDL-R) allele typing.

Important data concerning the services provided and used by this group of patients and their carers has been collected and can be shared with organisations working to find funding for presenile dementia in the health service.

Conclusions.

This study will provide a thoroughly documented and clinically detailed sample. The analysis of the work may help to identify if subgroups exist, according to the patterns of various clinical features, the rates of decline, and genetic variations. This will in turn, give a greater chance to plan appropriately for all those involved in caring for and managing these illnesses.

An overview of the thesis is given below:

Introduction.

I. Historical Perspective.

Background to the study, originating in the interest in Prion Disease.

II. Epidemiological Issues.

Aspects of the condition (including the definition of the condition and difficulties of early diagnosis) are discussed in the context of epidemiological issues. A brief literature review of epidemiological studies of presenile dementia, is included.

III. The Genetics of Younger-Onset Forms of Dementia.

A review of the genetic understanding of dementia. The major part of this refers to research into Alzheimer's Disease.

Method.

I. Ascertainment of the sample.

Describes the use of the case register to obtain cases and details the search for cases. The case note survey is also described.

II. Choosing an Assessment Battery.

The details of choosing an assessment battery are discussed. The general requirements are described, as well as the following areas of data collection: demographic; behavioural; psychopathological; neurocognitive; neurological.

The refinements made for the second assessment are discussed.

III. Contacting the Sample and data Organisation.

The organisation of the pilot study is described as a model for the working of the study as a whole. The process of contacting the doctors and relatives, and making the first and second individual visits, is described. The organisation of the data base and application of the diagnostic criteria are discussed.

IV. Genetic Method.

This describes the process of blood collection and storage. The protocols for the molecular analyses are also given.

V. Statistical Method.

Describes the statistical analyses used.

Results.

A very large amount of data was collected for the study. A selection of the results of greatest interest and relevance, are given.

Discussion.

The results are discussed in the framework of other studies and research done into related areas. The findings and limitations of the results obtained in the study are discussed.

Conclusions.

Appendices.

Individual Case Studies.

For each of the 126 cases seen, an individual clinical vignette is given, with details of the onset and course of the illness, together with other features of interest.

Relatives, Carers and the Services.

This chapter looks at some of the issues arising from the emotional reactions of the families and carers seen.

Protocol.

The letters used to establish contact with the study sample are given. The parts of the first and second assessment procedure, which are not published elsewhere, are given here.

Glossary.

A list of the abbreviations used in the study, and a brief explanation, where relevant, is given.

References.

Author's Comments on the Thesis.

The study aims to investigate presenile dementia, which previously has not been widely researched. No other study to date, has attempted to take such a sample and investigate it in this way. The study provides a wealth of data for exploration. Not all the possible avenues of analysis have been included here, but consideration is given as to where the study can lead to in the future.

The study covers a range of dementia types, and also a variety of clinical features, as well as genetic associations. There are therefore hundreds of potential variables to consider, and ask if associations exist between them. The difficulty is thus to maintain some specific purpose and direction to the work, rather than it becoming over-inclusive in an attempt to be complete.

No full clinical description of the presenile dementias, or detailed discussion of their possible causes is given in this text. This can be found in superb detail and completeness, in Lishman, (1990). Also, this thesis does not attempt to cover areas such as: neuroimaging; investigation; and treatment. These extremely important areas are not of relevance to the study here.

Because of the consideration of such a large topic, there is likely to be overlap between the various parts of the thesis. Where this happens, attention is drawn to the relevant cross-references within the text.

Much of the literature quoted, describes findings from the study of senile dementia, which provides a basis for beginning to describe presenile dementia. Furthermore, the study has a broader remit than looking at Alzheimer's Disease alone, but much of the work quoted, is based on the detailed clinical and genetic studies undertaken in the study of this dementia type.

The relevance of the literature to various sections throughout the thesis, means that there is not only one section for a literature review.

The study is not a true epidemiological survey, and so there are limitations in trying to compare its findings with certain

other work. It does not aim to identify risk factors for the population.

This thesis is a document to describe the study in full, from its conception, and to indicate how far it has achieved its aim, and the future work it could give rise to.

The study was devised by me, and I alone carried out the clinical assessments. There has been collaboration with Dr. A. Brookes for the genetic analysis and with Dr. A. Carothers and Alan Finlayson for the statistical analysis.

I declare that this thesis has been composed by me, and that the work of the study is my own.

Introduction:

I. A Historical Perspective To The Study.

In 1992, there were several news headlines bringing 'mad cow disease' to the public's attention, and raising the question as to whether this posed a threat to the human population. The human spongiform encephalopathies, Creutzfeldt-Jakob Disease (CJD) and Gerstmann-Straussler-Sheinker syndrome (GSS) have classically been defined by their clinical presentations of neurological signs and dementia. The diagnosis of a spongiform encephalopathy has been confirmed by the neuropathological examination of brain tissue, which shows changes such as cortical atrophy, spongiform degeneration, neuronal loss, astrocytosis, vacuolation and amyloidosis. Also, an added criterion for the neuropathological diagnosis of these diseases, is the detection of Prion Protein (PrP) aggregates in the brains of patients with these conditions. Mutations of the PrP gene have been linked with the susceptibility to develop the disease (Baker and Ridley 1992). Certain other conditions have been linked to mutations in the prion protein gene, such as Fatal Familial Insomnia (Medori et al 1992). Work such as that published by Collinge et al (1989 and 1990) and Medori et al (1992), indicated that the phenotype of prion disease was perhaps more varied than was previously believed, and that causes of dementia due to this, could represent a greater number than had been thought previously.

Several mutations in the human PrP gene have been identified (Prusiner 1991). These are summarised in the Introduction: Genetics. The relationship between the known mutations and various clinical conditions is given.

The original plan for the study was similar in some aspects to that actually carried out. However the original plan for the genetic study, was to see how many of the cases were associated with PrP gene mutations.

The emphasis of the study changed during the course of the next year, because of the increasing evidence that prion protein mutations, were not likely to be as relevant as had been thought previously. Work by Schellenberg et al (1991a), implied that cases of prion protein gene mutations are extremely uncommon in screening large numbers of cases of dementia. Brown et al (1993), also concluded that cases of unsuspected prion dementia are extremely unlikely. The decisions about which genetic tests were actually done, are discussed later.

There was further major media coverage of the Bovine Spongiform Encephalopathy (BSE) story during the time of the study. In December 1995, several cases of BSE were discovered to have occurred in teenagers and also in farmers. The likelihood of this having happened by chance was debated. Meanwhile, beef was taken off the school menu. Will et al (1996), reported on cases apparently representing a new variant of CJD, again raising the debate of the possible transmission to humans from cattle. Some of the headlines which have appeared over the past few years, are presented at the end of this chapter.

A further development of the study was the decision to assess each individual at two points in time, in order to provide data to measure change. A limitation of this approach is that each case was not at the same point of the illness to start with.

The aim of the study was thus to have identified a population of live patients with presenile onset of dementia (of various aetiologies) in the Lothian area, and to characterise the clinical and genetic profiles of each, with neuropathological assessment whenever possible. After a period of about a year each case would then be re-assessed. The study would provide a carefully worked up clinical sample, which would be a useful resource, both for the current study and in the future.

Data from the second assessments would allow the patterns of decline of the group to be analysed. An aim of the study was to see if different subgroups of dementia could be described, based on various clinical features including the different rates of decline. The genetic studies could also help to

identify such subgroups in the sample, and demonstrate if clinical differences in presentation are explicable at the molecular level.

Apart from these aspects of the study, the information gathered would provide a detailed investigation of a large number of cases of younger-onset dementia, which had never been described before.

Farmer in BSE case dies of dementia

BY MICHAEL HORNSBY

SCIENTISTS have reported the first death from a rare form of dementia of a human being who had also been exposed to potential infection by "mad cow" disease, a related condition that has killed more than 80,000 cattle.

Writing in the latest issue of *The Lancet*, the scientists say the coincidence raises the possibility that contact with an infected animal might have caused the dementia, but they stress that there is no evidence to support this conjecture.

Neuropathologists at the Western General Hospital in Edinburgh have been monitoring all British cases of Creutzfeldt-Jakob Disease (CJD), a fatal brain condition that aff...

any change in its character or incidence that might suggest a causal link with bovine spongiform encephalopathy (BSE).

In their letter, the scientists say CJD was the cause of a 61-year-old farmer whose herd had BSE in 1989.

The first report of individual cases of BSE and its relationship with CJD is likely to find immediate condemnation by the medical microbiology community, says a government spokesman.

The death of a second dairy farmer from a rare brain condition after his herd was struck by "mad cow" disease was no cause for undue concern, the health department said yesterday. The reassurance was immediately condemned by clinical microbiologist Professor Richard Lacey, who said the government was "not taking any action".

BY NIGEL HAWKES
SCIENCE EDITOR

Second farmer death raises fears 'mad cow' cover-up

■ A dairy farmer whose cattle had BSE has died from a rare brain illness. The government denies that there is any link

August 1993

Are we mad to eat sausages?

The horrors of 'mad cow disease' reveal an insanity at the Ministry of Agriculture, Geoffrey Cannon writes

Sausages and meat pies are now so great a health risk that no one would eat them if they knew what they contained, according to some health campaigners.

Their arguments have force for brain and spinal tissue from cows dying of a horrifying and always fatal brain disease are included in many meat products. And it is possible that the disease can be transmitted from animals to humans through food.

The line in Whitehall is that bovine spongiform encephalopathy (BSE) - or "mad cow disease" - is "likely" not to be passed on from cows. But nobody knows for sure. And pathologists who study brains are taking care to avoid eating anything that lists "animal protein" on the label, including British sausages, meat pies, patties.

Neuropathologist Dr Helen Grant, of the Charing Cross Hospital in London, says that the only logical approach is "to assume that every beef animal is incubating the disease". In retirement, Dr Grant is campaigning to put the facts about BSE before the public. She quotes colleagues as saying to her "Mind you do something about this" and "What in the world are we going to do about this catastrophe".

Donald Thompson, a junior agriculture minister, has said that BSE is the worst disaster for British farmers since the war. Cows in more than 3,000 herds have gone mad with it as their brains become spongy, like and are destroyed and the rate is now running at approximately 150 cows a week. All cows obviously infected with BSE must be destroyed following the urgent recommendation of the government's advisory committee.

But, Dr Grant says, the government is not taking any action to prevent the disease. This is because the government is not taking any action to prevent the disease. This is because the government is not taking any action to prevent the disease.



Doomed: a cow suffering from BSE has no chance of survival.

committee has been set up to see what happens. Dr Grant is blunt: "You and I might be incubating the disease already," she says. She points out that the possibility of scrapie transmittable to cattle was dismissed in 1986.

What do other secrets One that he imprisoned

Although CJD is a rare disease, two cases in their sixties; if Mr Templeman had been a younger man, the cause for concern. The number of CJD cases is



Mad, bad and dangerous

'Mad cow disease' spread by a protein, and are humans at risk? Nigel Williams assesses the latest evidence that could shake the foundations of established wisdom on infection

BOVINE spongiform encephalopathy, the "mad cow" disease, is a new member of a group of diseases that have been known since the 19th century. It is a disease of the brain and spinal cord, and is caused by a protein called prion. The disease is transmitted from one animal to another, and is also transmitted to humans. The disease is fatal, and has a long incubation period. The disease is caused by a protein called prion, which is a misfolded protein that can induce other proteins to misfold. The disease is transmitted from one animal to another, and is also transmitted to humans. The disease is fatal, and has a long incubation period.

to a lesser extent, on cells of the lymphatic system. This protein is the brain which appears to be the normal nerve cell function with the disease eventually leads to the destruction of the brain. The disease is fatal, and has a long incubation period. The disease is caused by a protein called prion, which is a misfolded protein that can induce other proteins to misfold. The disease is transmitted from one animal to another, and is also transmitted to humans. The disease is fatal, and has a long incubation period.

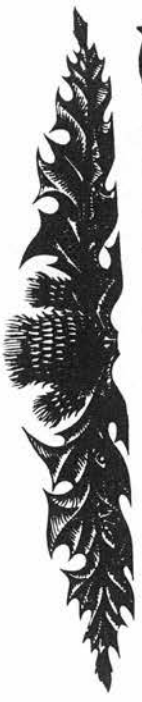
be associated with, but are not directly linked to, the PrP^{Sc} gene. No unexpected results have been found to have any of the unusual forms of PrP^{Sc} associated with the disease, but Dr Grant says that only about 10 per cent of the population are carriers of the gene. The disease is fatal, and has a long incubation period. The disease is caused by a protein called prion, which is a misfolded protein that can induce other proteins to misfold. The disease is transmitted from one animal to another, and is also transmitted to humans. The disease is fatal, and has a long incubation period.

THE SCOTSMAN
Thursday, 21 March 1996

Reutzfeldt Jakob Di
feared - some people at

Research identifies human BSE link

RYAN CHRISTIE
With Correspondent
LHR suggested
arriving in four has stopped
one beef because of disease
fears over "mad cow people"
More than 50 per cent of people
questioned in a survey said they
were "very" or "fairly" by BSE. The
about the risks posed by BSE. The
report, which will also be broad-
cast tonight, have either less beef
eating beef or are eating in partic-
ular were found to be concerned
about the potential risk to health.
It comes warned that they faced
prosecution if they failed to ensure
that cattle offal linked to the



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18 CINEMA
Let's hear it
for Toy Story

19 SCOTSMEN
Key questions
for insurers

24-PAGE TABLOID
PROPERTY
WEEKLY

Beef crisis over 'mad cow' link to humans

Wide rer for Cull inquiry

Dunblane: Te

Health: Government admits deaths may be connected to contaminated meat

THE TIMES MONDAY NOVEMBER 13 1995

By A STAFF REPORTER

AN ESTIMATED 600 cows infected with 'mad cow' disease are being eaten each week in spite of safeguards to stop the food chain, a claim will

therefore if I was certain a particular piece of meat came from an infected animal I would choose not to eat it." Dr Graham Medley, an epidemiologist at Warwick University, says that after studying this year's government data, the estimate for this year suggests that there were two subclinical cases for each one reported, that is a calculation are a "yes, made, that there are a significant number for slaughter that could be going in, incubating the

that, with the help of a dealer, it bought BSE at two auctions in the North West of England. They were later inspected by a Ministry of Agriculture vet and slaughtered. The programme claims that government safeguards such animals, posed to identify such animals. Mr Meldrum said: "There chain animals going into the food chain that could be incubating disease and that we ensure that controls in place to remove any infectivity is minimised. That the risk to man is minimised by a separate consumer programme

Watchdog has discovered that one person in four has stopped eating over "mad cow people". More than 50 per cent of people questioned in a survey said they were "very" or "fairly" by BSE. The about the risks posed by BSE. The report, which will also be broad-cast tonight, have either less beef eating beef or are eating in particular were found to be concerned about the potential risk to health. It comes warned that they faced prosecution if they failed to ensure that cattle offal linked to the

transfer of the disease did not get into the food chain. Representatives of the slaughterhouse meeting were summoned to the Agriculture with Douglas Hogg, evidence that some carcasses could be leaving the Ministry, after evidence that some carcasses without all the official abattoirs. Under new Ministry of Agriculture are required to remove and destroy all offals, including the brain, spinal chord, thymus glands and intestines. BSE is capable of carrying BSE. However, a recent survey by State Veterinary Service of four cases of small pieces of remaining attached to the

Introduction:

II. Epidemiological Issues.

Presenile, early- or younger-onset dementia, is arbitrarily defined as beginning before the age of 65. The arbitrary nature of this age cut-off is discussed by Netten and Kavanagh (1993). It is a much rarer condition than older-onset dementia. As yet, there is only a small number of studies which has aimed to establish figures for the prevalence and study of this condition. There are various methodological problems associated with trying to discover the prevalence figures, and these issues are explored in this chapter.

The basic questions: Why ?, What ?, Who ?, When ?, Where ? and How ? are useful starting points and headings for consideration, to introduce the subject. Why ?, being the reasons why these issues are of importance. What & Who ?, being the definition of presenile dementia and the description of the people with the types of illnesses which could be included in the definition. When ?, being the issues of defining the effect of time on prevalence figures. Where & How ?, being the issues involved in the ascertainment of a complete sample of cases.

In a review of the literature by Liston (1979a), he states that :

"There are in fact relatively few composite or systematic clinical studies of presenile dementia of even modest sample size; and many of these, it will be seen, present, with the general exception of demographic information, conflicting pictures Reported epidemiological data, symptoms and signs, and results of ancillary tests often vary widely from study to study, especially as regards findings of history and of mental status and neurological examinations Indeed on the basis of the literature, one might even question whether there exists a syndrome called presenile dementia, which can be characterised on the clinical grounds with reasonable reliability in the absence of definitive pathological study."

Liston himself published a report of 50 cases of the clinical findings in presenile dementia (Liston 1979b). Rosenstock (1970), studied eleven cases of Alzheimer's presenile dementia, and Sjogren et al (1952), published their findings from 34 families, of the genetic, clinical and patho-anatomical study of Alzheimer and Pick's disease. Many of their cases were of younger onset. Nine presenile dementia cases were described in great detail by Stengel (1943).

Why?

Epidemiological research enhances the understanding of a particular disease in several ways. By accurately determining the prevalence and incidence of a condition, risk factors can be more accurately identified. Questions as to whether a condition is becoming commoner can only be answered if the figures at the first point in time are known. In terms of presenile dementia, where at present no prevention or treatment cure is possible, the epidemiological figures can help the policy makers and service providers to make decisions based on real needs. Juva et al (1994), comment on the need for epidemiological figures and ability to predict prognosis, to effectively plan services for people with Alzheimer's Disease.

The relevance of this is in terms of the people involved. That is to say, not only the people who suffer from the illness, but also their relatives and carers. If, by examining the statistics, it is possible to say with certainty how many people there are who suffer from this condition in a given area, it is then the next step to provide comprehensive and adequate services for them. The extrapolation of the findings of an appropriate survey of the frequency elsewhere, to the demographic characteristics of a particular area in question, would allow planning, even where no such surveys have been carried out.

In regions where the identified target population then fell short of the expected total, concerns would be raised as to the

adequate detection of the cases in the area. Plans to identify them could then be initiated.

Service planning is not a particular matter for this chapter, but two key issues which arise and are of immediate relevance to the discussion of the prevalence of the disease are:

1. The small numbers and geographical spread of the group within one area mean that a centralised service would necessitate the provision of adequate transport facilities to and from it. Other models of an outreach variety may well be more suitable.
2. There are also the considerations as to what other patient groups would be suitable to share in any organised service provision for this group of people. (This issue is discussed in greater depth in the 'What & Who ?' section below.)

What & Who ?

An important starting point is to look at the definition of dementia and so decide who should be included when a population is studied.

Defining Presenile Dementia.

Dementia is used in two contexts which must be clearly distinguished. First, it is used to describe a group of **specific disease entities**; and second, to refer to a **clinical syndrome** which can have many other causes.

When denoting a **syndrome**, the term is best defined as an acquired global impairment of intellect, memory and personality, but without impairment of consciousness. (As such it is almost always of long duration, usually progressive, and often irreversible.)

Certain intrinsic degenerative diseases of the brain occurring in middle or late life have attained the title of dementia as signifying **specific disease entities**. These are the so-called

primary dementias, and need to be distinguished from secondary degenerative brain processes. These latter are dementias secondary to the pathological processes underlying them, such as the cerebrovascular disease underlying Multi-infarct dementia.

The next question is, taking the broad definition of dementia, what are the most commonly found causes for the condition? Among the presenile dementias it is probable that Alzheimer's Disease is more frequent than the other varieties. This group may in fact be made up of a number of different sub-types of dementia. With the present clinical differentiations possible, such placing into different sub-groups tends to become, in part, an issue of the current research interests and prevailing fashions. The position of Lewy Body dementia in the frequency table of dementias, needs to be clarified. Some believe that for dementia as a whole, it may represent the second most common form, see McKeith et al (1994). Shergill et al (1994), investigated the reports of the clinical prevalence of Lewy Body dementia, and found it to vary from 12 - 20% in post mortem series. They concluded that because of the variation in the frequency of the diagnosis using different criteria, the criteria needed revising.

Another type, which could be the next most frequent, is arteriosclerotic or Multi-infarct dementia (MID). Pick's Disease, Huntington's Chorea and Creutzfeldt-Jakob Disease constitute the best known of the remaining primary dementias and are all very much less common.

An exhaustive list of all the rarer forms of dementia would have to include neurological and medical conditions. Neurological conditions would include multiple sclerosis and motor neuron disease, and medical conditions would include epilepsy and diabetes. In these conditions, cognitive decline is only a mild feature of the overall clinical picture. Another example would be Acquired Immune Deficiency Syndrome (AIDS)-associated dementia, but here the overall clinical picture trumps the additional presentation of a dementing illness, in a patient whose survival time is in general, severely shortened by that stage. There are consequently a number of specialties which

would need to be included if a comprehensive survey of cases were to be made. It is beyond the range of this chapter to attempt to define them all.

This illustrates the broad approach required in a wide-ranging search of what the condition includes, and who it affects, but also highlights problems in defining dementia when it occurs as part of another condition. This is also seen when the overlap between Multi-infarct dementia, vascular dementia and cerebrovascular disease is examined. This is reviewed by Amar and Wilcock (1996). Breteler et al (1994), suggest that the total impact of atherosclerosis on the amount of cognitive impairment in the population at large, may be much greater than that contributable to severe atherosclerosis resulting in clinically overt disease.

A stroke may contribute to dementia but will not necessarily cause this pathology. The assessment of cognitive deficiency in stroke-affected patients, is notoriously difficult. It is the presenting symptomatology which decides to which speciality a stroke case is referred. Predominant physical impairments would be the province of general physicians and neurologists, whereas cognitive effects would be cared for by the old age psychiatrists and counted as cases of dementia. The overall pattern of impairment would influence whether the patient is specifically diagnosed with a dementia, and entered on a register as such.

In the section on the 'Why?' of epidemiological research, it was mentioned that a wide range of patient groups could be considered as suitable to share the services for presenile dementia. For example, the age group is obviously younger than the older-onset cases of dementia, for whom various services exist. But difficulties arise in the sharing of facilities, especially in the early and more insightful stages of the illness, when a person may be unhappy at attending a group which they perceive to be of a much older age. Furthermore, the activity levels of the younger group would be correspondingly much greater, and their additional physical problems likely to be less.

Apart from senile dementia there are other forms of adult illness which could be grouped with the presenile dementia sufferers. These fall into the progressive and non-progressive forms.

First, taking the progressive forms of dementia, there are many distinct dementias to include: Alzheimer's; Multi-infarct; Pick's; Lewy Body and Parkinson's Disease with associated cognitive decline; the extremely rare spongiform encephalopathies such as Creutzfeldt-Jakob Disease; and Huntington's Chorea. There is also a significant problem of Alzheimer's occurring in the population of Down's Syndrome adults. Consideration of this diversity raises the obvious difficulty for health providers in catering for the needs of such groups, with a single service.

Second, there are the non-progressive forms of dementia, which share to some extent the same problems, although they do not progressively decline. Cases of post head-injured patients displaying behavioural problems and cognitive deficiencies are one such example.

(In the next section on 'When?', issues about the difficulty in differential diagnosis are discussed.)

Having made this distinction in the definition of the term dementia, the standard clinical diagnostic criteria available to classify it, will be briefly mentioned. These allow some distinction between the different types of dementia to be made. The Feighner Criteria for Organic Brain Syndrome (Feighner et al 1972), and the American Psychiatric Association, DSM3R criteria, (APA 1987), are discussed later.

There exist further agreed criteria to aim to provide more reliable clinical diagnoses during life, such as the National Institute for Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for Alzheimer's type dementia (McKhann et al 1984). There is currently work to

attempt to provide an internationally agreed set of criteria for Lewy Body dementia too.

At this point however, it is important to stress that the most reliable way to establish a diagnosis, is retrospectively at post-mortem. Even this can generate confusion when various pathologies co-exist. Operational criteria are used for this too. Perhaps as the molecular and genetic understanding of these illnesses increases, it will be possible to define dementias in the most accurate way of all, and during the lifetime of the patient. This may indeed go together with the development of novel treatment possibilities, as a natural consequence of the greater molecular understanding of the conditions.

However until then, definition by clinical and pathological means, is vitally important.

When?

Another factor which will influence any attempt to define how great the problem is in a population, is the question of its recognition. In other words, appreciating when it is possible to make a diagnosis, and how straightforward this is. Morris and Fulling (1988), consider the difficulty in the early diagnosis of Alzheimer's Disease. This also becomes a discussion of the mechanism and routes of referral.

Regrettably the diagnosis of presenile-onset dementia is a very hard one to make, especially in its early stages. This is unfortunate for the epidemiological approach but, far more significantly, can greatly add to the difficulties of the sufferer and the relatives.

Factors leading to such a delay exist in the difficulties in early clinical diagnosis by the doctors, and in other subtle factors intrinsic to the illness itself and its effect on the sufferer and the family.

The onset and progress of very insidious and worrying symptoms, may initially be explained away by the family as

stress-related, or attempts made to "cover- up" and deny. Consequently establishing when the onset of the illness took place is notoriously hard to pinpoint. It is often the case that symptoms have existed for a considerable period before a hospital diagnosis is made. This point in time may well be the most accurate available - since it had a specific date. Immediately the problem of underestimating presenile onset cases becomes apparent, since if symptoms began at age 64 but diagnosis is made at 66, this case is lost, although it represents a bona fide presenile-onset case.

Returning to the worried and confused family unable to explain their relative's increasing difficulties in coping, the next problem which arises is that of involving the family doctor. For example, the person with the cognitive impairments may be very unwilling to see the doctor, directly denying the deficit, or feeling threatened by such a suggestion. Further delay ensues; further tension and worry accumulates.

Because of the progressive nature of the condition, the behavioural problems which would follow would lead to increased levels of distress - thus making contact with the GP almost inevitable at some stage of the illness. When eventually the GP is made aware of the issues, it is more than likely that he or she would refer to a specialist for diagnostic testing. At the earlier age of onset the unexpected nature of cognitive decline makes looking for treatable causes such as a tumour, much more pertinent.

So, assuming that the GPs are not the only medical personnel aware of the person and their family, who is involved next?

It would depend partly on the local service organisation, but also on the presentation problem, as to whether a neurological or psychiatric referral would be made in the first instance by the GP. For example any neurological abnormalities would bias to a neurological referral and predominant behaviour problems to a psychiatrist. Allen and Baldwin (1995), compared the case notes of 28 patients with presenile dementia presenting

to a neurology service with 26 who had presented to a specialist old age psychiatric department. It was concluded that specialist old age psychiatric services in Britain have a role in the management of patients with presenile dementia, but that diagnosis should be undertaken by neurologists. Ryan (1994), looked at misdiagnosis in dementia and compared the diagnostic error rate and range of hospital investigations according to medical speciality.

Even with the aid of scanning equipment, the diagnoses of certain forms of dementia will be possible only on the grounds of excluding other possible causes. Without positive evidence to back up such a doom-ridden prognosis it is a particularly difficult diagnosis for the doctor to declare. Furthermore in less clear-cut cases, the use of serial assessments to document cognitive decline might be the best solution, rather than basing the diagnosis on the scant information of one visit to the specialist. The result of this would be a further time lag until all concerned know what they are facing.

The differential diagnosis of a primary degenerative presenile onset dementia is very extensive, ranging from depressive illness to space-occupying lesion. Several surveys from neurological units, evaluated the in-patients consecutively admitted to hospital with a presumptive diagnosis of dementia. Since the majority of the patients were below the age of 65, the results can be seen as an indication of what could be expected in a presenile group. In some studies, about 15 % were not thought to be demented after full evaluation, but to have some other organic psychosyndrome or functional psychiatric disorder.

Marsden and Harrison (1972), studied the outcome of investigation of patients with presenile dementia. They found that of 106 patients admitted for investigation to a neurological hospital with a presumptive diagnosis of dementia, 84 were confirmed to have intellectual impairment or loss of learning and memory function or both. A possible aetiology for the dementia was found in 36 of the 84, the commonest being intracranial mass lesions, arterial disease and alcoholism. 15 of the 106 were found

not to be demented, most commonly being depressed. 15% of cases had conditions that were amenable to treatment. Smith and Kiloh (1981), studied 200 patients admitted consecutively to a neuropsychiatric institute and confirmed the diagnosis in 164. 13 cases were found to have potentially reversible conditions, representing 11.5% of those in the 45-64 year old age group, and 3.8% of those 64 and older. They recommended that those with a provisional diagnosis of dementia be investigated early on in the course of the illness. Freemon (1976), studied 60 patients with progressive intellectual deterioration and found 18 (30%), to have underlying disease of a potentially reversible kind. All their subjects were male, with an average age of 62.2 years. Victoratos et al (1977), examined 52 patients thought to be suffering from dementia when first examined at a neurology out-patient clinic, 44 were below the age of 65 years. Of them, four had tumours, and five had treatable causes.

The difficulties of making an early diagnosis are also illustrated in two studies of groups of cases of presenile dementia seen in psychiatric settings. In the study of Ron et al (1979), a follow-up study of patients diagnosed with presenile dementia, revealed a high incidence of wrong diagnoses. Of 52 cases, 51 were followed up between five and fifteen years on and the initial diagnosis was rejected in 16. Nott & Fleminger (1975), followed up 35 patients diagnosed as having presenile dementia and in only 15 cases did progressive deterioration confirm this.

Prevalence is a function of incidence and also of various factors related to the timing of the illness. As has already been indicated above, the definition of onset can be at the time of symptom onset or at the age of diagnosis; and the latter is probably the more reliable of the two. The definition will affect the comparison of age-specific rates when based on age at onset. The progress of the illness, its duration and overall survival time will likewise be influential on the figures. Dealing with a heterogeneous condition means that differences between subgroups may get lost in overall figures, unless they are separated out.

Also the age range in question has to be decided on. Obviously the cut off point here is 65, but at the lower end should a line be drawn ? Usually the age of 40 or 45 is taken but it is reasonable to assume that onset after the age of 30 will effectively exclude cases of learning disability, as the effect of dementia on the developing nervous system is hard to differentiate.

Vital for prevalence figures is to have an accurate estimate for the population of the relevant age, in the area. There also needs to be specified, a defined period of time, during which the patient group was identified for the study.

Where & How ?

As the previous quote by Liston indicates, the studies that do exist can give conflicting results for prevalence figures. What could account for such an inconsistent picture found between studies ?

To explore this further it is necessary to ask questions about how the cases were ascertained, and scrutinise in detail the methodology used for each. For estimating the population of people with the problem, how extensive has the search been, what has been the case definition, and what have the inclusion and exclusion criteria been ?

Some health services have computerised patient registers which enables the identification of a particular group of people, with a specified diagnosis. However these systems are prone to problems, due to factors such as inaccurate data, duplications, misclassification and miscoding.

Some groups have looked at case note information, and depended on the clinical information provided for diagnoses, rather than on live individual assessments. Such surveys however mean an inevitable drop out due to missing notes and incomplete information to meet criteria etc.

Further attrition occurs when the study involves contacting subjects, for example due to death, or to finding that people have migrated away from the area, or simply because the person may not wish to participate in the study. Attrition will inevitably lead to incompleteness, which is the nature of clinical studies.

Other pertinent questions would be :

Have all potential parts of the service been explored? For example, psychiatric (general adult psychiatric and psychiatry of old age), neurological and medical sources, including those of the elderly? Have in-patient, out-patient (including memory clinics) and day hospitals been included? What of community contacts such as nursing homes, both private and public, and day centres?

It has already been indicated that the majority of cases would be likely to be referred to these services. A very small number of people could theoretically be missed - say, if they were living rough and not registered with a GP, or with such concomitant problems (such as heavy alcohol abuse) as to make assessment of underlying cognitive decline very difficult.

Brief Literature Review of Epidemiological Figures.

Some prevalence studies have used data collected from populations within which are a substantial proportion of cases below the age of 65. Studies taking presenile cases only, are few, and the number of cases ascertained usually small, with correspondingly large confidence intervals. The case-finding techniques differ too. However, the prevalence rates for Presenile Dementia of the Alzheimer's Type (PDAT) are consistent across the studies. Thus the cases being identified must be similar. Not all studies were based on population sampling and individual assessment. Those that are, are probably biased towards the severer forms of the illness. Likewise hospital cases are also going to be severer too.

Sulkava et al (1985), in the Finnish national study, used personal interviews and psychological tests to make a diagnosis

and based their rates on a probability sample of the general adult population. Their figure for primary degenerative dementia, for 30 - 64 year olds, were = 32.7/100,000 (2 cases, population = 6120).

Schoenberg et al (1985), also used interviews and neurological examinations to detect dementia, and included all households and institutions, in Copiah County, Mississippi. For 40 - 64 year olds, the figures for PDAT were = 18.2/100,000 (1 case, population = 5489). In their 1987 figures, the calculated incidence rate for probable presenile Alzheimer's were = 2.4/100,000.

In the Rochester study, USA, Kokmen et al (1989), used a system of ascertainment incorporating general practice records and nursing homes, the so-called "centralised medical record-linkage system". The group's 1988 figures for PDAT, for 45 - 64 year olds, were = 31.8/100,000 (3 cases, population 9431).

Molsa et al (1982), describe a Finnish urban study, where the diagnosis was supported by neurological testing and laboratory investigations. Hospital data and reports from community agencies were used. The prevalence figure for degenerative dementia, for 45 -64 year olds, were = 46.7/100,000 (17 cases, population = 36,409).

In terms of incidence studies, the rates of Treves et al (1986), were obtained by a method based on retrospective case-note review of cases entering institutions and informants were interviewed to determine the date of onset. This was a nationwide epidemiological study of presenile dementia of the Alzheimer's type in Israel, for those under the age of 60 years. The Israeli National Neurologic Disease register and clinical records of all patients discharged from hospitals between 1974 and 1983 with a neurologic or psychiatric diagnosis suggestive of dementia were reviewed. The age of onset was taken as between 43 and 60 years. The annual incidence rate of the population at risk, aged between 40 -60 years, were = 2.4/100,000.

Newens et al (1993a), published figures for clinically diagnosed Presenile Dementia (PSD), under 65, of the Alzheimer's

type, in the Northern Health Region, for the years 1979 - 1986. This was based on the case ascertainment through medical and other care agencies, by case note review. They argue that prevalence would be 25% under-estimated if in-patient data alone were used, rather than their system of day hospital, and neuroradiology records being included as well. From the same source, Newens goes on to say:

"The assessment of true need requires data collated from a variety of health social and voluntary sources, underlining the importance of completeness and accuracy in health information systems."

Their figures for the Northern Health Region, for 45-64 year olds were:

Alzheimer's (PDAT)	= 34.6. (227 cases, pop = 655,800).
Vascular	= 11.7
Other (Secondary)	= 27.0
Total	= 73.3.

The point prevalence was estimated at 34.6/100,000.

The annual incidence at 7.2/100,000 for those aged 45-64. The annual incidence at 3.4/100,000 for those aged 40-60.

The pattern was of diagnosis followed by a period in community care. They estimated that for an average health district with a population of 60,000, between the ages of 45 and 64, about 20 people would be identified with PDAT. Furthermore, >50% of them required hospital or community support for over 5 years.

McGonigal et al (1993), did a retrospective review of hospital records (of patients <75 years old with various diagnoses of dementia) who had been admitted to psychiatric hospitals, as well as from neurology out-patients and general hospital records. This was to ascertain the cases of PDAT in Scotland between 1974 and 1988, with the onset 40-64 years. The minimal incidences, between the ages of 40 and 64, were 22.6/100,000 for probable Alzheimer's and 40.5/100,000 for broad Alzheimer's.

Denominators for incidence were taken from the 1981 census .
The annual incidence of probable AD = 1.6.

The paper was criticised as its rates were based predominantly on admission to psychiatric hospital. The classification for MID type dementia was based on the Hachinski score and did not appear to take into account the group of mixed aetiology.

The various studies are compared in the following tables, after Newens (1994a).

Comparison Between Studies of Incidence Rates of PDAT
per 100,000 per annum.

N.B. Years shown are those of data collection.

<u>Years</u>	<u>Molsa</u> (1973-1974).	<u>Treves</u> (1970-1974).	<u>Kokmen</u> (1970-1974).	<u>Mc Gonigal</u> (1981).	<u>Newens</u> (1985-1986).	<u>Signif. of difference between NHR rate and other studies.</u>
	Age on prevalence date rate (95% CI)	Age at onset of disease rate (95% CI)	Age at onset of disease rate (95% CI)	Age at presentn to hospital rate (95% CI)	Age at diagnosis of disease rate (95% CI)	
<u>40 -64</u>				3.5 (2.6-4.7)	5.6 (4.5-6.8)	<u>NS</u>
<u>30 -59</u>			1.2*		2.1 (1.5-2.8)	<u>NS</u>
<u>40-59</u>		2.4 (1.9-3.0)			3.4 (0.7-9.9)	<u>NS</u>
<u>45-54</u>	6.3 (2.1-14.8)				2.9 (1.7-4.5)	<u>NS</u>
<u>55-64</u>	16.5 (8.2-29.5)				11.3 (8.9-14.1)	<u>NS</u>
<u>45-64</u>	11.11 (6.3-17.8)				7.2 (5.8-8.8)	<u>NS</u>

CI = Confidence Interval.

* = Confidence interval not calculable from authors' published data.

N.B. dates shown are the period covered by the study not that of publication.

Comparison Between Studies of Prevalence Rates for PDAT

<u>Investigator.</u>	<u>Location.</u>	<u>Age Group.</u>	<u>Type of Dementia.</u>	<u>No. of Cases.</u>	<u>Popul. at risk.</u>	<u>Rates per 100,000 (95% CI*).</u>	<u>Signif. of difference NHR and other rates.</u>
<u>Newens et al (1992)</u>	Northern Health region, U.K.	45-64	PDAT	227	655,800	34.6 (30.2-39.5)	
<u>Molsa et al (1982)</u>	Turku, Finland.	45-64	Degenerative Dementia	17	36,409	46.7 (27.2-74.7)	<u>NS</u>
<u>Sulkava et al (1985).</u>	Finland National Survey	30-64	Primary Degenerative	2	6,120	32.7 (3.9-118.0)	<u>NS</u>
<u>Kokmen et al (1988).</u>	Rochester USA.	45-64	PDAT	3	9,431	31.8 (6.6-92.9)	<u>NS</u>
<u>Schoenberg et al (1985)</u>	Mississippi, USA.	40-64	PDAT	1	5,489	18.2 (0.5-101.4)	<u>NS</u>

* calculated for other studies from the published data

NHR = Northern Health Region

CI = Confidence Interval.

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Putting The Medical Genetics of Dementia in Context.

It is now clear that many of the major diseases of unknown cause, for example vascular disease, diabetes, rheumatic disease, mental illness, and cancer, have an important genetic component. Until the advent of the 'new genetics', (the study of inheritance at the molecular level) in the early 1980's, little was known of the way in which genetic factors contributed to the causation of common disorders. The advances in molecular biology have allowed the development of the methods required to isolate and determine the fine structure of human genes, and to study their function in vitro. This has allowed the understanding of many diseases in terms of their molecular pathology. As well as allowing an approach to prevention, the molecular understanding could eventually lead to definitive therapies for many genetic disorders.

By being able to define the main genes involved in increasing the likelihood of developing a particular disease, the difference between the gene product in affected and non-affected individuals, would potentially lead to the understanding required to prevent and manage the condition. A good introduction to the subject is given by Weatherall (1991), and a recent review by Yates (1996).

Application of the methods of the 'new genetics' to mental illnesses, has inherent difficulties, as outlined below.

The 'New Genetics' Applied to Mental Illnesses.

In an article by Alper (1993), some of the difficulties of establishing the genetic basis of mental disease are discussed. Another review is given by Owen and Craddock (1996). During the late 1980's, genetic linkages were reported for schizophrenia and manic depression. However, it is now known that the evidence for the reported linkages is not as convincing as it originally appeared to be.

One of the main difficulties is that defining the phenotypic boundaries for linkage studies is a complex task. There is no single set of objective criteria for the diagnosis of a

mental disease, as there is in the diagnosis of physical diseases. Even the diagnostic criteria of guidelines such as the DSM3R (APA 1987) are not uniformly applied. Some researchers might use a broad definition, diagnosing the condition if only a few of the most important symptoms are present, while others might use a more narrow definition, requiring that most, or all of the symptoms associated with the disease be present.

Another assumption of linkage analysis is that the illness is caused by a single diallelic Mendelian locus. The mode of transmission of mental disorders is unclear. The evidence for a genetic basis of a disease can be enhanced by adjusting the degree of penetrance assumed for the genotype. Many traits are incompletely penetrant; not all individuals with a particular genotype will manifest the associated phenotype. The degree of penetrance for any of the major mental disorders (assuming they have a genetic basis) is unknown. The locus may display incomplete penetrance which is age dependent. Thus, the age-at-onset function also needs specifying.

Because of aetiological heterogeneity (different genetic and non-genetic mechanisms underlying different subsets of the illness), the correct mode of inheritance parameters for a given pedigree is uncertain. A true given mode of inheritance in a family may involve more than one locus e.g. a disease may result from the interaction of alleles at more than one locus.

These considerations also apply in the genetic study of the dementias.

Defining the Dementia Types for Study.

The genetic basis of Huntington's Chorea and Down's Syndrome, have been established. The genetic and molecular basis of Alzheimer's Disease is still uncertain and great efforts are currently underway to elucidate it. The following discussion will largely be based on a review of the knowledge of the molecular genetics of Alzheimer's Disease. The genetics of vascular dementia, and other types of dementia, such as Huntington's, will also be considered.

Developments in the field have been extremely rapid, making the literature review of the area a daunting task. During the summer of 1995, the rate at which new Alzheimer-linked genes were being published, was one a month! The following review will aim to give the background to the current understanding of the genetics of dementia, as up-to-date as can be.

Some discussion is given to the overlap between various dementia and neurodegenerative disorders, and other interconnecting themes emerge. Ben-Shlomo et al (1996), highlight some of these issues. For example, the amyloidoses as a set of conditions, allow the relevant knowledge gained from the study of the prion diseases to be applied to the molecular study of Alzheimer's Disease. The β -protein in Alzheimer's Disease and Down's Syndrome, and the PrP protein in Scrapie and Creutzfeldt-Jacob Disease are discussed in the paper by Roberts et al (1988). In the discussion on the Apolipoprotein E ϵ 4 allele (APOE ϵ 4) findings in different conditions, the common threads between different disorders is again evident. The vascular effects, via free radicals, of β -amyloid in Alzheimer's disease, reported by Bradbury (1996), is another example of how the molecular processes involved may provide links between Alzheimer's and vascular dementia.

Vascular Dementia.

As reviewed by Wright (1991), the molecular basis of vascular dementia, is poorly understood, as compared with Alzheimer's Disease. Rating scales exist to help to distinguish this from Alzheimer's Disease, but the existence of mixed states remain a problem in obtaining a 'pure sample' of cases. Few satisfactory family studies have been conducted, but those done, show an increased morbidity risk in the first-degree relatives of probands compared with the general population, hence indirectly implicating genetic factors. Twin studies provide little evidence for or against a genetic hypothesis (Jarvik et al 1980). However,

predisposing factors such as hypertension do appear to be under some degree of genetic control (Mongeau 1987). A rare autosomal dominant form does exist, as identified by Sourander and Walinder (1977). Another rare autosomal dominant type of cerebral haemorrhage, caused by a cystatin C defect, called congophilic angiopathy (CAA), is described by Ghiso et al (1986). Palsdottir et al (1988), similarly reported a mutation in the cystatin C gene causing hereditary brain haemorrhage.

Linkage of a hereditary type of Multi-infarct dementia on chromosome 19 (C19) has been reported. The CADASIL locus on C19 has been found to be associated with stroke and dementia. Familial hemiplegic migraine is also linked to the same locus, for example, see Joutel et al (1993). Tournier-Lasserre et al (1993), mapped to 19q12, a gene causing an autosomal dominant cerebral arteriopathy with subcortical infarcts and leukoencephalopathy, as did Jung et al (1995).

St. Clair et al (1995), report the evidence of probable locus heterogeneity in a large Scottish pedigree with a hereditary Multi-infarct dementia unlinked to the chromosome 19q12 locus. At the time of this publication, there were seven reports on the condition, variously known as: chronic familial vascular encephalopathy; hereditary multi-infarct dementia; or cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy.

The Transmissible Dementias, Spongiform Encephalopathies, or Prion Diseases.

The historical relevance of these diseases to the study has already been mentioned in the Introduction: Historical Perspective.

The Prion Protein (PrP) plays a significant role in the aetiology of Creutzfeldt-Jacob Disease (CJD), Gerstmann-Straussler-Sheinker Syndrome (GSS) and Kuru, and similar neurodegenerative diseases in animals e.g. Scrapie in sheep and Bovine Spongiform Encephalopathy (BSE) in cattle. These dementias can be experimentally transmitted to a variety of

animals through intracerebral inoculations of infected brain homogenates.

CJD. Was first described in the early 1920's. It is a rare disease (one in a million) with a rapidly deteriorating course. It is confirmed by neuropathological findings of spongiform changes in the brain, astrocytic proliferation and neuronal cell loss and occasionally amyloid plaque deposition. Most cases are sporadic but 10-15% are inherited and show a mainly autosomal dominant pattern of inheritance. A small number of cases are due to iatrogenic transmission. It has already been mentioned that Will et al (1996), reported on cases apparently representing a new variant of CJD, which may be unique to the U.K. The possibility is raised that they are causally linked to BSE.

GSS. Was described in the late 1920's, and presents as a cerebellar syndrome, with a slower course, with dementia emerging later on in the disease. It is almost entirely familial, the mode of inheritance likewise being that of autosomal dominance. Neuropathological changes are similar but here the extraneuronal amyloid plaque deposits are common and spongiform changes may be slight.

Kuru. The Fore speaking people of Papua New Guinea, were found to have an acquired prion disease as a result of the tribal tradition of ritual cannibalism of infected tissue.

The Prion Protein (PrP), is a 253 amino acid protein which appears to be resistant to inactivation by heat, UV light, formalin and X-rays. In the disease form, the prion is largely composed of an abnormal isoform (PrP^{sc}), derived from the cellular protein produced in normal brains (whose function remains unclear). It is expressed in a wide variety of cells and tissues. The PrP gene is encoded on the short arm of chromosome 20 in man. It is a single-copy gene of simple structure and organisation. The highest concentration of PrP mRNA occurs in the brain in neurons (Kretzschmar et al 1986). Various post translational modifications of PrP occur.

The accumulation of the abnormal isoform causes the disease. It is still unknown how a purely proteinaceous agent has

the ability to induce the production of the abnormal protein form. The abnormal isoform of the PrP in the host, is host encoded. It was postulated that a nucleic acid genome for the agent was using the host PrP as a coat. But there is no evidence for this. The PrP appears to be a molecular chaperone required for its own assembly, and it seems that the abnormal isoform is misfolded in a way that caused others to assume the same configuration. Weissmann (1991), describes a unified theory of prion progression. However, there may be more than one mechanism for abnormal isoform production. Table 1 shows the known mutations in the human PrP gene.

Table 1. The known mutations in the human PrP gene:

<u>Codon</u>	<u>Amino acid change</u>	<u>Condition linked to.</u>	<u>Reference.</u>
Point mutation			
102	proline - leucine	GSS	Hsiao et al (1989).
117	alanine - valine	GSS	Doh-Ura et al, (1989).
129	valine-valine	CJD	Palmer et al, (1991).
129	methionine - valine	GSS	Dlouhy et al (1992).
178	aspartate - asparagine	CJD	Nieto et al (1991). Goldfarb et al (1991b).
178	aspartate - asparagine	Fatal familial insomnia	Medori et al, (1992).
198	phenylalanine to serine	GSS (Indiana)	Hsiao et al, (1992).
200	glutamate to lysine	CJD	Goldgaber et al, (1989).
217	glutamine to arginine	GSS (Swedish)	Hsiao et al, (1992).
<u>Insertions ORF between codons 51 & 90. (bp)</u>	<u>Extra octapeptide repeats.</u>	<u>CJD/GSS</u>	
96	4		Goldfarb et al (1991a).
120	5		Goldfarb et al, (1991a).
144	6		Owen et al (1990).
168	7		Goldfarb et al (1991a).
192	8		Goldfarb et al (1991a).
216	9		Owen et al (1990).

The insertion mutation was also demonstrated in an affected member of a pedigree where the illness was originally suspected to be familial Alzheimer-type dementia, Collinge et al (1990). As mentioned, this was one piece of evidence that raised the possibility that prion diseases may not be so rare as previously thought. A range of familial and sporadic dementias were therefore screened for the insertion mutation and also for the point mutations that had been detected at that time, i.e. the mutations in codons 102, 117 and 200 (Owen et al 1991). The only mutation detected in a total of 101 samples was an insertion that was detected in five apparently unrelated individuals. Two of these individuals had clinical diagnoses of familial Alzheimer's disease and the diagnoses of the remaining three individuals were Pick's disease, Huntington's disease and presenile dementia with myoclonus and extrapyramidal symptoms, providing further evidence of the diversity of clinical presentation associated with this mutation. The genotype, neuropathology and clinical phenotypes of these diseases are therefore diverse.

The demonstration that GSS and familial CJD are associated with a wide variety of mutations in the open reading frame (ORF) of the PrP gene has greatly strengthened the notion that the PrP plays a central role in the pathogenesis of these diseases. In particular, transgenic mice harbouring the equivalent of the codon 102 mutation in man, spontaneously develop neurological disease and neuropathological changes consistent with spongiform encephalopathy (Hsiao et al 1990). As mentioned, the mechanism by which the normal PrP isoform is converted into its abnormal isoform remains unknown, although in the case of humans carrying point mutations or insertions in the ORF of the PrP gene it has been suggested that mutant PrP molecules might spontaneously convert into the abnormal isoform. If this process was relatively inefficient, it might explain why individuals with such mutations do not develop the disease for decades (Prusiner 1991). Although human prion diseases are rare, the detection of mutations in the ORF of the PrP gene in a range of atypical dementias suggests that these diseases must be

considered. Only when the normal cellular function of the PrP and the mechanism of replication of the abnormal isoform are elucidated will a rational therapy for prion-related diseases become a realistic possibility.

Huntington's Chorea.

Introduction.

This is a condition in which choreiform movements are combined with dementia. It is a relatively rare condition, with a variably reported prevalence. Myrianthopoulos (1966), considered 4-7/100,000 of the population to be a reasonable overall estimate. An astonishingly dense focus was reported in the Moray Firth area of Scotland, of 560/100,000 of the population (Lyon 1962).

The disease is associated with a single autosomal dominant gene with virtually 100% penetrance. A family history is not always forthcoming, perhaps due to the early death of a parent, lack of detail due to illegitimacy or inadequate history, or concealed and circumscribed knowledge in the immediate family circle. The condition may also arise due to the occurrence of spontaneous new mutations.

Huntington's Chorea was one of the first conditions in which the genetic location for a disorder of completely unknown aetiology was located using restriction fragment length polymorphisms (RFLP's). In 1983, the disease was located to a gene on chromosome 4 (Gusella et al 1983). But it was only about ten years later that the gene itself was found. Currently, although the gene responsible has been localized by linkage analysis, to the short arm of chromosome 4, the precise mechanism by which the molecular and biochemical defect cause the neuronal degeneration, is unknown.

RFLP linkage.

The discovery of restriction endonucleases (REs) provides an opportunity to approach the analysis of genetic

diversity. In the genome are harmless base changes that produce or remove sites: variability is inherited in a simple Mendelian fashion. The inherited difference in the size of DNA fragments (RFLPs) provides a large number of linkage markers for following mutant genes through families. Also, in addition to single point polymorphisms there are regions of the genome in which the length of DNA between specific RE sites varies between different persons; and variability is inherited. These hypervariable regions offer a rich source of genetic markers.

For this method to proceed, the DNA is purified and digested. The mix of differently sized fragments is subjected to electrophoresis on an agarose gel. After separation of the fragments according to their size, the DNA in the gel is denatured by alkali treatment, and the separated fragments are transferred to a nitrocellulose filter by Southern blotting. The filter is then exposed to a radioactively labelled gene probe and the position of the fragments containing the gene determined by autoradiography. Different enzymes can cleave around the gene being studied and a map can be built up.

RFLP linkage analysis can be used to determine chromosomal location of loci in single gene disorders. It is not necessary to know anything about the gene or its product and it is therefore possible to determine the sites for conditions of completely unknown cause. If the study is of the inheritance of a gene for a product that is not identified, and there are RFLPs close enough to the gene, it should be possible to use them as markers to follow the inheritance of the particular gene through families. If the RFLP site is known, then the adjacent gene can be found.

RFLP changes in the DNA at the tip of the short arm of chromosome 4 have been known for many years but it was only in the early 1990's that the actual gene was precisely identified at position 4p16.3 (MacDonald et al 1993). The specific abnormality was a polymorphic trinucleotide repeat (CAG)_n that is expanded and unstable. With the gene identified, the size of the

repeat can be monitored, to make the diagnosis in anyone and thus eliminate the need for linkage analysis

Mutational Mechanism: Trinucleotide Repeat Expansions.

The genetic abnormality is similar to that found in myotonic dystrophy (CTG)_n, spino-bulbar muscular atrophy (CAG)_n, and fragile X syndrome (CGG)_n.

The diseases mostly display some degree of unusual inheritance pattern, such as incomplete penetrance or genetic anticipation (with the severity of the symptoms increasing and, or, the age of onset decreasing in successive generations). This mechanism can be understood in the context of the behaviour of unstable and expanding trinucleotide repeats.

MacDonald and the Huntington's Disease Collaborative Research Group (1993), reported the identification of the HD gene and its transcript, referred to as IT15 (for interesting transcript 15). This identifies a 10.4 kb message predicting a 348 kD protein. Near the 5 prime (5') end of the message a repeat of 21 CAG trinucleotides was observed predicting a polyglutamine stretch in the protein. This trinucleotide repeat was found to be normally polymorphic with an allele length ranging from 11 to 36 CAG repeats with 98% of normals having alleles at or below 24 triplets. Among patients with HD, this repeat expands to between 42 and approximately 100 repeats. The increase of glutamines beyond 44 residues is likely to result in a gain-of-function.

The length of the repeat appears to be correlated with the severity of the disease, such that juvenile cases fall within the high end of the abnormal allele lengths. But repeat length accounts for only about 50% of the variance in age of onset. Other factors may be modifying genes, which influence the effects of the abnormal IT15 allele. The repeat lengths vary from generation to generation with both expansion and contraction occurring and an overall tendency to increase over the generations. This could be a way that the disease could become of increasing prevalence. The sex of the transmitting parent has a significant influence on the magnitude of the repeat-length

changes. When transmitted from the mother, repeat-length increases or decreases within a range of approximately four CAG units, with a mild tendency towards repeat-length increase. When transmitted from the father, there is a much larger range of expansions, up to a doubling of paternal repeat length. The early-onset of symptoms in Huntington's appears to be associated with paternal transmission.

In summary, the change in the CAG trinucleotide repeat would predict a variable number of glutamines within the HD protein (termed huntingtin).

The Mechanism of Action of the HD Trinucleotide Repeat.

The DNA sequence of the gene and predicted protein sequence, bear no significant extended similarity with any other previously reported sequence, making any inferences concerning the normal function of this gene impossible.

The mechanism of the repeat expansion remains poorly understood and even if it is similar in different diseases, the consequences of the expansion may be unique. Any explanation of the manner in which trinucleotide repeat expansion causes HD must deal with its selective toxic effect on cells in the striatum, despite apparent expression of the gene in many other tissues.

Regional differences in splice-variant expression could play a role in the pattern of pathology. An alternative explanation for the regional specificity would be somatic instability of repeat number, but it is unlikely. The susceptibility of the striatum is likely a function of a unique feature of these neurons. A precedent exists in familial amyotrophic lateral sclerosis, where some cases are caused by a point mutation in Zn²⁺/Cu²⁺ superoxide dismutase. The enzyme is expressed widely but only specific neuronal populations are affected.

The expanded repeat is not a simple inactivator of the gene but many other possibilities for the mechanism of action remain. If the (CAG)_n stretch is expressed as polyglutamine in the gene product, then the mechanism of action might be at the protein level. The complete dominance of the disease phenotype

could then be explained by the mutation conferring a new property on the protein. Such a property could fall into many categories, including for example, the increased affinity for a normal substrate, or the ability to interact with a new cellular component, or the capacity to inactivate the normal gene product and alter its localization in the cell. If the (CAG)_n is in the gene's 5' untranslated region and even if it is in the coding sequence, it could have its effect at the RNA level, conferring a new property on the RNA, such as altering its efficiency of translation, its half-life, its ability to bind regulatory or other factors, cell localization and splicing patterns. Finally the (CAG)_n repeat could have its effect at the DNA level, altering the regulation of transcription of the gene, or possibly another gene in the immediate vicinity.

The expansion in Fragile X syndrome can lead to transcriptional silences, whereas in myotonic dystrophy the change is in message stability. In Spinal and Bulbar Muscular Atrophy (SBMA), Huntington's Disease (HD) and Spinocerebellar Ataxia type I (SCAI), the change is in the length of the glutamine tracts perhaps separating critical domains and leading to a gain-of-function mutation.

Further theories are discussed in Albin (1995). The Huntingtin protein possesses the leucine zipper motif associated with gene regulatory proteins. Furthermore, polyglutamine, is a sequence found commonly in transcription factors. Several hypotheses have been put forward to explain the effects of excessive CAG repeats. It has been suggested that polyglutamine stretches are potential substrates for transglutaminases which cause crosslinking of proteins and the formation of permanent glutamyl adducts. Alternatively, the length of the polyglutamine tract may influence the efficiency of transcriptional factors with a probable optimal length. A variant of the gene-regulation hypothesis has also been put forward. Excessive CAG repeats might cause Huntingtin to act as a sink for transcription factors that possess polyglutamine stretches and so disrupt neuronal function, or polyglutamine aggregates could result in insoluble and ultimately toxic precipitates within neurons.

Another variant of the transcription regulation hypothesis, is the mechanism as with the CTG triplets in myotonic dystrophy. They potentiate the stable nucleosome formation at the site of triplet expansion. The generation of aberrant nucleosome positioning by expanded triplets could lead to blockade of transcription or the alteration of local chromatin structure, or both. These effects could influence the expression of genes that contain the repeat and those nearby.

Another theory is that the Huntington protein may undergo normal processing to produce polyglutamine-containing polypeptides. These might not be catabolised adequately. The effects of polyamines, such as the potentiation of N-methyl-D-aspartic acid (NMDA) receptor activation and modification of mitochondrial function, could be relevant in the mechanism.

Barinaga (1996), reports on the more recent finding that huntingtin may interact via its polyglutamine region with glyceraldehyde-3-phosphate dehydrogenase (GAPDH). GAPDH is a key enzyme in glycolysis, the essential metabolic pathway by which cells convert sugar glucose to energy. The mutant proteins in Huntington's Disease may shut energy production down by interfering with GAPDH.

Repetitive Sequences.

These repetitive sequences, have been found in the genomes of all other organisms although they are more common in mammals than bacteria. Although they are normally seen outside genes, in the so-called "junk" regions, they also occur fairly often inside the DNA of certain key types of genes e.g. transcription factors, which control the gene action and embryonic development. With triplet expansion disease the symptoms worsen with each generation as the unstable sequence lengthens. These diseases are all found to affect the nervous system. The build up of repetitive sequences may have played a part in the evolution of complex organisms. They are more common in animals made up of billions of cells. The CAG repeat has accumulated in certain transcriptional factors during

evolution. These are involved in a complex web of interactions between proteins. They would therefore be especially crucial in the evolution of the human brain. For the mechanism to occur, there is the need for a triplet sequence in a sensitive area that has grown unwieldy and become unstable and an error-prone copying machinery that makes mistakes in the process of cell division. The gene causing HD has a longer triplet array in humans than other primates even in the non-diseased form. Perhaps the "critical mass" effect is at work such that the presence of one more triplet triggers the problem. Psychiatric conditions that do not follow Mendelian inheritance are good candidates for such mechanisms.

Table 2 shows some other conditions and the trinucleotide repeat expansions associated with them:

<u>Disease</u>	<u>Triplet</u>	<u>Chromosome</u>
<u>Unwanted triplet outside gene</u>		
Fragile X-A	CGG	X
Fragile X-E and mental retardation	GCC	X
Myotonic Dystrophy	CTG	X
<u>Unwanted triplets inside gene</u>		
Huntington's Disease	CAG	4
Dentatorubral pallidoluysian atrophy	CAG	12
Machado-Joseph disease	CAG	14
Spinal and bulbar muscular atrophy	CAG	X
Spinocerebellar ataxia	CAG	6

Diagnostic Implications.

The most immediate impact of delineating the (CAG) n repeat expansion in HD is the capacity to directly diagnose individuals based on their DNA alone. After the discovery of DNA markers for HD in 1983, it was possible to perform presymptomatic or prenatal diagnostic tests using linkage markers. But this was cumbersome and prone to inaccuracy and was only applicable to at risk individuals for whom several family members were willing and able to donate their DNA.

The PCR amplification of the triplet repeat should revolutionize the testing procedure and provide a reasonably inexpensive method, applicable to any at risk individual, without the need for relatives taking part. But there are complicating factors that must be considered for the diagnostic use of the repeat. For example, the current distinction between a chromosome that can cause HD and one that does not is only 3 repeat units. It is currently impossible to draw a firm conclusion from repeat lengths in the 34-38 unit range. Also, from linkage analysis over the past few years aimed at delineating the HD candidate region, several individuals were identified, who were diagnosed with the disorder, despite inheriting a normal chromosome .

The carefully designed counselling programmes for presymptomatic testing should certainly not be abandoned, but modified, to include the peculiarities of this direct test.

Genes In Early-Onset Dementia Alzheimer's Disease.

Introduction.

Alzheimer's Disease is believed to be the commonest of the primary dementing illnesses. It is a leading cause of morbidity in the elderly and is also important at a younger age. For a more definite diagnosis, neuropathological confirmation is also required. The differentiation from other dementias and the possibility of overlap with these conditions, is crucial to clarify. The possibility of the molecular understanding of the illness may therefore provide the best diagnostic tool available.

i). Clinical Genetics.

There are several difficulties in the genetic study of this condition. First, as already stated, the diagnosis depends on the clinical diagnosis in life and the subsequent histopathological confirmation on death. Second, because it usually has a late age of onset, susceptible individuals may die of unrelated things before acquiring the condition. At risk relatives may be studied at too early an age, and retrospective diagnosis means unavailable data.

Alzheimer's is a familial condition, and this is most clearly demonstrated by looking at the relatives of cases of presenile dementia. Heston et al (1981), studied the relatives of autopsy-proven cases and found higher rates of illness in the relatives, particularly in early-onset rather than late-onset cases. These findings are widely interpreted as supporting the view that early-onset Alzheimer's Disease has a greater genetic component than late-onset cases.

Heyman et al (1984), studied forty cases of onset prior to the age of seventy years, and a series of matched controls. The aim was to identify the presence of illnesses among subjects' parents, aunts, uncles, sibs, children and grandchildren. Dementia was more frequent among the families of patients (55.3%) compared with controls (14.5 %). But the reliability of reports and certainty of diagnosis, are not good with this method.

Alzheimer's Disease with onset between the ages of 60-70 years, is generally sporadic, although studies report that between 16-41% have an affected first degree relative. In general, a presence of dementia in the family history is obtained in 30-50 % of cases (Wright, 1991).

There exist rare pedigrees in which inheritance follows an Autosomal Dominant pattern, providing the best evidence to implicate genetic factors in the aetiology of Alzheimer's Disease. These are known as cases of Familial Alzheimer's Disease (FAD). But there are no consistent clinical or neuropathological features to allow distinction from sporadic cases. Most of these examples are of cases whose disease onset has been in the presenium. The low intrafamilial variation in the age of onset has been studied by Van Duijn et al (1991). It is estimated that only 0.1% - 1% of all Alzheimer's Disease cases are FAD, and the majority do not show such striking patterns of familial transmission.

Another important clinical observation was that adults with Down's Syndrome appear to be at high risk of developing the Alzheimer's pathology, at a relatively early age, see Kolata (1985). This is thought to be due to the extra chromosome 21 that they carry.

The evidence from the concordance rates in monozygotic and dizygotic twin studies, demonstrates that genetic susceptibility is insufficient as a cause for developing the condition, see Wright (1991).

The best genetic model to explain the transmission, is of an autosomal dominant gene with age-dependent penetrance, working on a multifactorial genetic and environmental background. There exists evidence for familial effects but little indication as to whether this really reflects a substantial genetic component to the aetiology of the condition.



ii).Molecular Genetics.

Chromosome 21.

APP gene.

As mentioned, there is a known link between adults with Down's Syndrome (trisomy 21) and Alzheimer's. People with these conditions develop a similar pattern of brain pathology, as described by Mann (1988). Therefore chromosome 21 was the first autosome to be tested by a linkage analysis strategy, in segregation studies with polymorphic markers from the chromosome. The AD pathology in Down's results from an overexpression of the amyloid precursor protein (APP) gene on 21q21.2 which codes for the β A4a peptide found in AD lesions.

St.George-Hyslop et al (1987), reported linkage between Alzheimer's in four early-onset pedigrees and several DNA markers on the long arm of chromosome 21. At about the same time, the APP gene was mapped to the same region of chromosome 21, suggesting that this gene could be in some way be the cause of the disease. Initial excitement at this possibility was followed by evidence not in its favour, as the regional location of linkage was different from the APP gene, see Tanzi et al (1987) and Van Broeckhoven et al (1987). Goate et al (1989), found linkage of markers in other pedigrees, but at sites on chromosome 21 even further from the APP gene. It was postulated that aetiological and possibly genetic heterogeneity exists with chromosome 21 linkage, restricted to a subset of early-onset families. The initial results were thought to be due to chance cosegregation.

As all cases were not C21 linked (Schellenberg et al 1991b and St. George Hyslop et al 1990), the APP gene was reanalysed and more mutations in the APP gene were identified, both in AD families and in families segregating haemorrhagic stroke due to congophilic β A4a angiopathy (CAA).

The role of APP was stimulated by work on the rare genetic disorder Hereditary Cerebral Haemorrhage with

Amyloidosis of the Dutch type (HCHWA-Dutch), found in two villages in the Netherlands. The pathology is of severe β -amyloid deposition in the cerebral blood vessels, which causes death by middle age of cerebral haemorrhage or survival with a dementia syndrome like that of Multi-infarct dementia, see Haan et al (1991).

The β -amyloid is coded for in exon 17 of the APP gene, and the angiopathy caused by the protein is found in both HCHWA-Dutch and AD. In HCHWA-Dutch, however, there is absence of neuronal involvement (e.g. dystrophic neurites and neurofibrillary tangles).

The continued interest in APP led Goate et al (1991), to sequence exon 17 in their FAD pedigrees, revealing a mutation at codon 717 of the APP₇₇₀ transcript, causing a valine to isoleucine substitution. It has been found in a few other FAD families since. Chartier-Harlin et al (1991), has since found a mutation in codon 717 segregating with the disease, resulting in a valine to glycine substitution, and Murrell et al (1991), another resulting in a valine to phenylalanine substitution. Finding three mutations in the same codon strongly suggests that they are pathogenic. But they are rare, and not found in many cases of FAD, nor a large number of non-familial cases.

Mullan et al (1992a), identified a double mutation at codons 670 & 671 in exon 16, changing lysine to asparagine and methionine to leucine respectively.

In the CAA related haemorrhagic stroke cases, in families with HCHWA-Dutch, a mutation was identified by Levy et al (1990), affecting codon 693 of the APP, changing glutamine to glycine, (at the site of cleavage). Hendricks et al (1992), reported a mutation at codon 692, adjacent to that causing HCHWA-D, and changing alanine to glycine. This was relevant for both patients with the haemorrhagic stroke type illness and those with presenile onset dementia of the AD type.

The APP mutations are summarised in table 3.

Table 3. Known APP Point Mutations.

<u>Point mutation.</u>	<u>Exon.</u>	<u>Amino acid substitution.</u>	<u>Author.</u>
670	16	lysine-asparagine	Mullan et al (1992a).
671	16	methionine-leucine	Mullan et al (1992a).
692	16	alanine-glycine	Hendricks et al (1992).
693	16	glutamate-glutamine	Levy et al (1990).
713	16	alanine-threonine	Jones et al (1992).
717	17	Valine-isoleucine valine-phenylalanine valine-glycine phenylalanine-glycine	Goate et al (1991). Murrell (1991). Chartier-Harlin (1991). Chartier-Harlin (1991).

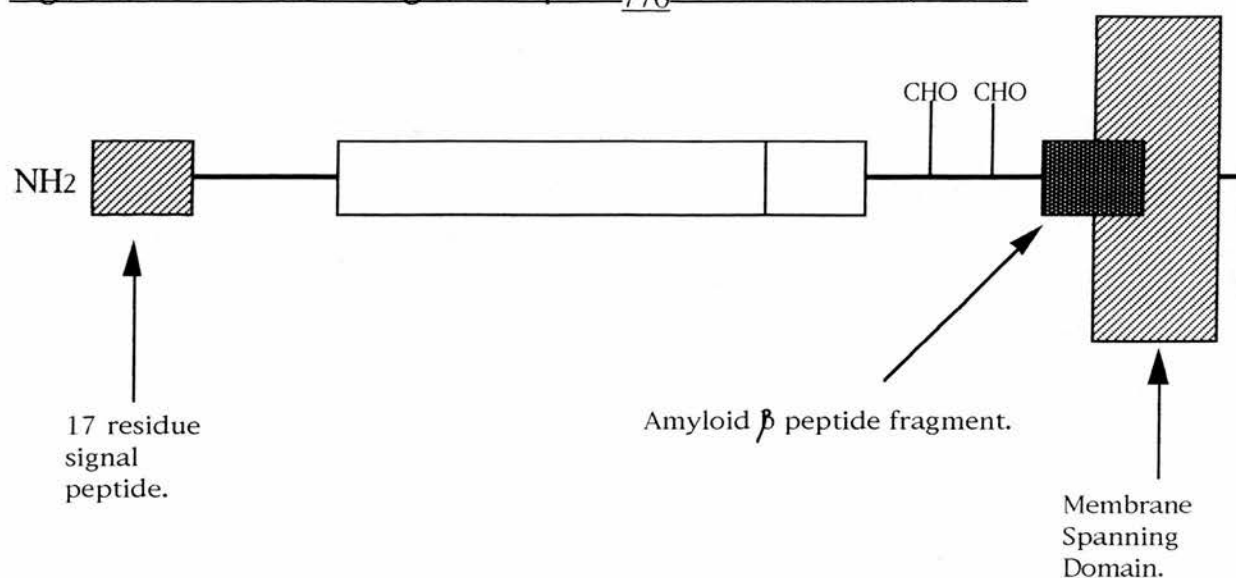
The APP gene is implicated in having a key role in the pathogenesis of AD. Also of note is that the phenotypes resulting from the mutations are varied, leading in the one case to a dementia and in the other to cerebral haemorrhage. This may raise an issue as to whether Alzheimer's should be separated from other neuropsychiatric phenotypes.

Figure 1, shows a schematic diagram of the primary structure of the β -amyloid precursor protein. The molecule depicted here, is the largest of the known APP transcripts, comprising 770 amino acids. Several regions of interest are indicated at their correct relative positions, such as a 17 residue signal peptide which occurs at the N-terminus, and two sites of glycosylation (CHO), found at residues 543 and 571 (CHO).

The amyloid β peptide ($A\beta$ P) fragment, is indicated by the dark box, and includes 28 residues just outside the

membrane plus the first 11-14 residues of the transmembrane domain.

Figure 1. Schematic Diagram of β APP₇₇₀. After Selkoe (1991).



Relation Between APP Mutations and APP Processing.

The relation of APP mutations to AD pathogenesis can be studied either *in vivo* by constructing transgenic animals, or *in vitro* by transfection experiments using either a mutated cDNA or a Yeast Artificial Chromosome (YAC) containing the mutated APP gene. Transgenic overexpression of one of the mutations in APP was achieved by Games et al (1995), showing age-linked cerebral deposition of β A4a is accompanied by pathology in mice.

cDNA transfection experiments have indicated that the AD related APP mutations at codons 670/671, 692 and 717 interfere with the normal processing of APP causing either an overproduction of β A4a or generating a longer β A4a that is more prone to aggregation.

The alteration of several gene products may underlie the progressive dysfunction and dystrophy of neurons and glia that occur in the limbic and association cortices and in certain subcortical nuclei that project to them. Attempts to place the

observed morphological and biochemical changes into a temporal sequence of pathogenesis is a challenge.

There is a marked decrease in choline acetyltransferase as well as many other transmitters, and numerous functional and anatomical classes of neurons are altered in AD. There are also the characteristic depositions, plaques and tangles, which are described below.

The neurofibrillary tangles, are fibrous deposits of pairs of 10 nm twisted filaments in neuronal cell bodies. They are associated with tau protein, certain forms of which appear to be abnormally phosphorylated. In addition they are often associated with ubiquitin. The tangles and tau can be seen as a nonspecific response by certain CNS neurons to a variety of insults.

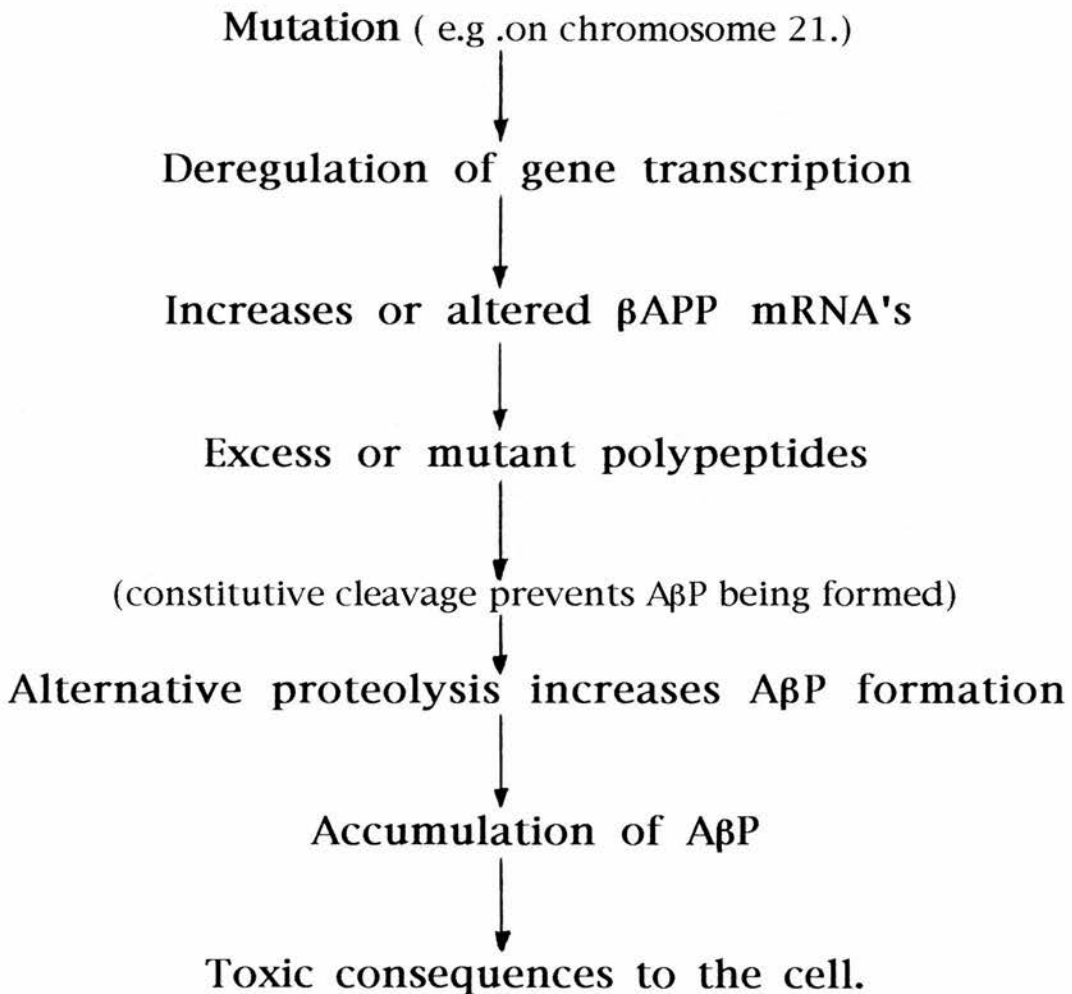
The plaques, consist of a central deposit of extracellular amyloid fibrils (unpaired and about 8 nm in diameter), surrounded by dystrophic neurites and activated microglia and fibrillary astrocytes. They are also present in cases of dementia associated with trisomy 21 and to a lesser extent also occur in normal aging. The fibrils closely resemble the biochemically diverse amyloid filaments that accumulate extracellularly in non-neural tissues, in a variety of unrelated systemic amyloidoses.

Amyloidoses, is a general term in pathology that designates diseases in which deposits of 5-10 nm proteinaceous fibrils (amyloid) accumulate progressively in the extracellular spaces of tissue and their vasculature. Filaments are usually composed of proteolytic fragments of normal or mutant gene products, but in each case the particular polypeptide varies. The amyloid fibrils under present discussion also occur in the walls of some cerebral and leptomeningeal blood vessels, in AD.

Glennner and Wong (1984), first reported the composition of amyloid filaments as being an amyloid β -protein ($A\beta$ P or $\beta A4a$). The initial cloning of $A\beta$ P cDNA's revealed it to be a proteolytic fragment of a 695 residue precursor protein, β APP, whose sequence predicted a glycosylated polypeptide spanning the membrane once near its c-terminus. The 39-42 residue $A\beta$ P region is shown in figure 1.

Other proteins in the β -amyloid deposit are of interest, since they may be crucial in the pathogenic process. α -1-antichymotrypsin (a serine protease inhibitor) and complement factors are present, suggesting that there is an inflammatory process occurring within the plaque. Also present are heparin sulfate proteoglycans and serum amyloid β component protein. The latter may be important in delaying the cells ability to digest amyloid fibrils. It is likely that other proteases and protease inhibitors will also be found in association.

Figure 2 shows a flow diagram of how mutation in APP leads to disturbance of proteolytic processing which leads to AD pathology.



β A4a: cause or effect?

Do the amorphous A β P deposits precede or follow the alterations in neuritic and glial and vascular cells and extracellular substances? The basis for the pro- and anti-amyloid factions is discussed in Marx (1993). There is in vitro evidence that people with a particular hereditary form of AD with a mutation in the β amyloid gene, had an increased amount of amyloid produced. It was a key issue as to whether intact and normal nerve cells in culture secreted β amyloid, or whether neurons had to be damaged to release it.

As stated above, the APP is inserted into the membrane of the cell and two thirds of the β amyloid sticks out, with the rest buried. Most of the extracellular part is clipped off by secretase which precludes β amyloid production. Other enzymes could cleave the molecule at different places, but as one end remains buried, it would be inaccessible to cutting enzymes unless the membrane were damaged. This would favour the reasoning that β amyloid is a by-product released by dying cells.

Evidence then appeared that the secretase was not the only way APP is broken down and alternative pathways in cell lysosomes contain the β amyloid molecule too. This could occur in healthy cells. Furthermore, β amyloid was also found in the CSF of AD and control cases.

Besides early onset FAD, two other diseases characterised by early and excessive A β P deposition have been linked to alterations of chromosome 21, namely Down's and HCHWA-Dutch, as described. Genetic defects on chromosome 21 can cause a form of FAD marked by early and severe A β P deposition. Some FAD gene defects may alter the regulation of β APP transcription resulting in the increased biosynthesis of one or more isoforms in selected cells or tissues and the presentation of an excess number of precursor molecules for proteolytic processing. In both FAD and Down's, some portion of these excess β APP molecules are not subjected to constitutive cleavage within the A β P region but undergo alternative proteolysis. Other mechanisms for enhanced A β P fragment production could be

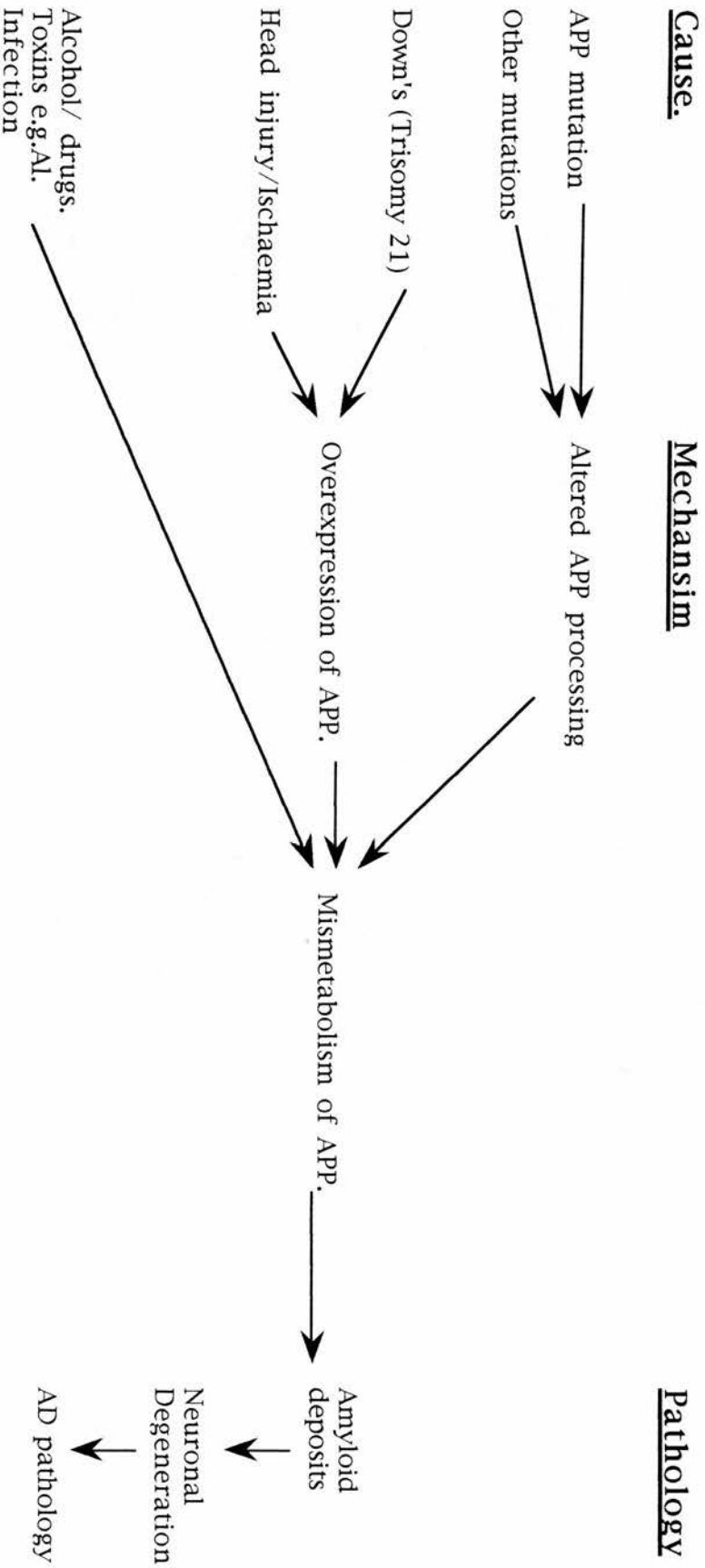
mutations altering the primary substrate, or by alternative splicing of the A β P, leading to different fragment lengths and altered susceptibility to deposition.

Altered regulation of the β APP gene, or other gene products modifying APP post translationally could result in A β P deposition. For example, by reduced secretase or increased protease activity.

The result of the multiple cellular and molecular changes that are brought about by augmented A β P deposition and plaque maturation is the progressive dysfunction and death of many neurons (including profound synaptic loss). The selective vulnerability of neurons has been difficult to explain. The biochemical reasons for greater or lesser vascular deposition of A β P among AD patients and between patients with AD and HCHWA-Dutch, is also required.

Therapeutic approaches will be the result of the understanding of detailed molecular mechanisms, see figure 3 overleaf.

The next figure is a schematic diagram of the molecular pathology of Alzheimer's Disease, with possible indicators of the points for therapeutic intervention. After Royston, 1992.



Chromosome 14.

Because most early onset AD does not cosegregate with C21 and mutations in the APP gene are not found in all cases, other chromosomes have been tested. This led to the identification of a second and more important locus at 14q24.3.

In 1992, four groups found linkage of Alzheimer's Disease with a new locus in the middle of the long arm of chromosome 14: Schellenberg et al (1992); Mullan et al (1992b); St.George-Hyslop et al (1992); and Van Broeckhoven et al (1992).

The linkage was to a site proximal to a serine protease inhibitor, α 1-antichymotrypsin (ACT), and distal to the protease cathepsin G. Two genes on the YAC contig were also of potential interest, the cellular oncogene c-fos and the transforming growth factor b 3 subunit (TFGB3). c-fos was a potential candidate as the APP gene promoter contains a binding site for the transcriptional activating complex of c-fos, but infact it turned out not to be relevant. Another candidate included the heat shock protein HSPA2, which like c-fos responds to neuronal stress and could in theory cause over-expression of APP.

Sherrington et al (1995), published more findings about the gene on C14. This appears to be responsible for 70-80% of early onset familial cases of AD, comprising up to 10% of cases in total. The group began by collecting pedigrees of early onset Alzheimer prone families, of diverse ethnic origin, inwhich the disease was linked to C14. Using positional cloning, they searched the 14q24.3 region for DNA markers near the gene that would help narrow the search area, by defining regions of interest. Having identified two stretches likely to carry the gene, they used direct hybridization with complementary DNA to recover transcribed sequences from these regions, including some cDNA's with complex and conserved structures that recommended them as candidate genes. By searching for sequence differences in these genes between affected members of 6 tightly linked pedigrees and a group of controls, they came upon S182 in which 5 different nucleotide changes (that altered the predicted amino acid sequence) occurred only in family members affected with

AD. The evidence was strong that this was a true finding, since the mutations were absent in the controls and the substitutions occurred in highly conserved domains and appeared unchanged in the murine homologue.

The primary structure of the longest open reading frame predicted a 467 amino acid protein in both man and mouse. S182 contains 7 hydrophobic, putatively membrane spanning domains. It may therefore be a protein embedded in a cell membrane, which could be a receptor, channel protein or structural membrane polypeptide i.e. involved in transport, signal transduction or ion transport. It has similarity with the 465 residue protein SPE-4 from the nematode worm *Caenorhabditis Elegans*, which has the function of transporting protein between cellular compartments during the formation of sperm, see Harrison (1995a). Levitan and Greenwald (1995), investigated the true function of S182 and found the facilitation of lin-12-mediated intercellular signalling, specifying cell fate, by the *C. elegans* gene *sel-12*. This gene encodes a protein, similar to that encoded by the S182 Alzheimer disease gene.

How could this link in with the β amyloid hypothesis? The families with these mutations are developing plaques and tangles about a decade earlier than those individuals with β APP mutations. The $A\beta$ peptide (the principal component of the plaques) is secreted by β APP expressing cells (e.g. neurons, glia and endothelial cells). Normally the APP is carried by vesicles to the cell membrane where it is clipped in the middle. The formation of $A\beta$ occurs in mildly acidic membrane vesicles, see Selkoe (1994). Even in normal brains, it has been shown that some APP in lysosomes is clipped to form β amyloid. A mutation in the APP gene, or a change in the transport of the molecule could tip the balance in favour of overproduction or amyloidogenesis. Thus, mutations in S182, or an alteration in its hypothetical role in membrane trafficking intermediaries, might allow β APP to stay longer in amyloidogenic (or less in non-amyloidogenic) organelles, and so enhance $A\beta$ production. There

is evidence from Querfurth et al (1995), that increased A β secretion may occur in the cells of the C14 linked cases.

By May 1996, at the Lancet Conference on the Challenge of the Dementias, over 28 mutations in the Presenilin I gene had been reported, the majority being missense mutations especially in exons 5 and 8. For example, Clark et al (1995), reported on the structure of the S182 gene and six novel mutations, and Cruts et al (1995), described two more novel mutations. Wragg et al (1996), comment that Presenilin I accounted for about half as much of the risk for late onset Alzheimer's Disease as did ApoE ϵ 4, in their series.

Chromosome 1.

Apart from the chromosome 21 and 14 loci, a third autosomal dominant locus was localized to chromosome 1 (1q31-42), as reported by Levy-Lahad et al (1995 a & b). Harrison (1995b), also comments on the new gene. This gene was responsible for AD in the Volga German kindreds who the group studied, with mean onset ages between 50.2 and 64.8 years. The gene appears to be relevant in both early and late onset forms of the disease. The Volga Germans emigrated from the Hesse region of Germany, to Russia in 1763 - 1765. They established 60 farming villages on the banks of the Volga river and remained culturally distinct.

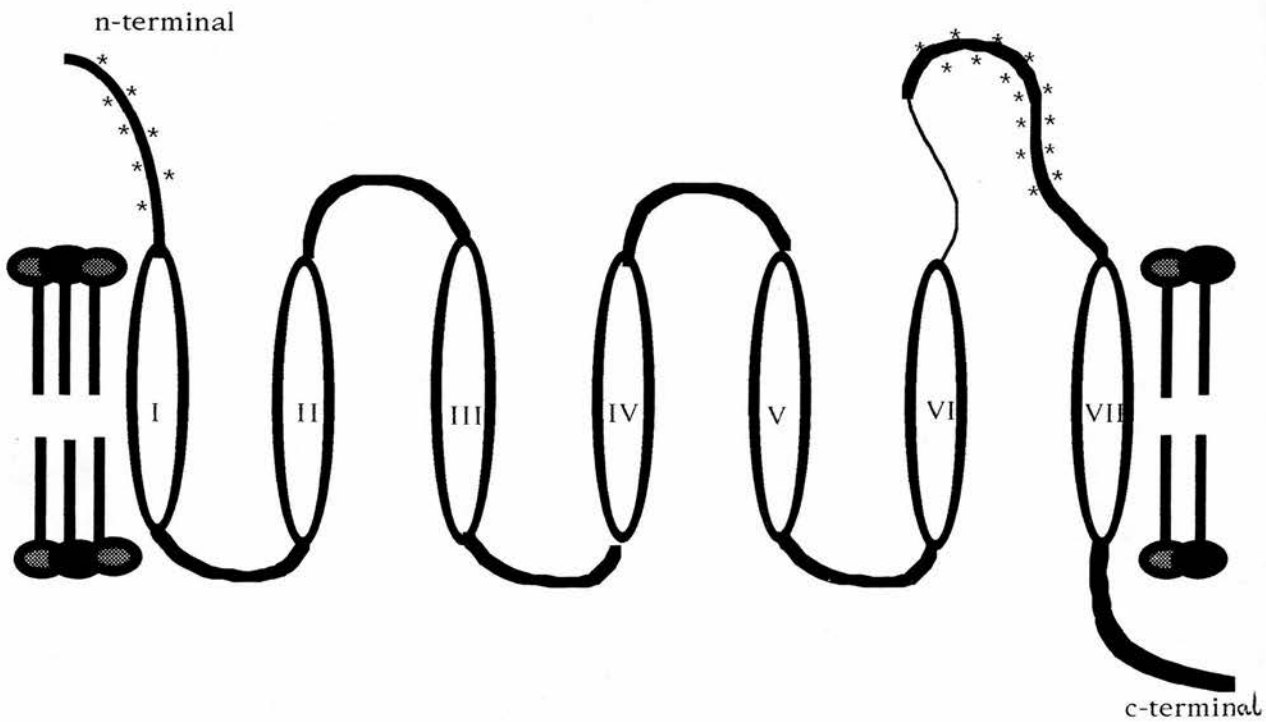
One strategy to isolate the responsible gene, was to test for mutations in candidate genes. (The other used YACs to clone the region as defined by linkage analysis). The first candidate gene was 1q31 encoding Cathepsin E, a protease present in elevated amounts in the brains of AD patients and capable of cleaving APP at the β -secretase site. This was not apparently altered in affected individuals. The second candidate was a homologue to S182, the recently cloned C14 gene. The entire coding region of this so-called F-T03796 gene was screened for mutations, in affected individuals from the kindred, and the mutation was found at codon 141, substituting isoleucine for asparagine. The amino acid sequence predicted by F-T03796

exhibits about 67% homology with the S182 sequence and to a similar degree with the mouse S182. The three mammalian genes are similar to the *Caenorhabditis elegans* genes as described above.




The codon 141 mutation in this gene and some of the reported mutations in S182, occur in sequences conserved between the chromosome 1, and human and mouse S182 genes. Hydropathy plots predict the encoded protein to have 7 transmembrane domains and is referred to as STM2 (the second, seven-transmembrane gene associated with AD). Within the putative transmembrane domains the sequence similarity between STM2 and S182 is 84%. The mutations may adversely affect the insertion or anchoring of these proteins in the membrane. Rogaev et al (1995), reported the cloning of the E5-1 gene. Analysis of the nucleotide sequence in the ORF, revealed two missense substitutions at conserved amino acid residues, in affected members of pedigrees with a form of Familial Alzheimer's Disease. They found that these individuals had a later age of onset of dementia, between 50-70 rather than 30-60 years old.

Although the normal cellular functions of STM2 (E5-1 or Presenilin II) and S182 (or Presenilin I) are unknown, if they are functionally similar to those of *spe4*, they may be involved in the cytoplasmic partitioning of proteins. Mutations in them could alter the intracellular protein trafficking of APP and ultimately lead to altered APP processing and increased production of A β . They may also function as G protein-coupled receptors or ion channels. They may be different subunits of the same receptor complex. Similarity to *sel-12* would indicate a possible function of mediating intercellular signals, and cell fate decisions important in neurogenesis.

Figure 4, shows the simplified features of the seven transmembrane proteins (STM's), based on STM-2. It is an integral membrane protein with 7 membrane spanning domains and a large exposed loop between the 6th and 7th transmembrane domains. After Rogaev et al (1995).



Key:

-  alternatively spliced domain.
-  hydrophilic acidic domains, divergent sequences.
-  sequences conserved between Presenilin I and II.

Chromosome 19.

In the section earlier on the genetics of vascular dementia, chromosome 19 has already been mentioned.

The identification of Apolipoprotein E ϵ 4 (APOE ϵ 4) as a genetic risk factor in Alzheimer's Disease, is a classic example of how biological studies of β A4a associated proteins can lead to the identification of candidate genes in AD.

The long arm of C19 was first implicated in late onset AD by Schellenberg et al (1987), who found an association between familial AD and the allele at the polymorphic Apolipoprotein CII (ApoCII) locus. This was confirmed by Pericak-Vance et al (1991).

Strittmatter et al (1993), reported that the frequency of the APOE ϵ 4 was increased in late onset AD patients (50%) compared with controls (16%). The APOE and ApoCII genes are part of a gene cluster 40 kB apart.

Subsequent studies confirmed that sporadic and familial late-onset AD are associated with APOE ϵ 4, see Corder et al (1993) and Chartier-Harlin et al (1994). Corder et al (1993), demonstrated that the APOE ϵ 4 has a dose effect on the risk of AD, age of onset and survival, in both familial and sporadic late-onset forms of the disease. The risk for Alzheimer's Disease increased from 20% to 90%, and mean age at onset decreased from 84 to 68 years with an increasing number of APOE ϵ 4 alleles, in 42 families with late onset AD. One APOE ϵ 4 increased the risk of late onset AD three fold compared with those with no APOE ϵ 4 alleles. APOE ϵ 4/APOE ϵ 4 homozygotes had an eight fold increased risk. The effect was strong enough that 80% of homozygotes would develop AD by the age of 80. Saunders et al (1993), also demonstrated how APOE ϵ 4 is associated with late-onset familial and sporadic Alzheimer's Disease, in comparison with the general population.

The strong association between APOE ϵ 4 dose and susceptibility to late onset AD suggests that the gene plays a causal role in the pathogenesis of AD. (The alternative would be that the effect was of linkage disequilibrium, with the pathogenic

allele of a nearby gene.) However, late onset AD occurs with no APOE ϵ 4 alleles, so either AD is polygenic, with APOE ϵ 4 a major effect gene, or AD is genetically heterogeneous.

APOE ϵ 4 has also emerged as a risk factor for early onset AD, see Okuizumi et al (1994). Van Duijn et al (1994), showed an increased risk of early-onset Alzheimer's Disease, for APOE ϵ 4 heterozygotes, only in subjects with a positive family history. Norman et al (1995), have shown that APOE ϵ 4 is enriched in presenile cases but find no evidence that it affects the rate of progress of the disease, although the degree of pathology may be increased. The clinical information came retrospectively, from case notes and informants.

It has also been suggested that by gene-gene interaction of the APOE ϵ 4 and APP loci, the presence of APOE ϵ 4 reduces the age of onset in patients with APP mutations, see St. George Hyslop et al (1994). In familial AD the onset age respectively decreased or increased when APOE ϵ 4 or APOE ϵ 2 alleles were present, and a similar effect was observed in AD families segregating the APP670/671 or APP717 mutations. In the HCHWA-Dutch families and the AD/CAA family, segregating respectively the APP693 and APP 692 mutations, no effect of the APOE genotype was detected on the clinical expression of the disease. No modulation of age of onset is detected in the C14 linked AD families. A potential gene-gene interaction between APOE ϵ 4 and ACT has been reported by Kamboh et al (1995).

Recent studies suggest that APOE ϵ 2 is associated with a protective effect in late onset AD, see Chartier-Harlin et al (1994), Corder et al (1994), and Rubinsztein et al (1994). The protective effect appears to be independent of the over-representation of APOE ϵ 4 in late onset cases.

Extending APOE ϵ 4 testing to other neurodegenerative conditions.

Alzheimer's, Parkinson's and Lewy Body Disease.

There is a debate as to the risks conferred in other conditions such as Parkinson's Disease (PD). Arai et al (1994),

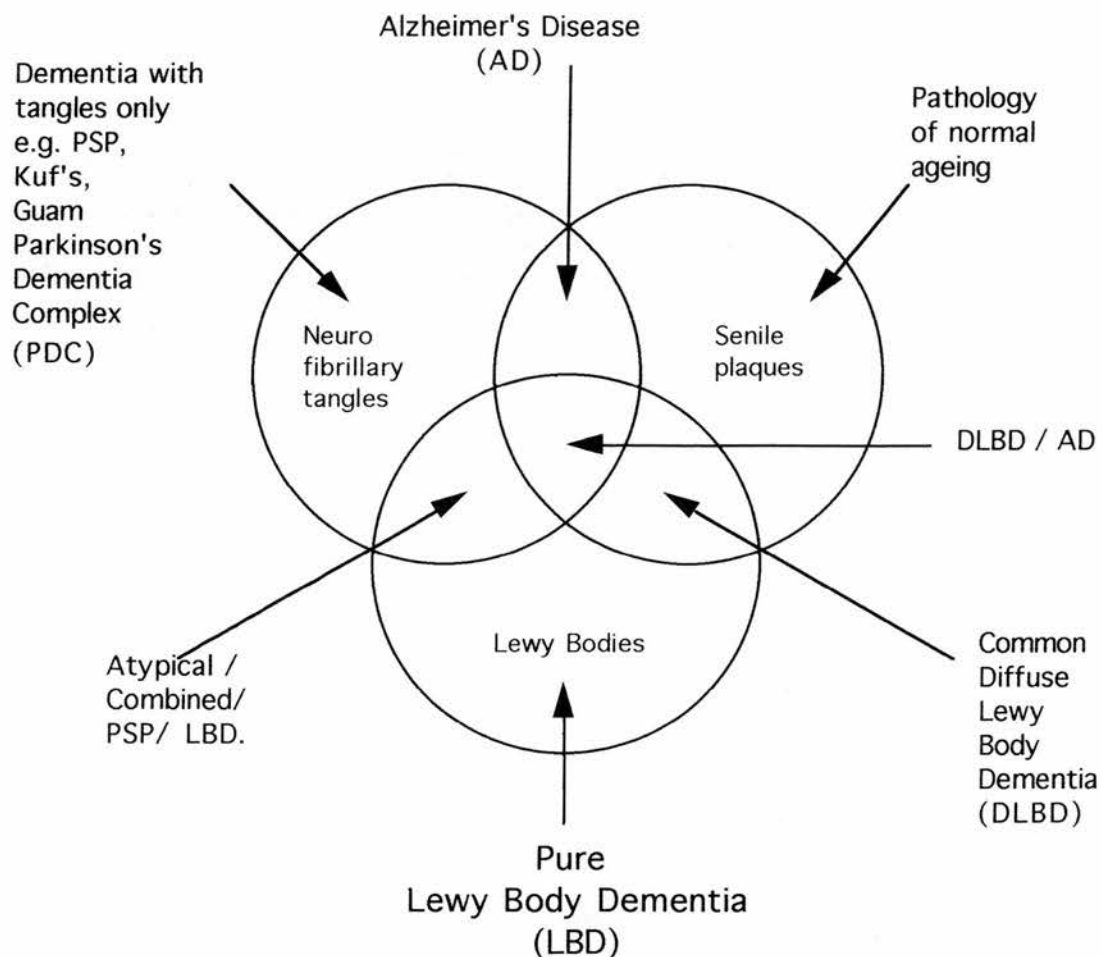
demonstrated that APOE ϵ 4 is a risk factor contributing to the emergence of Alzheimer's Disease type dementia in Parkinson's Disease. The results were of an increase frequency of APOE ϵ 4 in those patients with Parkinson's Disease and dementia, but not PD alone. However the work of Marder et al (1994), did not substantiate this. Using different criteria for dementia, they found no association of the APOE ϵ 4 allele with patients with dementia in Parkinson's Disease. Benjamin et al (1994), found the frequency of APOE ϵ 4 greater in both AD and Lewy Body Dementia but as shown previously, not in Parkinson's Disease. Hansen et al (1994), suggest that APOE ϵ 4 can account for much of the overlap between AD and LBD.

APOE ϵ 4 is therefore a definite risk factor for late-onset, familial and sporadic Alzheimer's Disease and also cortical Lewy Body Disease. This is further substantiated by the work of Pickering-Brown et al (1994) and Galasko et al (1994). The evidence for its association with Parkinson's Disease, is less certain. But it is likely that it is at least one of the determinants as to whether cortical dementia occurs in patients with Lewy Body Disease.

McKeith (1995) points out the usefulness of investigating individuals with Lewy Body pathology, in order to clarify the overlap between Alzheimer's Disease and Parkinson's Disease, and to define the aetiology of the dementia in these conditions. Clinically these issues are unclear. Hughes et al (1992), looked at the clinico-pathological details of 100 cases of idiopathic Parkinson's disease. They questioned the concept of Parkinson's being a distinct morbid entity.

The Venn Diagram in figure 5, shows the overlap between the different pathologies (tangles, plaques and Lewy Bodies). Chromosome 22 has been implicated as relevant to the dementias characterised by tangle pathology.

Figure 5: Overlap Between Plaques, Tangles and Lewy Body Pathology.



There is an overlap in the pathologies and molecular lesions, for example as demonstrated by Lantos et al (1992), that Lewy Bodies were found in cases where the 717 APP mutation was present. Furthermore, the cytochrome P450 debrisoquine 4-hydroxylase mutant B allele (CYP2D6B), has been found to be a susceptibility gene for Parkinson's Disease. Saitoh et al (1995), found that CYP2D6B was over-represented in the Lewy Body Variant of Alzheimer's Disease, suggesting that the gene may be involved in cognitive impairment in Parkinson's Disease and the Lewy Body Variant of Alzheimer's Disease. The interaction of the APOE ϵ 4 and CYP genetic traits at the molecular and cellular levels may result in the altered expression of the two genetic traits.

Chen et al (1995), found the association of the CYP2D6B mutant allele with Lewy Body formation in both Parkinson's Disease and the Lewy Body Variant of Alzheimer's Disease and with the milder synaptic pathology in pure Alzheimer's Disease without Lewy Bodies. They suggested that depending on the contribution of other genetic and environmental factors, this mutant allele may be involved with different aspects of neurodegeneration.

Other.

Rubinsztein et al (1994), looked at cases of Multiple Sclerosis, Parkinson's Disease, Schwannomas and late onset Alzheimer's Disease. This was to test the hypothesis that if apolipoprotein E mediated transport of lipids is the rate limiting step in the process of the response to central nervous system injury, then the functional differences between the alleles would be associated with varying predispositions to neurodegenerative and demyelinating diseases. They postulated that if apolipoprotein mediates cholesterol uptake, and limits neuronal growth, then the APOE ϵ 2 allele would slow CNS tumour growth. The group simply confirmed APOE ϵ 4 as a risk factor for Alzheimer's Disease, and APOE ϵ 2 as a factor reducing risk.

Amouyel et al (1994), looked at cases of Creutzfeldt Jacob Disease, and found that the APOE ϵ 4 allele was a risk factor for the disease, in both definite and probable cases, and for patients with and without prion protein mutations. In affected subjects, the APOE ϵ 2 allele delayed the occurrence of death, independently of other known mutations influencing the phenotype of the disease. They comment that these effects on neurodegenerative disease associated with APOE alleles suggest a strong involvement of the APOE locus in brain metabolism.

APOE ϵ 4 has also been associated with Multi-infarct dementia, see Shimano et al (1989), and Noguchi and Murakami (1993). This may be a direct causal effect as the APOE ϵ 4 would lead to increased low density lipoprotein (LDL) Cholesterol levels and lead to an increased risk of thrombosis.

The APOE allele system has also been investigated in Down's Syndrome. Royston et al (1994), found that the APOE ϵ 2 allele promoted longevity and protected Down's Syndrome adults from developing dementia. Avramopoulos et al (1996), has looked at the distribution of APOE alleles in the parents of Down's Syndrome children. They found that APOE ϵ 4 may be a risk factor for meiosis II non-disjunction in young mothers.

The importance of the APOE ϵ 4 allele in predicting the outcome after head injury has also been of interest. Roberts et al (1991), demonstrated the deposition of β A4 in the brain after head injury. More recently, Nicoll et al (1995), showed that APOE ϵ 4 is associated with the deposition of A β P following head injury. Alberts et al (1995), demonstrated a strong association between the APOE ϵ 4 gene and a poor neurological outcome after intracranial haemorrhage, and Sorbi et al (1995), confirmed and extended in vivo, the possible role of APOE genotype in determining a genetic susceptibility on the effect of head injury.

Henderson et al (1995), found that APOE ϵ 4 was a risk factor but not sufficient (even in the homozygous form) to cause cognitive decline and ultimately a diagnosis of dementia of the Alzheimer type. In this study, 638 people were interviewed and followed up. Those with one or two APOE ϵ 4 alleles were found to be more likely to have a family history of Alzheimer's Disease. Petersen et al (1995), showed APOE status to be a predictor of the development of Alzheimer's Disease in memory-impaired individuals.

Mechanism Of Action.

The APOE gene lies in the apolipoprotein cluster in chromosome 19q13.2, and APOE plays a role in nerve development and repair. The three common alleles APOE ϵ 2, APOE ϵ 3, APOE ϵ 4 have a major impact on the total and LDL-Cholesterol levels in the serum and are highly correlated with the risk of atherosclerosis and cardiovascular disease.

Apolipoprotein E is expressed in large quantities in the brain, where it binds to β -amyloid with an affinity that is highest

for the APOE ϵ 4 isozyme. Wisniewski et al (1993), suggested it may act as a pathological chaperone that binds to soluble β amyloid and promotes a conformational change leading to fibril formation by reducing the amyloid solubility. This in turn would predispose to deposition of diffuse plaques. However, this may be a secondary phenomena.

Diedrich et al (1991), have shown that APOE mRNA and protein expression are increased in AD. So, deposition maybe the consequence of APOE ϵ 4 acting elsewhere, such as receptor mediated endocytosis of APOE- β amyloid complexes, followed by their dependent dissociation in primary lysosomes. APOE maybe pathogenic intracellularly, as it is associated with tangles. APOE ϵ 4 does not bind to tau, and microtubules are stabilised by tau binding. It could be that abnormal tau phosphorylation reduces the microtubule stability, and leads to degeneration and cell death. APOE ϵ 4 may enhance this.

The importance of APOE ϵ 4 is that it represents the first identified molecular genetic risk factor for common Alzheimer's Disease. Results suggest that multiple genes may contribute to an increased susceptibility, but that one alone would not be sufficient to cause the disease.

Rubinsztein (1995), has reviewed the role of apolipoprotein E in lipoprotein metabolism, neuronal growth and repair and as a risk factor for AD.

Other Candidate Genes.

Synuclein Proteins.

Synuclein/non-amyloid β component of Alzheimer's Disease amyloid (NAC) proteins are found in presynaptic cholinergic nerve terminals that degenerate early in Alzheimer's Disease, and are found closely linked to β -amyloid fibrils in senile plaques.

Synuclein /NAC proteins provide a potential molecular link between the degeneration of cholinergic nerve terminals and the formation of plaques, and might have a primary role in their

development. Synuclein proteins have been reviewed in an article by Brookes and St.Clair (1994). Apart from synuclein α or NACP (NAC precursor), synuclein β or gamma synuclein, maps to chromosome 17 and has been implicated in the genetic aetiology of rare frontal lobe degenerating conditions, such as Steele-Richardson Syndrome (SRO).

A cDNA was cloned for an unrecognised component of AD amyloid deposits, NAC, from a precursor NACP, see Ueda et al (1993). Immunochemical analyses of AD brains (with antibodies raised against two separate fragments of the NAC peptide), showed staining of amyloid on diffuse primitive and mature plaques, as well as on cerebral blood vessels. Electron microscopy reveals localisation of NAC peptide specifically on amyloid fibrils, and therefore differs from other plaque components where co-association with amyloid is only demonstrable with the light microscope. This suggests that NAC-peptide and amyloid are very tightly linked. Yoshimoto et al (1995), suggest that NACP stimulates the aggregation of the amyloid.

The match with rat synuclein revealed 90% homology, and the proteins translated were 95% identical. Thus the genes are equivalent within different species. The gene is encoded on chromosome 4, and exists as a potential candidate in the aetiology of Alzheimer's Disease.

Synuclein was first isolated from the cholinergic-rich synapses of Torpedo fish, and the rat gene was subsequently cloned. The expression of the latter mirrors the distribution of typical AD pathology. The protein appears to be located at the synaptic junction between two main types of neurons implicated in AD; the choline acetyl transferase (ChAT) positive neocortically projecting magnocellular cholinergic neurones of the nucleus Basalis of Meynert and cortical pyramidal neurones containing muscarinic receptors that use phospholipase C as a second messenger. Bowen et al (1994), suggested that disturbed cholinergic transmission might encourage the deposition of amyloid plaques, and the function of synuclein/NAC might therefore provide a crucial molecular link into this process. Being

presynaptic, it may be involved in nerve terminal degeneration and promote amyloid deposition in a variety of ways. Perhaps certain isoforms exist that confer an increased susceptibility to AD by such processes.

Mitochondrial Genes.

Details of the nuclear genes encoding enzymes of oxidative phosphorylation (OxPhos) and the evaluation of their possible involvement in human inherited dementia, is given by Wallace (1992 a & b).

A number of disorders of Ox Phos are due to mutations in the Electron Transport Chain (ETC) enzyme subunits, encoded by the mitochondrial genome. Dementia features as a symptom in many of these disorders and the disorders possess multiple overlapping pathologies. The activity of the Ox Phos cycle varies in different tissues, with myoblasts and neurones requiring the greatest oxygen supply. The precise defect which results, is reflected in the severity and specific pathology in each tissue. Considerable evidence now suggests that mitochondrial defects are relevant to the aetiology of AD and PD, in which brain pathology is the primary abnormality. Other factors, both genetic and environmental, are presumably involved in the precipitation of neurological symptoms. Other features of mitochondrial disorders are the occurrence of minor symptoms, such as widespread optic nerve degeneration, and the early mitochondrial changes in frontal cortex dendrites in AD.

The enzyme components for Ox Phos are multi-subunit complexes in the inner mitochondrial membrane, numbered I to V, as well as adenine dinucleotide translocase, and the ETC itself. 65 of the 78 enzyme subunits are encoded by nuclear DNA (nDNA). Of the nDNA components, less than a half have been cloned. The nuclear sequences comprise a complex family of genes and pseudogenes, about which relatively little is currently known.

Mitochondrial DNA (mtDNA) has been fully sequenced, as the mitochondrial genome is relatively small. It is complex, in

part due to the fact that it has a high mutation rate. The mtDNA content of a cell can comprise various different genomes and the content of any tissue will be of a mixed population of sequences, a phenomenon known as heteroplasmy. The accumulation of abnormal mtDNA with ageing reflects the reaction of free radicals with mitochondrial nucleic acid. When mutant mtDNA's are inherited, and individual starts with less 'reserve capacity' and is therefore more vulnerable to this progressive decline.

Parker (1992), demonstrated cytochrome oxidase deficiency in Alzheimer's Disease. Soong et al (1992), investigated the levels of a specific mitochondrial DNA deletion measured in twelve different brain regions of adults. Striking variation among anatomical locations was found. The authors suggest that this represents the tip of an iceberg of the spectrum of somatic mutations produced by oxidative damage. Corral-Debrinski et al (1992), examined the role of somatic mitochondrial DNA (mtDNA) mutations in human ageing by quantifying the accumulation of a common nucleotide pair deletion in various parts of the brain. They suggested that somatic mtDNA deletions may contribute to the neurological impairment often associated with ageing. Lin et al (1992), did work on the detection of point mutations in codon 331 of mitochondrial DNA encoding part of a dehydrogenase enzyme, in the brains of people with Alzheimer's Disease. It is also of interest that the free oxygen radicals, which destroy neurons, are naturally defended against by Superoxide Dismutase (SOD). This enzyme is easily measurable in the red blood cells. The Cu/Zn Superoxide Dismutase (SOD-1) is encoded for on chromosome 21.

Hutchin et al (1995), investigated a mutation at point 4336 of the mitochondrial DNA, that was represented at an increased frequency in individuals with Alzheimer's Disease. Ikebe et al (1990), found an increase of deleted mitochondrial DNA in the striatum of patients with Parkinson's disease and senescence.

Does a relationship exist between mutations in the nuclear encoded OxPhos enzyme subunits and the inherited

dementias? The involvement of the nDNA in the aetiology of the disease has not yet been evaluated. But, as for the mtDNA, it is likely that nuclear gene mutations will cause disorders, perhaps with other groups of symptoms, including inherited dementia.

Trinucleotide Repeats. See discussion of Huntington's Disease.

ACT

The α 1-antichymotrypsin (ACT), a serine protease inhibitor, is encoded for on chromosome 14. It has been mentioned in the context of the history of the search for the locus of major importance on this chromosome, but actually lies far from it. Proteases and protease inhibitors may cause the abnormal cleavage of the APP molecule and are therefore candidate genes for contributing to the genetic understanding of Alzheimer's Disease. Kamboh et al (1995), present some of the background to α 1-antichymotrypsin as a candidate gene. Like apolipoprotein E, ACT binds to β -amyloid peptide (A β P) with high affinity in the filamentous deposits found in the AD brain and serves as a strong stimulating factor in the polymerization of A β P into amyloid filaments. In AD brains, ACT expression is enhanced, particularly in areas that develop amyloid plaques, suggesting it plays an important role in the pathogenesis of AD. The paper shows that a common polymorphism in the signal peptide of ACT, confers a significant risk for AD. It is also shown that the APOE ϵ 4 gene dose effect associated with AD risk, is significantly modified by the ACT polymorphism. This work identified a unique combination of ACT and APOE genotypes as a potential susceptibility marker for AD. It shows that ACT behaves as a modifier gene, altering the AD risk conventionally associated with the APOE ϵ 4 allele. Wragg et al (1996), report that this has not been repeated.

VDRL R.

Okuizumi et al (1995), reported on the genetic association of the Very Low Density Lipoprotein Receptor gene

(VLDL-R gene) with sporadic Alzheimer's Disease.

HLA-A2

Payami et al (1991), found that HLA-A2 or a closely linked gene confers a susceptibility to earlier-onset sporadic Alzheimer's Disease in men.

Summary.

How is it possible to study the majority of cases which do not show autosomal dominant transmission? An alternative to the linkage strategy is to study the affected families using non-parametric methods of linkage analysis such as the affected pedigree member method, and the extended sib-pair analysis. Neither require the mode of transmission to be specified.

Further candidate genes and loci are likely to be identified by studies of early-onset FAD families and looking at the genes involved in the expression and metabolism of APP.

A complimentary approach is to study individual genes for allelic association, looking either directly for functional mutations that determine disease susceptibility or for DNA polymorphisms that are in linkage disequilibrium with them. This can be done by studying multiply-affected families and population samples of unrelated patients and controls. This approach has the advantage of being able to detect genes of relatively small effect. It is especially applicable as candidate genes are identified and may prove more effective than linkage studies in allowing the identification of the contribution of genetic factors to the common form of AD.

The molecular genetic approach has been very successful in the analysis of early-onset FAD, as it is mainly inherited as an autosomal dominant disease, which allows the use of the positional cloning strategy. This is based on cosegregation analysis of the disease with polymorphic genetic markers of known chromosomal localization, in multiply affected families.

Once the chromosomal location is found, the gene is isolated based on its position, using gene cloning techniques.

Using this method it has been shown that in about 5% of the families with early onset FAD, the disease cosegregated with a mutation in the gene coding for the APP located at chromosome 21q21.2. The S182 gene, localized at chromosome 14q24.3 seems to be responsible for about 70% of early onset FAD, and of the remaining 25% of the families, a gene located on chromosome 1 is another cause. This gene has striking similarity to that on chromosome 14.

The APOE ϵ 4 is located at chromosome 19q13.2 and confers a higher genetic risk for the development of both late- and early-onset AD on individuals carrying 1 or 2 APOE ϵ 4 alleles. This effect starts from an age of at least 50 years old, and seems to influence other aspects of the course of the illness too.

Other autosomal dominant forms of AD await identification. How these and APOE ϵ 4 triggers or modifies the cascade need determining. The genetic factors in other familial and sporadic cases must be identified and other susceptibility genes are likely to exist. Environmental factors also need clarifying and therapeutic agents to halt the pathology need developing. A reliable diagnostic test may also become available as a result of the genetic understanding. With a more sophisticated classification of the dementias based on molecular subtypes, it may be possible to predict the clinical course of an individual's dementia.

It is likely that a combination of environmental factors and genetic loci (genetic risk factors) are interacting in the majority of cases of Alzheimer's Disease, to give rise to the condition.

Table 4 overleaf summarises the findings.

Table 4: FAD genes and other genetic influences.
After Barinaga (1995), and Eastwood et al (1996).

Chromosome	Gene Type	Age of Onset, yrs	% Cases (approx)		Protein Product
			Familial	All	
14 (28 known mutations)	Autosomal Dominant	30 - 55	70-80 (< 100 families)	5.0-10.0	S182, PS-I, Presenilin I
19 ($\epsilon 2, \epsilon 3, \epsilon 4$)	Risk Factor	40 - very old		40-50	ApoE
21 (4 known mutations)	Autosomal Dominant	40-65	2.0-3.0 (20 families)	< 1.0	APP
1 (3 known mutations)	Autosomal Dominant with variable penetrance	40 - 90	approx 20 (3 families)	approx 2.0 - 3.0	STM2, E5-1, PS-2, Presenilin II

The Implications Of Genetic Testing.

This topic is mentioned as it is of crucial importance in the context of the rapid development of the field. It is not however discussed in detail here.

Some of the issues involved in the genetic testing for Alzheimer's Disease are discussed in the paper by Lovestone and Harper (1994), and the clinical application of APOE testing is discussed by Roses (1994). The role of APOE testing in the differential diagnosis, rather than the prediction of Alzheimer's Disease is discussed by Roses (1995). Breitner (1996) and Tanzi et al (1996a), give guidance as to the clinical use of the test. Poirier et al (1995), commented on the use of the APOE status as a predictor of cholinergic deficits and treatment outcome in Alzheimer's Disease. Karlinsky et al (1994), present the discussion

of issues in molecular genetic testing of individuals with suspected early onset familial Alzheimer's Disease, based on the APP mutations.

As discussed, in a very small proportion of cases with clear familial patterns of inheritance, mutations in chromosome 21, 14 and 1 have been found to be responsible for the illness. For the small proportion of AD showing clear familial inheritance, with a recognisable genetic mutation, the presymptomatic testing of those at risk is feasible, but only in the framework of counselling and support.

Furthermore, the identification of APOE ϵ 4 as a genetic risk factor, raises the possibility of developing predictive or diagnostic tests. Such predictive testing raises ethical concerns, some of which apply to Huntington's Chorea. But for AD, the condition is more common, and there would be a greater demand for the service. Currently, it is only possible to indicate susceptibility by these tests.

Method :
IV. Ascertainment of the Sample.

The ethical approval for the study was obtained from the Lothian Research Ethics Sub-Committee for Psychiatry and Clinical Psychology, in July 1993.

The aim of the case ascertainment for the study, was to identify a population patients with presenile dementia, who had been identified by hospital contact, within a defined period of time, and who were currently alive, in the Lothian area. The issues relevant to the gaining of as complete a sample as possible, and some of the biases introduced in the study are discussed elsewhere. The method used in the study is described here.

The main method of case identification was to use the Lothian Psychiatric Case Register (LPCR), listing referrals to the Psychiatric Service, but in addition, the records of the Neurology Services were also checked. All the relevant International Classification of Diseases Ninth revision, ICD9, Mental Disorders (WHO, 1978) diagnostic codings were used, to ensure that as complete a search was done as possible. The Lothian Register covered the City, East and Mid Lothian and a separate search of records was also made at West Lothian. A map of the area is shown in the context of mainland Scotland, on the next page. The approximate population between the ages of 30 and 70 years old, is 350,000 (Census Lothian Region, 1991).

In addition, the responsible consultants in the service were all contacted to ensure no cases had been missed. Some cases were identified by word of mouth.

The sample came from those whose illness had been diagnosed between the years 1988 to the end of 1993, and who were 65 years of age or under at the time of diagnosis.

The cases were those with a first time diagnosis of presenile dementia, at contact or admission or discharge, for out-patients and in-patients. By looking at the dates of births, the people who were 65 or under at the time of diagnosis were identified.

Map of Mainland Scotland, to show the location of the Lothian Area.

W = West Lothian.

C = City of Edinburgh.

M = Mid Lothian.

E = East lothian.



It became apparent that, if the search were extended any further back than 1988, the majority of people under review had deceased; and so the cut-off year 1988 was kept.

Great care was taken to try to find as many of the case notes as possible. The Feighner Criteria for Organic Brain Syndrome, Feighner et al (1972), were applied to each set of case notes. The criteria are broad-based and are given here:

Feighner Criteria for Organic Brain Syndrome.

This diagnosis is made when either criterion A or criterion B is present.

A. Two of the following manifestations must be present. (In the presence of muteness the diagnosis must be deferred.)

- 1) Impairment of orientation.
- 2) Impairment of memory.
- 3) Deterioration of other intellectual functions.

B. This diagnosis is also made if the patient has at least one manifestation of (A) in addition to a known probable cause for organic brain syndrome.

Lothian Psychiatric Case Register Surveys.

Three separate searches of the register were in fact made. The first search included only a restricted group of diagnoses to be searched for. The second search requested other categories of diagnoses which the target group may have fallen into.

For out-patients, the following register diagnostic categories were included;

- 01, for senile dementia
- 02, for other dementia (e.g. Multi-infarct).

For in-patients, the following ICD9 codes were included:

- 290 Senile and presenile organic psychotic conditions.
- 290.0 Senile dementia, simple type.
- 290.1 Presenile dementia.
- 290.4 Arteriosclerotic dementia.

- 294 Other organic psychotic conditions (chronic).
 - 294.1 Dementia in conditions classified elsewhere.
 - 331 Other cerebral degenerations.
 - 331.0 Alzheimer's disease
 - 331.1 Pick's disease.
 - 331.5 Jakob-Creutzfeldt disease.
 - 333 Other extrapyramidal disease and abnormal movement disorders.
 - 333.4 Huntington's' Chorea.
- (This category was later excluded, see discussion in Method: Contact.)

From this search, a total of 200 cases were found to meet the Feighner criteria, on inspection of the case notes.

A third register search was made, of those cases who had an outpatient diagnosis of 03 (other organic condition), with a subsequent diagnosis of one of the diagnoses listed above. At the time of the diagnosis of dementia, the subject would have to be 65 or under.

From this, a further 14 cases were found, who met the Feighner criteria. In total, from the register searches, 214 cases were found.

Alcohol Related Diagnoses.

Because of the inclusion of cases of Alcohol-related dementia, a separate search of the register was made to find such cases. The diagnostic categories included were:

- 291 Alcoholic psychoses.
- 291.1 Korsakoff's psychosis, alcoholic.
- 291.2 Other alcoholic dementia.

From this a further 14 cases were found to meet the Feighner criteria, and in total, including the other searches, the number of Alcohol-related cases was 44.

Cases From The Neurology Department.

The neurology records were also inspected for the study. The benefits of the computerised Psychiatric Register became very apparent, as the neurology records were haphazard in comparison. Only the clear cases of dementia were kept. Cases of hydrocephalus, and alcoholics who had sustained head injuries, were excluded. It is of note that the neurology cases of Parkinson's did not necessarily state if there was associated dementia and hence many possible cases could have been excluded because of this.

There was some overlap in the referral between this group and the psychiatric service, particularly at the time when the Medical Research Council, Brain Metabolism Unit (MRC-BMU) had been involved in research into dementia.

A total of 15 cases were found from the neurology department who had not been discovered previously.

Other Ascertainment.

From the records kept at West Lothian , a further 13 cases were identified. Individual contact also brought 34 cases to the study. This seems rather a high figure, and illustrates the problems of any register being totally inclusive of all cases. During the course of the study, after the period of case ascertainment, various other cases were referred, but were not included.

At the stage of inspecting the case notes, further attrition of the sample became apparent, due to death, or to wrong diagnoses, or to being too old (or diagnosed pre-1988), or to being out of the area. Some of the wrong diagnoses, without documented cognitive decline, were: bipolar illness; depression; schizophrenia; learning disability; personality disorder; alcohol abuse. Some of the wrong diagnoses were due to miscoding, which is one of the inaccuracies arising from this method. Some of the case notes were not traceable.

Any cases excluded were double-checked and a note kept of why the exclusion had been made, including those found to have already deceased at this stage of the ascertainment. The case note inspection also provided the opportunity of collecting various items of data as described in the Method: Battery.

The results of the ascertainment are given in the Results. The further details of ascertainment, after contact was attempted, is given in the chapter on Method: Contact.

Further information not given here, is available on the data obtained from the register, for example a year by year breakdown of the ascertainment figures.

Method:

V. Choosing an Assessment Battery.

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In 1383, a lady called Emma De Beston, formerly of Cambridge, was assessed for idiocy, with the following assessment battery:

- I. In what town she was?
- II. How many husbands she had had?
- III. How many days there were in a week?
- IV. How many shillings there were in forty pence?
- V. If she would rather have 20 silver groats than forty pence?

Neugebauer (1978).

The assessment of impairment in dementia, has developed greatly since then.

The next step, having identified the target population as described, was to decide on a suitable assessment battery for the group. Currently, there are not any instruments in existence, designed specifically for younger dementia sufferers.

Furthermore, the group under study here, was diverse in aetiology and severity, so that the study covered a broad range of conditions and stages of disease. Several key points were

necessary to consider for the purpose of deciding what tests to use, both academic and pragmatic. The tests were chosen taking a balanced account of the need to provide scientific value and clinical usefulness. Another feature of this study was to provide an opportunity to revisit the subjects after a period of a year (between 12 and 15 months) and therefore to measure the rate of decline of each individual.

Some of the main issues to consider in choosing the testing instruments are given below in points 1-6. The assessment procedure is given in the Appendix: Protocol.

1. Appropriateness to subjects and relatives

The tests had to be applicable to the study population in terms of **brevity and acceptability**. Could the subjects concentrate long enough, and were the tests easy enough, to allow the majority of that population to attempt them? The population would cover a range of severities and so the instruments used would have to be as broad-based as possible, but not to the extent of losing valuable information, or only providing a superficial picture for an individual.

The interviews also depended on a reliable informant, and the questionnaires needed to be appropriate for them too. The emotional strain apparent at the interviews made this a very real consideration. The level of the informant's contact with the affected person was also of relevance, and their reliability was important for good data. For consistency, wherever possible, the same informant was used at both assessments.

2. Standardised and well used.

Needless to say, the tests used, ideally had good **validity and reliability data**, which whenever possible, was relevant for the age group being investigated. The use of recognised instruments also allows for comparisons to be made with other work in the field. It was also important to use a complete instrument rather than an edited version, even if

surplus information was gathered, it could be ignored at a later date.

3. Covering all areas of interest.

At the start of the study it was necessary to consider all the data that would be needed to provide a comprehensive picture of each individual. But constraints of time and logistics made it necessary to look carefully at the level of detail potentially collected, and balance the problem of too little detail on many things, or too much detail on a limited number of items.

The areas necessary to consider were:

- i) **A review of the case notes** to fill in details: addresses of informants and GP's; date of referral; diagnosis; investigation results; relevant history from notes.
- ii) **An interview with an informant**, for the demographic details of each subject: past health; family history; social history; and any other relevant information, including the history of the onset and progression of the subject's symptoms. Also a chance to assess the impact on the carer and the opportunity to ask about the supports used and available to each .
- iii) **The behavioural and psychopathological assessment** of the individual, with the information from an informant most closely involved with caring.
- iv) **A cognitive examination** of the subject including a measure of their previous IQ, when possible.
- v) **A physical examination** with particular emphasis on the nervous system and the assessment of any extrapyramidal features.
- vi) **The collection of a blood sample**, for immediate freezing and later DNA extraction.
- vii) **Discussion of Post-Mortem.**
- viii) **Application of diagnostic criteria** to the data in order to confirm case fulfillment.

Taken as a whole, the assessment would also provide a measure and description of the **general level of functioning** for each individual. From the evidence collected (including data

from all parts of the interview and including a historical perspective) a **diagnosis** would be possible. After the repetition of the tests, it would be possible to detect progressive deterioration. The **severity** of the condition could also be quantified.

The possibility of cases in which a global score would appear satisfactory but specific impairments be gross, would have to be identified.

4. Comparison after one year.

The study was designed to repeat the visit to each individual and their informant, after a year. The same instruments were used on both occasions, so a direct comparison could be made between the scores at each visit. The interval of a year allowed a sufficient time to elapse to see a deterioration, rather than pick up short-term fluctuations in an individual's state. The tests at the first assessment would provide a baseline of function so that subsequent **change could be measured**.

The study aimed to identify possible **predictors** of decline, and see if patterns emerge to suggest **subgroups** of early-onset dementia. There would be likely to be differences between the groups, such as between Alcohol-related dementia and Alzheimer's, but it would also be of great interest to see if differences occur within the Alzheimer population.

5. Time constraints of single investigator.

There were also **time constraints** from the interviewer's perspective. Apart from the issue of the amount to reasonably expect the interviewee to tolerate, there was the need for logistically making the visits of a reasonable length, so that the potential number of cases could be seen, by a single investigator, for the two assessments, during the time of the study. When the tests were familiar to the examiner, the first assessment took about three hours, and for the second, about two.

6. Location of the individual with dementia.

The group interviewed were in a variety of settings: home, nursing home and hospital. The instruments needed to be able to cover this diversity. However, the setting occasionally influenced the scoring. For example, wandering out of the building is prevented when the subject is on a locked ward, or spending time in bed during the day may not be part of the ward policy. A patient newly admitted to respite, may be apparently more disorientated initially, and this could involve increased episodes of incontinence and disorientation. The judgement of what would constitute constructive activity, especially within the hospital setting, becomes subjective.

Having reviewed the possible options as to the instruments available for the study, it was of great value to discuss the advantages and disadvantages of each with more experienced researchers in the field.

Based on the decisions using the advice from this, the pilot study was then carried out and minor adjustments made to the battery, following the lessons learnt.

Complete Assessment Schedules.

The CAMDEX.

The Cambridge Examination for Mental Disorders of the Elderly, CAMDEX, Roth et al (1986), is a single, standardised instrument with all the components needed to make an accurate clinical diagnosis of the most common forms of dementia. It aims to detect dementia at an early or mild stage, but covers a range of severity and different types of dementia. It also allows the detection of depressive and other psychiatric symptoms, and provides an overview of behavioural problems. It is designed for use with patients in a medical setting, and with general population samples of the elderly, in epidemiological enquiries. The CAMDEX can also be used to match criteria relevant for a differential diagnosis of dementia, and incorporates a number of

scales which yield estimates of the severity of dementia or cognitive impairment. Burns et al (1990b), used the informant interview and CAMCOG sections of the CAMDEX, in their study.

It provides a sensitive and considered interviewing style in a potentially upsetting area, as exemplified by the suggested introductions: for the informant interview:

"I'm going to ask some questions relating to changes in behaviour and character of....These changes don't always appear.. and may not be relevant to him/her. But we ask these of everybody because the replies might prove valuable in helping people who do have difficulties."

and for the CAMCOG:

"I am going to ask you some questions now which have to do with your memory and concentration. Some of them seem rather easy, others may be difficult, but we need to ask everyone the same questions."

Several parts of the CAMDEX were used for the study, these were:

- i) A structured interview with a relative or other informant to provide independent information regarding the subject's general mental functioning, previous history, everyday competence and adaptation, current symptoms and previous medical history. In the rare instances where no informant was available (and the degree of competent independent living cast some doubt on the diagnosis), the structured interview was done with the subject, incorporating questions regarding the previous personal and medical history and the family history.
- ii) A brief physical examination including a neurological examination.
- iii) A record of a range of laboratory findings and radiological investigations. Whenever available, blood count, levels of vitamin B12 and folate, urea and electrolytes and results of liver function tests, Venereal Disease Reference Laboratory tests (VDRL), skull

X-ray and computed tomographic (CT) scan, were recorded. (This was completed when the case notes were inspected.)

iv) The cognitive examination, referred to as the CAMCOG.

Apart from the CAMDEX, several other complete assessment batteries exist. Among them are the Consortium to Establish a Registry for Alzheimer's Disease, CERAD (Morris et al 1989). This includes an assessment for non-AD dementias: vascular; dementia with Parkinson's; dementia syndrome of Depression; Alcohol-related dementia; less common forms such as focal cortical syndromes e.g. Frontal Lobe Dementia, Progressive Aphasia, or Progressive Supranuclear Palsy (PSP).

The Geriatric Mental State Schedule (GMSS), Copeland et al (1976), is a full mental state examination, and can be combined together with the history and aetiology schedule (HAS), computerised as the AGE-CAT system (Dewey et al 1992). The Revised Elderly Persons Disability Scale, REPDS (Fleming and Bowles, 1994), covers an assessment of physical problems; self-help skills; confusion; behaviour; sociability; psychiatric observation; and nursing dependency. It is popular with nursing staff, and also useful in more general terms, in ward audit. Validity data exists for institutions only. Rosen et al (1984), reported on a new rating instrument, the Alzheimer Disease Assessment Scale, specifically designed to evaluate the severity of cognitive and non-cognitive behavioural dysfunctions in Alzheimer's Disease.

There are also scales developed for assessment in severe dementia, including The Guy's Advanced Dementia Schedule of Ward et al (1993), and that of Panisset et al (1994). Ritchie and Ledesert (1991), describe the development and validation of a scale for the assessment of intellectual functioning and adaptive behaviour in the severely dementing elderly. Albert and Cohen (1992), have also developed a reliable and valid test of cognitive function for severely cognitively impaired individuals. Saxton et al (1990), also developed a neuropsychological battery for severely impaired individuals, covering a range of functioning in

fundamental cognitive abilities, such as nonverbal social behaviour, simple matching tasks and colour identification.

In the next four sub-sections of this chapter, the areas of review covered in the assessment are discussed in more detail.

- i) Demographic data.
- ii) Behavioural and Psychopathological rating scales
- iii) Neurocognitive testing.
- iv) Neurological assessment.

In each, some of the different options available are discussed and reasons given for the eventual choice. Specific problems and shortcomings became apparent gradually during the time of the study, and are discussed in the next chapter.

i) Demographic data.

Section H of the CAMDEX schedule was the most obvious choice for the basis of collection of demographic data. It comprises of a structured interview, in the absence of the subject, with a relative or carer who knows the subject well. The interview should be face to face whenever possible, but satisfactory information can be obtained by telephone interviews. The nature of the interview, relationship of the informant to the subject, and a rough idea of how often they see the subject, are all coded. Any personality change, difficulty in functioning in everyday life, or indications of cognitive difficulty observed by the informant are noted. Items which permit the Dementia Scale of Blessed et al (1968), to be scored are incorporated in this section. Questions referable to the presence or absence of depressive or paranoid phenomenology, are included. A history of the onset of the illness, family history and past history are investigated. The items referring to everyday activities are of interest in the assessment of behavioural problems too, and the enquiry into depressed mood complements the Cornell scale, as discussed later.

In the CAMDEX interview, the family history of Down's syndrome and leukaemia, amongst other conditions, are enquired into. This is because of the evidence available at the time the interview was compiled on the association, see Heston and Matri (1977). Another schema for taking a family history was used by Breitner and Folstein (1984). The reliability of the family history method in genetic studies of Alzheimer's Disease and Related dementias is discussed by Silverman et al (1986). But the more widely recognised and used CAMDEX H informant interview was used. For example, the question relating to a family history of dementia is: "*Did any of his/her relatives have trouble with memory, or get very confused and have to go into a home to be looked after?*" The response is recorded for female relatives (mother, sisters and daughters) and male relatives (fathers, brothers and sons). Aswell as taking the data from the CAMDEX, a family tree was drawn for each individual to make an additional check on any missed features of interest, in more distant family members. No further verification of this information was made.

In addition to this informant interview, there were several other details which seemed important to gather. This gave rise to the 'data sheet' which included the following sections:

A. The onset and presenting symptoms.

Because of the often insidious onset of dementia (as discussed in the Introduction: Epidemiological Issues, it is of interest to know what the first signs of something being wrong were. But the information is retrospective and to some extent subjective. This question was simplified to four main areas of functioning: memory loss and disorientation; mood and personality change; movement disorder; and other. In a paper by Chenoweth et al (1986), the issue of early symptom recognition was investigated in much greater detail than was possible in this study. Most of their 289 family informants, described several ways inwhich their relative experienced memory impairment and difficulty in performing the usual activities of daily life.

B. Current medical health and medications, and additional symptoms

Although the CAMDEX informant interview deals with some questions regarding cardiovascular history, the possibility of a more detailed series of questions was explored. This however was not pursued but note taken that there was no way of standardising the data. For example, for evidence of a past MI, ECG evidence and a fuller description of the symptoms would be required.

Some additional symptoms such as headaches, dizziness, and myoclonic jerks, were also included.

C. Additional details of alcohol consumption, past and present.

This was included in the hope that it would provide a clearer picture of heavy alcohol consumption. Infact it did not really help to achieve this.

Brandt et al (1983), in their study of cognitive loss and recovery in long-term alcohol abusers, give a guide to estimated excessive past drinking: with at least a 10 year history of daily alcohol consumption and abstinence at least one month, but no more than 59 months at the time of testing. Consuming a minimum of 6 drinks daily (85 mls alcohol) and an average of 12 drinks daily (170 mls). Another definition is given by Rosen (1993), who defined alcohol over-use as having the minimum of 6 units per day (14 mls of ethanol) for 10 years.

D. Social history including educational achievement, occupation etc.

E. Risk factors not included elsewhere.

Some of these questions were formulated with particular interest in the risk factors for prion dementia. They were based on the questions used by the Creutzfeldt-Jacob Surveillance Unit (Dr. R. Will, personal communication.)

The added question as to the whereabouts of each subject, and with whom they were living, was also of value, especially when assessing the impact of disturbed behaviour, and service provision issues.

In the first interview, the supports used by the carers and the subject were enquired into. The second interview gave a chance to structure this approach, and is discussed later.

ii) Behavioural and Psychopathological Rating Scales.

The importance of the non-cognitive features (psychopathological symptoms and behavioural disturbance) in Alzheimer's Disease have been emphasised by Burns et al (1990b). There are several reasons why these symptoms are important. The strains they place on the carers, and the disruption they cause, make them extremely relevant for health care planning. Also, the behavioural and psychopathological profiles, and the patterns of their changes with time, may provide clues as to different subtypes of dementia. By investigating the neuropathological correlation in Alzheimer Disease patients with and without psychiatric symptoms, light may be shed on the neuropathology of the functional disorders.

The means by which information about the phenomenology is obtained is the main methodological problem. The severity of the illness makes the reliance on relative's and caregiver's reports essential. See Hope and Patel (1993), and Patterson and Bolger (1994).

Behavioural Features.

Burns et al (1990b), have demonstrated that behavioural change is a common accompaniment to dementia. It is these problems which pose the greatest burden on carers, and are the most common reason for involvement with the medical profession, see Teri et al (1989). Behaviour in the context of dementia is most simply defined as the observable acts which can be measured. Examples of the phenomena to be included are:

aggressive behaviour; sleep; sexual behaviour; eating; and activity disturbance or wandering.

The development of a variety of methods for the assessment of disturbed behaviour, allows for far greater accuracy in describing the problem. The purpose of the assessment has to be considered, in order to choose the most appropriate test. In this study, the purpose is to describe fully and concisely the behavioural phenomena in each individual, and to indicate the effects of these on the main carers.

Methods will be discussed as those involving information gathered from the carer and then from the subject.

Methods involving the collection of information from the carers.

From what has been said above, carers are therefore the main source of information on behaviour. Rating scales, structured or semi-structured interviews, can be used to collect the information. Although the semi-structured approach is likely to be the most accurate, it is a time consuming exercise. Furthermore, some instruments have been designed for use by the home-based carer, whilst others are for completion by nursing staff in institutional settings. An area of potential inaccuracy arises because of the biases that may operate from such reports, and little work has been done to elucidate these. For example, some carers may be more, or less likely to report difficulties. The individual carer tolerance may affect the severity of the disorder reported, as much as the actual severity of it, see Teri et al (1989). In many areas of behavioural assessment it is impossible to know what the motive behind an action is. Some degree of observer-based bias will come from the subjective judgement of the nature of the action. An example of this is the lady who continually and ineffectually trails a duster over the surfaces of her room. Is this purposeless activity?

The Present Behavioural Examination (PBE), Hope and Fairburn (1992), is the only semi-structured interview whose main aim is to study behaviour in dementia. The interview is done with the main carer, and covers behaviour over the

preceding month. It consists of 121 items, and is therefore a lengthy procedure, although subsections can be used on their own. It provides data on behaviour in dementia, investigates the course and nature of abnormal behaviour, and studies the relationship between abnormal behaviour and other features of dementia, such as cognitive impairment.

Greene et al (1982), used The Behaviour and Mood Disturbance Scale, which measures the behaviour likely to cause stress to the carer. It is a rating scale for completion by the main carer of home-based patients. Less than a half of the 31 items are behavioural. The Behaviour Severity Rating Scale of Swearer et al (1988), is a global behavioural and mood rating scale, which can be used in any setting and has been used over the telephone. It was designed to provide a relationship between disease severity and behavioural disturbance. Rabins (1994), reports on the validity of a brief caregiver-rated, Brief Behaviour Symptom Rating Scale (BSRS) for use in the cognitively impaired. The Behaviour Rating Scale for the Consortium to Establish a Registry for Alzheimer's Disease, is described by Tariot et al (1995).

Many other examples of instruments exist, which cover items that are not strictly behavioural. Other scales are more specific to a particular behavioural problem. Reichman et al (1996), demonstrates that negative symptoms are prominent in patients with Alzheimer's Disease and distinct from the depression. The scale used is for the Assessment of Negative Symptoms in Alzheimer's Disease. Scales specific to agitated behaviour, incorporating elements of aggressive behaviour and activity disturbance, include the Disruptive Behaviour Rating Scale of Mungas et al (1989). This is a rating scale for use in institutions, which comprises four items, termed "dimensions of disruptive behaviour". Two items concern aggressive behaviour and two concern activity disturbance. The severity of the behaviour is measured on the basis of the nature of the intervention response to the behaviour. Ratings are made on the behaviour over a seven day period. A total disruptive score is generated. Reliability and validity data both exist.

Other rating scales focus specifically on aggressive behaviour. The Rating of Aggressive Behaviour in the Elderly (RAGE) of Patel and Hope (1992), is a rating scale for use in institutions after a period of three days inpatient assessment. The reliability and validity have been established, and the instrument appears to be sensitive to change. Its main uses are in the longitudinal assessment of the natural history of aggressive behaviour, for treatment trials, and in the study of the relationships between aggressive behaviour and other variables.

The chosen scale was the Behavioural Rating Scale taken from the Clifton Assessment Procedure for the Elderly (CAPE-BRS) of Pattie and Gilleard (1979). This was developed from the Stockton Geriatric Rating Scale, SGRS (Meer and Baker 1966). This was used by Burns et al (1990b), and Forstl et al (1993). The CAPE-BRS, excludes items that are non-applicable outside hospital settings, and those with poor inter-rater reliability, see Gilleard et al (1977). The CAPE-BRS has been used to see how behaviour affects the nature and degree of nursing care required in demented patients. The behaviours enquired into are very broad, and do not target specific problem behaviours. By analysis of the items covered in this schedule, compared with other possible scales, it seemed that it comprehensively included the majority of important areas. It has a clear and easily scored system that neatly divides into four main areas of behaviour: Physical disability (Pd); Apathy (Ap); Communication difficulties (Cd); Social disturbance (Sd). It is also convenient because it is completed by an informant, either by a member of nursing staff or a home-based carer.

The information collected refers to the behaviours over the preceding two weeks. Any recent deterioration of health would be additionally noted as this would have an effect on the Pd score, and if the condition were a delirium, there could also be short-lived psychotic phenomena. These would be of relevance in scoring on a psychopathological assessment scale. The CAPE-BRS also has a note of any visual or auditory problems which may be

biasing the scores, especially of the communication section. These do not get included in the scoring system though.

However, this behavioural rating scale was only part of the entire behavioural assessment eventually decided on for the study. From the review done, it seemed that it would be valuable to include the PBE, but the time involved for this was not practical. Second, it was of interest to look for features of the Kluver-Bucy Syndrome in this group. Sourander and Sjogren (1970), drew attention to the frequency of behavioural abnormalities suggestive of temporal lobe dysfunction in presenile Alzheimer's disease. These phenomena were reminiscent of the Kluver-Bucy syndrome in animals after bitemporal lobe excision. Visual agnostic difficulties were often the first focal deficits to be noted, especially inability to recognise the faces of relatives or self in a mirror. Late phenomena included strong tendencies to examine and touch objects with the mouth ('hyperorality'), and tendencies to be stimulus-bound to contact and touch every object in sight ('hypermetamorphosis'). Hyperphagia was often a terminal phenomenon, with indiscriminate eating of any material. The emotional changes of apathy and dullness were similarly reminiscent of the pathological tameness of monkeys with the Kluver-Bucy syndrome. The authors found such signs in over 75% of their sample, some of them with the full picture. The question set, used by Burns et al (1990b), covers these areas. For further discussion and use, see Forstl et al (1993).

A novel instrument which combined a concise version of the PBE and incorporated questions covering the Kluver-Bucy Syndrome, was used in the study. This work is in press, (Allen et al 1996). The Manchester and Oxford University Scale for the Psychopathological Assessment of Dementia (MOUSEPAD), takes the form of a semi-structured interview with the informant. It takes both a present and historical perspective, and contains 59 items. This was available for the study before its publication (personal communication Professor A. Burns), and certain items were removed from the schedule, by the second assessment. The

questions cover the following psychiatric features: delusions; hallucinations; reduplications; and misidentifications. And the following behavioural features: agitation; wandering; sleep; eating; and sexual behaviour. A separate depression scale is required to cover mood adequately. Both symptom severity and frequency are rated, and the duration relative to the onset of dementia, as well as the presence in the last month. It takes 15-30 minutes to administer.

Methods involving the collection of information from the patient.

Because of the often impaired nature of insight in these conditions, self-report or interview-based scales are of limited value in behavioural assessment.

The Behavioural Pathology in Alzheimer's Disease, BEHAVE-AD (Reisberg et al 1987), is however an example of an assessment based on an interview with the patient, with its principal aim to evaluate treatment outcome. Only seven of the items are concerned with behavioural problems.

Direct Observation.

It could be said that the gold standard for behavioural assessment is by direct observation. But such procedures require a number of steps to be taken. First the identification and definition of the target behaviour, and then the adequate training and practice at rating by observers. Control of factors such as observer reactivity and bias have to be allowed for, and issues of reliability considered. Furthermore the level of arousal during the observation periods has to be adequate and representative of the general level. Such methods are not discussed further here, and were not suitable for the purpose of this study.

Indirect objective measures.

For example the use of pedometers and electronic monitoring have been used to assess hyperactivity, and electroencephalographic recordings can provide information about sleep disturbance. Physiological markers of diurnal

variation, weight change and biochemical indices of nutrition, and measurement of sex hormones are other possible approaches. However these measures may not in fact be directly enough related to the overt behaviours seen, to make them of use.

Psychopathological Features.

A full review of the measures of psychiatric symptoms in Alzheimer patients is reviewed by Weiner et al (1996). Some of the various instruments are described here, and those used in this study described.

Psychotic Symptoms.

In the work by Burns et al (1990b), the range of psychopathological features found in Alzheimer's Disease were studied and found to highly relevant and common. Disorders of thought, perception and mood were looked at, as well as the behavioural problems. As mentioned, one area of difficulty is the carer reported system, in which lack of clinical sophistication may lead to symptom misreporting. Many of the instruments used to investigate behavioural problems also include psychotic symptoms. For example the PBE includes a checklist of items covering psychopathological phenomena, taking about ten minutes to complete.

The General Mental State Schedule (GMSS) of Copeland et al (1976), is a comprehensive instrument covering current psychiatric symptoms, based on the Present State Examination (PSE) of Wing et al (1974). This was too extensive for use here, although a shorter telephone version also exists. Other scales include: the Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD), of Devanand et al (1992); and the Neuropsychiatric Inventory (NPI) of Cummings et al (1994).

Reisberg and Ferris (1985), report on a clinical rating scale for symptoms of psychosis in Alzheimer's Disease. Ballard et al (1995a), used a specially devised instrument, the Burns Symptom Check List, to screen for the prevalence and frequency of psychotic phenomena, together with the degree of insight and

distress caused by them. They required this because of the absence of any other instrument of sufficient detail, and with validation from previous research. Many of the questions are based on the symptoms from the description in the work of Burns et al (1990b). There are sixteen questions with several specific prompts which are put to both the patients and informants.

The assessment of these symptoms in this study was done using the MOUSEPAD, which covers the phenomena of delusions and hallucinations fully, in addition to its extensive questioning in the area of behavioural disturbance.

Affective Symptoms:

The Assessment of Depression in Dementia.

A review by Abrams and Alexopoulos (1994), and that of Burns (1991a), discuss the importance of affective disorders in Alzheimer's Disease. As with the other psychopathological features, different disturbances may reflect different subtypes. The symptoms also affect the carers, and are potentially treatable. A variety of approaches have been used to assess depression in dementia. Some instruments rely on the care giver's evaluation, some on clinical interview and some on observation, or a combination of these approaches. The use of the dexamethasone suppression test and depressive signs, in subjects with dementia, has been described by Katona and Aldridge (1985).

There are a number of difficulties in obtaining information about depression in subjects with dementia. First, there is overlap in the clinical manifestations of depression and dementia, and second, the demented person is unable to provide accurate information about their mood and inner life. Also, there is a narrow range of depressive symptomatology addressed by the instruments designed for the severely demented subjects, with the added difficulty of the transient nature of depressive symptomatology in cognitively impaired individuals.

Cummings et al (1995), used a variety of standardised instruments to assess mood changes in 33 patients with Alzheimer's Disease, and found the frequency of depression ranged from 6 -30% depending on the diagnostic criteria employed.

One potential mood assessment scale not used was that of Sunderland et al (1988), where ratings are based on direct observation and a semi-structured interview of the patient. Another fairly representative scale used in research with demented elderly subjects is the Hamilton Depression Rating Scale of Hamilton (1967).

In this study, as part of the CAMDEX history schedule, relatives were asked whether they regarded the patient as depressed or not. A past or current history of depression was also noted, defined as treated by a doctor with antidepressants. In addition, the Cornell Scale for Depression in Dementia, CSDD was used (Alexopoulos et al 1988). It quantifies depression in dementia patients, and was developed from a literature review of depressive manifestations in cognitively intact and demented patients, by the consensus of an expert panel. It evaluates a broad spectrum of depressive signs and symptoms and includes items from other depression scales. It includes nineteen items in five rationally determined domains of depressive symptoms: mood related signs, behavioural disturbances, physical signs, cyclic functions and ideational disturbances. Each item is rated on a three-point scale according to both severity and frequency of disturbance. It is completed by clinicians on the basis of their direct observations and interviews with the patient and caregiver. It was devised to measure changes in symptoms with disease progression and treatment. While the small range of rating points tends to yield good reliability, it may also make the scale relatively insensitive to change. It takes about twenty minutes to complete. In a paper by Vida et al (1994), the performance of the Cornell Scale for Depression in Dementia is compared with the Hamilton Depression Scale.

iii) Neurocognitive Testing.

Introduction and background.

The points made at the start of the section on choosing an assessment battery all apply here too. In addition, it is worth looking in greater detail at a few points which arise specifically from this area of investigation. Also see Morris and Kopelman (1992).

There is an empirical expectation, that by using tests which are sensitive to damage in specific brain regions, it would be possible to measure the functioning of these areas, in the different cases of dementia being researched.

There is a large amount of literature to demonstrate the differentiation of different types of dementia, based on the test performance profile. In fact, the neurocognitive profile can be used as one source of evidence in deciding on the differential diagnosis, but in isolation is not sufficient. Deary et al (1991), have investigated the neuropsychological profile found in Korsakoff's Psychosis. Hansen et al (1990), also reported on the distinct pattern of neuropsychology found in the Lewy Body variant of Alzheimer's disease, with greater deficits in attention, fluency and visuospatial processing. Sahgal et al (1992), suggest that short-term mnemonic processes mediated by temporal lobe structures, could be more severely affected in senile dementia of the Lewy Body type. The work of Kopelman (1986), describes the differences in clinical testing of memory, between organic and functional disorders. Evidence for the existence of subtypes within Alzheimer's Disease, is given in the Discussion.

Furthermore, as the disease advances, the patterns of impairment may change. For example in Alzheimer's, impairments may progress from temporal damage (manifest by, for example, memory difficulties) to frontal damage (manifest by, for example, language problems) and then to parietal damage (manifest by, for example, wandering behaviour).

It would be useful to have the possibility of specific areas of cognitive function investigated in detail, as well as a more

global description. However, such investigation requires very much greater emphasis on neurocognitive function than was possible in this study, whose aim was to cover a greater breadth of clinical findings. Furthermore, despite the potential here, in practice it is very difficult either early on in the course of the illness, or at greatly advanced stages, to distinguish between the different causes or types of dementia and to identify distinct patterns of neurocognitive deficits.

A more practical issue, is the consideration of the approach towards the subject, in this area of testing. If insight exists, the testing will be confronting them with their problem and could be an intensely painful reminder of their predicament. The words of Alban (1996) are of relevance here:

"without memory, the individual is dislocated from her past and locked in a present whose context (s)he no longer understands.....(s)he may only live in the "now", but within that narrow time frame, he can both suffer and feel pleasure."

In this population, the prerequisite of understanding the reason for the testing is usually met only to a limited degree, if at all. Hence compliance can be more difficult to obtain. The need for establishing empathic rapport is very great, and careful consideration of non-verbal cues (such as restlessness or anxiety) should be made. The experience must be as gentle and non-upsetting as is possible. It is also worth considering the best order for the tests to be done in, to maintain subject cooperation at the optimal level.

There are day to day fluctuations in mental state. There may also be more major fluctuations, due for example, to acute confusional states in secondary illnesses. Other conditions, such as Lewy Body Dementia, are characterised by fluctuations in performance. It would be hoped that such fluctuations would become insignificant when looking at the results of the group as a whole. It is also necessary to take note of any additional information about the subject, that would affect the results of the testing, such as: current health and treatment; articulatory or

dysphasic problems; and any sensory impairments, such as visual or auditory.

Possibilities and Choices.

The requirements for this part of the interview, were to establish where possible, a measure of the premorbid, and current intellectual, cognitive and general memory function. The repetition of this after an interval of a year would provide a measure of the rate of decline. This discussion is divided into: measurement of premorbid IQ and current intellectual, cognitive and memory function.

Premorbid Intelligence Measurement.

This provides a useful measure to assess subsequent degeneration, and also enables a judgement to be made as to whether the subject is currently impaired. The effect premorbid intelligence may have on the subsequent development of dementia is discussed later.

The National Adult Reading Test (NART) of Nelson and O'Connell (1978), requires the subject to read a series of irregularly spelt words, with the correct response impossible to give on phonological grounds alone. The authors showed it to be comparatively insensitive to dementia, in a sample aged 20-70 years. It can be used to estimate the premorbid IQ, having been standardised, most recently against the Wechsler Adult Intelligence Scale-Revised, WAIS-R (Nelson and Willison 1991). However, the validation of the NART, on the elderly and elderly Alzheimer group, has not always been consistent. See O'Carroll (1986,1987,1992, 1995).

The limitations of the NART, are that it is unsuitable to use if the subject has eyesight problems, aphasia, or speech production difficulties, such as slurring. The test only applies to first languages. Also, it has not been standardised on a large enough sample of elderly patients, and it is poor at discriminating between IQ's in the very low or high bands. There is also some evidence it does not hold as well in some conditions such as

Huntington's Chorea, see Crawford (1988), although this group has been excluded from this study.

In order to provide consistent rating of the test, each subject was tape-recorded, in order to allow for review. Some subjects found it easier to use the individual card format of the test, showing one word each page. In cases where a subject scored <10, the Schonell reading test was done (Schonell 1942). This comprises an even more basic reading test from which lower score IQ's may be calculated.

Current Intellectual, Cognitive and Memory Function.

CAMCOG.

What was eventually chosen to cover the areas of current cognitive function, memory and learning, was the Cognitive Examination (CAMCOG) part of the CAMDEX. From this the shorter Mini Mental State Examination (MMSE) of Folstein et al (1975), can be calculated. Schmand et al (1995), looked at what constituted a significant score change on the Mini Mental State Examination. They found that in individual patients, in the absence of other indications of a dementing process, a deterioration of more than five points after one year, would lead to the suspicion for a genuine cognitive decline. The Abbreviated Mental Test Score (AMTS) of Thompson and Blessed (1987), can also be calculated from the CAMCOG.

The CAMCOG includes subscores for : orientation; language; memory (remote, recall and recognition); praxis; attention; abstract thinking; calculation; perception; verbal fluency; and comprehension. It includes elements of various other test batteries: picture recognition (but not as extensively as in the Rivermead subtest); recall (likewise less extensive); similarities (as in the WAIS-R) ; verbal fluency (one test); and clock-face drawing. The clock-face drawing test involves parietal function, frontal planning and semantic memory, see Lezak (1995). It has been used in a study by Bourke and Castleden (1995), comparing it with the pentagon drawing test in Alzheimer's Disease, and by

Gnanalingham et al (1996), differentiating Lewy Body and Alzheimer type dementia syndromes.

A score of <80 on the CAMCOG, is indicative of acquired cognitive impairment. There is good validation data available on it, and it has been shown clinically to provide differentiation between different patient groups and dementia aetiologies. Its advantages are its ease of administration, in terms of test material and timing. It takes between 20 and 40 minutes to complete, and has the ability to look at individual areas of function (as described above) as well as gaining an overall global score. It was designed to cover a range of severities and different aetiologies, which made it suitable for the heterogeneous population in the study. Criticism of it, is that it is not very sensitive in the early stages of dementia. But this is not relevant in this study, as the diagnosis has usually been made. It has been used widely and is suitable as a tool for retesting after a year, without the need for new material. Infact it only provides fairly crude information on individual areas of function, which tend to all be highly correlated. Greifenhagen et al (1994), demonstrated an overlap and potentiation of different cognitive deficits in Alzheimer's Disease, by principal component analysis of empirical CAMCOG data.

The alternative to using the CAMCOG, would have been to use a series of different tests.

Alternative Tests.

The most commonly used tests for measuring fluid intelligence (verbal and non-verbal) are: the Wechsler Adult Intelligence Scale Revised, WAIS-R (Wechsler 1981); Mill Hill Vocabulary Scale (Raven 1958); and Raven's Coloured Progressive Matrices (Raven 1965).

Several studies report that some of the WAIS subtests are more sensitive to brain damage, and that the performance subtests are more vulnerable to dementia, leading to verbal/performance discrepancies. However not all dementing patients deteriorate like this - some show a uniform decrement,

some have greater verbal IQ's premorbidly and occasionally verbal IQ deteriorates faster than performance IQ. Attempts to distinguish between Alzheimer's disease and Multi-infarct dementia, and between dementia and functional disorders on the basis of WAIS profiles is difficult.

Another possible measure for current intelligence was The Quick Test, see Ammons and Ammons (1962), and Frith et al (1991). This involves the subject matching a series of words to the picture to which each is relevant. It has a good correlation with the WAIS, but little validation data exists for it.

The clinical tests of memory do not reflect the complexities nor the boundaries between the types of memory. There is indirect contamination of memory functioning by intellectual decline and also, specific impairments may affect memory abilities. Thus the overall memory score may ignore the complexities of the deficit. There are three main scales used: the Wechsler Memory Scale Revised version (Russell 1975); Rivermead Behavioural Memory Test (Wilson et al 1985); and Recognition Memory Test (Warrington 1984).

Another aspect of memory, semantic memory, is most widely tested by a verbal fluency test. These are discussed in Lezak (1995). A naming and word finding deficit occur early in dementia (Huff et al 1986 and Kirschner et al 1984). The test involves the retrieval of words to a letter (e.g. F, A, S) or category (fruit, flower, animals) on cue, see Hart et al (1988) and Miller (1984). There is good validation data for its use at different ages. It has been compared with the NART, see Crawford et al (1992). It also gives a crude measure of one aspect of frontal decline. Other tests of frontal function include the Wisconsin Card Sorting Test (Berg 1948) and Cognitive Estimate Questions (Shallice and Evans 1978).

iv) Neurological Testing.

A variety of neurological signs which can be elicited in subjects with dementia, may help to clinically differentiate between various types of the illness. Obviously the individual stage of the illness in each subject, will also determine to what extent the neurological signs are apparent. For example, in Alzheimer's disease, later on in the course of the illness, focal neurological signs, spasticity, hemiparesis and rigidity may occur. In vascular dementia, Birkett (1972) found that neurological abnormalities predicted arteriosclerosis more accurately than any other mental feature. Minor focal signs, such as unequal tendon reflexes, extensor plantars and impaired pupil reactions, may be found. Signs of pseudobulbar palsy occur, and syncope is common.

Parkinsonian features may be conspicuous in Alzheimer's Disease. As described in the Introduction: Genetics , there is an area of overlap in the dementia types of Alzheimer's and Lewy Body and the dementia associated with Parkinson's Disease. Ditter and Mirra (1987), studied a series of clinically suspected and autopsy-confirmed cases of Alzheimer's Disease and correlated pathologic findings and available neurologic data. They found extrapyramidal signs, especially rigidity, noted in many Alzheimer Disease patients, to be related to co-existent Parkinson's Disease pathology. Hansen et al (1990), examined the Lewy Body variant of Alzheimer's Disease, which is marked by extrapyramidal features and myoclonus.

Pick's Disease tends not to have gait and muscle tone as frequently affected, and only occasionally shows Parkinsonian features. Although not included in the cohort, Huntington's Chorea may present with choreiform movements, or less often with an unsteady gait, a tendency to fall and clumsiness in general. In Lewy Body Dementia the main neurological features are Parkinsonian, with rigidity, resting tremor and gait impairment. In the spongiform encephalopathy, Creutzfeldt-Jacob Disease, neurological signs may include: cerebellar ataxia; spasticity and

progressive paralysis; extra-pyramidal rigidity; tremor; and choreoathetoid movements. The involvement of the anterior horn cells can lead to muscular fibrillation and atrophy, especially of the small hand muscles. Other signs include speech disturbances, parietal lobe and cortical visual problems. Sensory problems are not apparent, but brain stem involvement can lead to nystagmus, dysphagia and uncontrolled lability. Frequent myoclonic jerks are common.

In terms of a specific feature such as epilepsy, differences across the various forms of dementia are apparent. Sim et al (1966), found that fits happening early on in the course of the illness were more common in non-Alzheimer type presenile dementia. In Alzheimer's, epilepsy is said to occur in up to 75% of cases, in vascular dementia about 20%, Huntington's 3% and in Creutzfeldt-Jacob Disease as a possibility only, see Lishman (1990).

In terms of the neurological examination, as mentioned previously, it is important to have an examination which could be tolerated by the individuals concerned, in which some basic data could be collected even when the subjects were unable to cooperate. As with the cognitive testing part of the examination, it was important to know the current health and medication of the subject, as these would influence the neurological examination. An informant could also add valuable information, not necessarily apparent during the examination, on the presence or absence of certain signs such as epilepsy or myoclonic jerks. Burns et al (1991b), rated myoclonus as being present when a 'brief shock-like muscular contraction' occurred during the physical examination or interview with the subject. Some aspects of the neurological assessment could be examined during the time spent with the subject, for example during the cognitive examination. The subject's speech, presence of tremor and writing could all be assessed during the CAMCOG, and were relevant to the Webster scale.

The physical examination check list, as used in the CAMDEX schedule, was completed. In addition, the Brief

Neurological Examination was done, see Owens (1985). This tests gross motor function, including cerebellar and cranial nerves. The Webster scale for Extra-Pyramidal Symptoms (Webster 1968), was also used. The items on self care and seborrhea were excluded. A data sheet with some additional questions was also included and covered the testing of primitive reflexes, as well as providing the opportunity to describe any abnormal movements.

The significance of frontal release or primitive reflexes, has been debated. It has been said to be no more than a measure of diffuse dysfunction. Primitive reflexes have been studied by: Youssef and Waddington (1988), on a mixed group of subjects with schizophrenia and bipolar illness; Paulson and Gotlib (1968), in the aged; Girling and Berrios (1990) and Burns et al (1991b) in Alzheimer's Disease; and Basavaraju et al (1981) in dementia. Bakchine et al (1989), investigated the significance of primitive reflexes and extrapyramidal signs, as indications of diffuse cortical dysfunction and their relationship to age and cognitive impairment. They found a significantly lower Mini Mental State score correlated with the number of primitive reflexes and in particular, the snout, sucking and grasp reflex. In the study of the neurological signs in Alzheimer's Disease by Burns et al (1991b), the primitive reflexes were also tested. For this study, the Hoffman, grasp, palmomentary, jaw, snout, sucking, glabellar and Babinski reflexes were decided as appropriate.

Two areas of potential interest, akathisia and soft signs, were not included. Akathisia, the motor restlessness accompanied by a subjective feeling of tension in the limbs, would have been too difficult to rate in a population whose ability to provide subjective judgements was limited. For example the scale devised by Barnes (1989) requires the participation of the subject. Soft signs are stated to reflect fronto-temporal and fronto-parietal abnormalities. However it could be argued that they represent a broad group of different signs, of no clear significance. King et al (1991), used ten of the widely used soft signs in a study of chronic schizophrenia. The signs were: mirror movements; speech; right/left confusion; finger-thumb opposition and mirror

movements; pronation-supination; foot taps right and left; face-hand sensory inattention; graphaesthesia and hopping on right and left.

Having decided on the instruments to be used, the data sheets were prepared and the published tests obtained. Each first assessment package had the assessment overview as a front sheet, followed by the consent form and then the case note data.

Second Assessment.

For the second assessment, a front sheet provided an opportunity to briefly review the outcome of the previous assessment. The parts of the first assessment re-tested were: CAMDEX H (the items concerned with the history of the present difficulty); the MOUSEPAD, CAPE and CORNELL; the CAMCOG; and the complete physical examination.

Additional parts of the assessment, provided the chance to detail the carer needs more fully. In a data sheet, the supports available and satisfaction with the service, were enquired into. Current treatment and changes over the year in the major areas of interest, were asked for.

Carer Strain Scales.

Various instruments exist to identify and measure the stress of carers. The Relatives Stress Scale (RSS), of Greene et al (1982), is a 15-item scale designed to measure the stresses experienced by a relative who is caring for an elderly dependent in the community. The questions relate to such topics as the effect the dependent is having on the relative's social life and mood state, and assesses negative feelings of the relative towards the dependant. Another scale is that used by Morris et al (1988). The emotional well-being of the caregivers was investigated using a rating scale to measure strain, and the Beck Depression Inventory (Beck et al 1961) to measure the current level of depression. A questionnaire was developed to measure marital

intimacy (both past and present). Another assessment is described by Gilleard (1984).

The questionnaire chosen to measure the strain on informal care providers in this study was The Caregiver Strain Index, CSI, validated by Robinson (1983). The results of his work indicated that the CSI was a brief, easily administered instrument which was therefore usefully included in the assessment to examine relations involving dependency and care. However it was not specifically designed for carers of subjects with dementia, nor presenile dementia, where the informal care giver is often the spouse, rather than an inter-generational family member. This was given to the carer when relevant, to aim to quantify the strain on them, either currently or retrospectively.

The next chapter of the Method will go on to describe the process of making contact with the subjects in the study.

Method:

VI. Contacting the Sample and Data Organisation.

Having described how the cases were identified and notes reviewed in the Method: Ascertainment, and then, how the battery was chosen, in the last chapter, this chapter will describe how the pilot and study itself was run. This describes the organisation involved in contacting and visiting the families and their relatives, and obtaining the necessary consent for this. The pilot study provided the opportunity for the familiarisation with the testing material, and organisation of questionnaires and equipment. Changes to the battery and observations on the instruments used, could then be made. The need for a very empathic and supportive approach became apparent. The requirement was for the study to be completed within three years. This included not only the time necessary for the visits, but also to sort the data, and organise the running of the study.

The pilot involved a group of about 20 cases. From the complete list of potential cases, a representative sample for the pilot study was obtained, by taking the equivalent percentage of each type of dementia, as was represented in the group of 290.

From the case note review, the address of the next of kin had been noted, as well as the General Practitioner's telephone number and address. A table of these was created to detail each case more efficiently. This list of all the potential cases was alphabetically arranged, and each given a number. The GP's and consultants involved were easily identified which made the contacting for consent more efficient. Another overview chart, enabled the progress of contact and case assessment for each subject to be visually accessible.

Making contact with the cases.

The first step, was to make contact with the GP's and consultants for each case, by letter. This was to explain the study, and ask their permission to approach the next of kin, or main carer for each subject. This also provided the opportunity to

gather any relevant recent information about the subject's current state and whereabouts, and any problems the family might be in. The most appropriate person to make contact with was also established. On occasions, the contact was felt to be inappropriate, because of family stresses or the diagnosis being questioned. If no reply was received after two weeks, contact with the doctor was established by telephone.

Having obtained the consent from the GP and responsible consultant, the next of kin was then written to. Occasionally the subject would be contacted too if this was appropriate. It became necessary at this stage to ensure that all forms for the study, which could be seen by the participants, were labelled in terms of being a memory study, rather than with the term dementia, which sometimes felt inappropriate.

If no contact was made following the first letter, the address was rechecked and a second copy sent. Following this, if no contact was received, a phone call was made where possible. When the subject was in long term care, a message could also be relayed to the family via the ward staff. If no contact was made, the GP was informed. All the study records of the cases not included were kept, together with the details of why the contact was not successful, or the case was not included.

The usual form of response was by telephone, and this initial discussion allowed the arranging of the time for the first visit. The visits were usually at the home of the next of kin, but if preferred, at the hospital. The visits were arranged to be at the most suitable time for the carer.

All the letters, information sheets and the study protocol sent out, are in the Appendix: Protocol.

The first visit.

The first visit would start with a careful explanation of the study and provide an opportunity for any queries to be raised by the relatives. At this stage, the consent form was signed, by the next of kin, and the subject where possible. Most

often, the rest of the interview would naturally follow this, but if preferred, an alternative date could be made for the next visit.

If the subject was at home, they could be seen on the same occasion or a follow-up visit arranged. Many subjects were in long-term care, and the visits would be made separately there.

The interview with the informant generally took about two hours and the examination of the subject about one and a half hours, if the subject was able to do the cognitive testing. At the end of the examination of the subject, blood was extracted. The details of the blood collection are given in the Method: Genetics.

After the visit.

After the completion of each visit, the relevant part of the overview was checked off, so a plan of the project progress was easily reviewed. A letter of thanks was sent following the visits, and if any matter had arisen requiring the GP's or consultant's attention, they were notified. Examples included concern over a lady living alone who lacked appropriate services, or the finding of hypertension on physical examination. Another situation was where the wife of a subject was abusive in manner at the interview, and through contact with the day hospital where the husband attended, it was explained she was abusing alcohol. When there was concern over how a relative or carer was coping, this was also discussed. Recent contact with the hospital service would make the reading of the recent medical notes of value, for the opinions of those involved and details of the subject's problem.

The data was entered into the data base. There were about 655 variables for each individual. The diagnostic criteria were applied as described below. Other aspects of data organisation were: the use of the Office of Population Censuses and Surveys, OPCS (1980), to apply the classification of occupations to each case. Also, the translation of the raw NART scores into IQ scores on the WAIS-R.

The second visit.

This generally took about 2 hours in total.

Between 12 to 16 months after the first visit, contact was again made with the main informants. This was facilitated as the first visits had already been done, and the consent obtained for the second contact. The majority of re-contact was made by telephone. The list of first assessment visits were placed in chronological order, providing a strategy for the follow-up visits.

The aim of the second assessment, was to establish and quantify the pattern of decline for each case, and investigate the carer's needs more fully. Additional questions and check items from the first assessment, were also included.

Note on Post-Mortem Examination.

This initially seemed to be a difficult topic to broach with relatives. It was certainly more appropriate to discuss at the time of the second visit, in cases where the subject was in long-term care and at a severe stage of the illness. The issue was raised as a discussion point rather than with the view to a definite decision being made. A previously designed information sheet was not used.

There is also the need to raise the awareness of the clinicians who are in contact with the subjects and their relatives at the time of death.

The importance of the information gained at post-mortem in contrast to the relatively imprecise premorbid diagnoses, made trying to gather this information a real priority.

At the Neuropathology Department at the Western General Hospital, Dr. J.Ironside and Dr. J. Bell kindly agreed to examine any of the sample who died, where the next of kin had agreed to the examination.

The low number of neuropathological post-mortem examinations of the subjects who died in the follow-up year, was a disappointment.

Preparation before the second assessment.

In advance of the visits, a folder was compiled for each case, with some key points to help orientate the second assessment. The date of the first assessment was noted and the contact address and whereabouts of the subject and their next of kin, provided. If the subject had not met the DSM3R criteria at the first visit, this was indicated. Also, a note was made if the cognitive testing had not been possible at the first assessment, and whether the discussion of post-mortem examination would be appropriate. A case vignette was prepared on each (see Appendix: Case Studies).

The visit.

The same informant was used at the first and second assessments, whenever possible. Occasionally, when the informant was a member of the nursing staff in long-term care, this was not possible. Inter-rater reliability was sometimes checked by comparing the responses from staff in long-term care and the relatives, if they were visiting regularly.

At the follow-up visit, the telephone number of a social worker involved in setting up a group for carers and the assessment of carer needs in Lothian, was given. If required, they would also be made aware of other carer groups in their area.

In cases where the subject had deceased during the follow-up period, the questionnaires were completed by the informant, to describe how the subject was at the time before their death. The hospital notes were also traced for review in these cases.

After the visit.

A note of anyone wishing to receive a resume of the study was also made. Thankyou letters were again sent out after each visit.

After each visit the data was again entered into the data base, and any change in DSM3R status or severity noted.

Data Base Organisation.

A data base was organised for the 126 cases seen, placed in the ascending order of study number. A note was kept of any missing data.

Diagnostic Criteria: Inclusion and Exclusion Criteria.

The decision was made before contact was attempted, to exclude cases of major head trauma, Huntington's Chorea and Down's Syndrome, see Discussion. Alcohol-related diagnoses were included.

The DSM3R dementia criteria (APA 1987), were applied in each case. These are given below. Other diagnostic criteria mentioned can be found in the references given. The 4th Edition was not available until after the beginning of the study, in 1994, and so was not used.

DSM3R Criteria For Dementia.

A. Demonstrable evidence of impairment in short- and long- term memory. Impairment in short-term memory (inability to learn new information) may be indicated by inability to remember three objects after five minutes. Long-term memory impairment (inability to remember information that was known in the past) may be indicated by inability to remember past personal information (e.g. what happened yesterday, birthplace, occupation) or facts of common knowledge (e.g. past Prime Ministers, well-known dates).

B. At least one of the following:

(1) impairment in abstract thinking, as indicated by inability to find similarities and differences between related words, difficulty in defining words and concepts, and other similar tasks.

(2) impaired judgement, as indicated by inability to make reasonable plans to deal with interpersonal, family, and job-related problems and issues.

(3) other disturbances of higher cortical function, such as aphasia (disorder of language), apraxia (inability to carry out motor activities despite intact comprehension and motor function), agnosia (failure to recognise or identify objects despite intact sensory function), and "constructional difficulty" (e.g., inability to copy three-dimensional figures, assemble blocks, or arrange sticks in specific designs).

(4) personality change, i.e. alteration or accentuation of premorbid traits.

C. The disturbance in A and B significantly interferes with work or usual social activities or relationships with others.

D. not occurring exclusively during the course of Delirium.

E. Either (1) or (2):

(1) there is evidence from the history, physical examination, or laboratory tests of a specific organic factor (or factors) judged to be etiologically related to the disturbance.

(2) in the absence of such evidence, an etiologic organic factor can be presumed if the disturbance cannot be accounted for by any non-organic mental disorder, e.g. Major Depression accounting for cognitive impairment.

The criteria for Primary Degenerative Dementia of the Alzheimer Type, Multi-infarct Dementia and Dementia Associated with Alcoholism, and the criteria for severity of Dementia, can be found in the DSM3R (APA 1987) publication.

Having made each assessment, a data file was organised to provide details on diagnostic criteria. As mentioned, all cases had met the wide-based Feighner criteria for organic dementia, from the case note survey. For each case, the parts of the DSM3R criteria which were and were not met using clinical standards, were recorded. The cases not meeting the DSM3R criteria were kept in the study, for re-assessment.

The next step was to categorise each case into either Alzheimer, Multi-infarct or Alcohol-related DSM3R Dementia. This again posed problems, as it was often not clearly possible to exclude all but one relevant aetiological agents. Therefore, it was decided to have the possibility of overlapping groups.

The DSM3R severity ratings were used, although these could be criticised for being too broad and subjective. The use of a general scale, often incorporating behavioural items, such as that of Blessed et al (1968), Hughes et al (1982), or Reisberg et al (1982), was not felt to be an advantage.

Other Diagnostic Groupings.

Alzheimer's Disease.

The NINCDS-ADRDA criteria (McKhann et al 1984), were also applied. Burns et al, (1990a), comment on the accuracy of clinical diagnosis of Alzheimer's Disease, using the McKhann criteria, and found these clinical criteria diagnosed pathologically confirmed Alzheimer's Disease in 88% of patients. This was a successful prediction. McGonigal et al (1992c), highlight the limits of the clinical criteria and suggest improvements. McGonigal et al's specifications for the minimum investigations required, to allow the use of McKhann criteria are: normal Thyroid Function Tests (TFT's), normal B12 or normal mean cell volume (MCV), and

a negative Venereal Disease Research Laboratory test (VDRL). Leach and Levy (1994) reviewed the McKhann criteria, and discuss various problems to which they give rise to, and ways these can be addressed.

Inadequate investigations (or access to the results) had left many gaps in this data for the study, and a note of these cases was kept. Also, efforts to tighten the definitions of alcohol misuse, based on the number of recorded units consumed, was confounded by the difficulties of taking an accurate history.

Vascular Dementia.

When there is a clear history of stroke and cognitive impairment, and a temporal connection between them, the diagnosis is straightforward. More usually, determining if cerebrovascular disease alone causes dementia is difficult. Diagnostic criteria exist to aid the diagnosis.

The DSM3R criteria for vascular dementia were used, although these criteria are not validated and are regarded as subjective. A series of risk factors, relevant to vascular dementia, were also available for each case. These provided clinically-based information as to the likelihood of the presence of this pathology.

The Hachinski ischaemic scale (Hachinski et al 1975), diagnoses vascular dementia when a patient is given a score of seven or higher. It is widely used, but has poor inter-rater reliability. It was not therefore used in this study. Attempts to correlate the clinical presentation with diagnosis confirmed at autopsy, such as by Rosen (1980), verified the usefulness of the Hachinski ischaemic score in differentiating between senile dementia of the Alzheimer's type and vascular type.

Patients presenting to clinics with Multi-infarct dementia, often have no history of stroke and no focal signs. A study by St. Clair and Whalley (1983), assessed the value of cardiovascular system examination (importantly blood pressure) at the time of admission, in differentiating between Multi-infarct dementia and Alzheimer's Disease.

Vascular dementia is classified in the latest World Health Organisation International Classification of Diseases, Tenth revision, ICD-10 (WHO 1992). This sub-classifies vascular dementia of : acute onset, multi-infarct dementia, subcortical vascular dementia, and mixed or unspecified types.

Two new sets of criteria have recently been proposed. The State of California Alzheimer's Disease Diagnostic and Treatment Centre, ADDTC (Chui et al 1992). The other was by the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et L'Enseignement en Neurosciences (NINDS-AIREN), a European panel of experts (Roman et al 1993). Both require the presence of (a) dementia, and (b) cerebrovascular disease, and (c) a relationship between the two (such as the onset of dementia within three months of a stroke).

Validation as to whether these criteria are more sensitive is awaited. Drachman et al (1993), critically review the NINDS-AIREN criteria. Apart from the ICD-10 and NINDS-AIREN criteria, all these criteria are based on the Multi-infarct concept of vascular dementia.

Lewy Body Dementia.

The proposed Operational Criteria for Senile Dementia of the Lewy Body Type (SDLT), from the Newcastle group (McKeith et al 1992), could be applied to each case too, as there is enough data to do this. These were developed to detect predominantly neuropsychiatric presentations. The Nottingham group also proposed a set of criteria (Bryne et al 1991). These place more emphasis on a requirement for Parkinsonian symptoms that may be mild and occur late in the disease, and allow for diagnosis of 'possible' or 'probable' Lewy Body Dementia to be made.

Other.

The Cambridge MRC Multi-centre study for cognitive decline in the elderly, headed by Professor N. Day, has produced criteria for frontal lobe dementia, as part of their complete

assessment, (personal communication with the group). These criteria could also be applied.

Because the nature of this study was to include all cases rather than seek out, for example, only cases of Alzheimer's type, there were many cases not neatly fitting the criteria. Another way to subdivide between the cases clinically, would be on the basis of the presence or absence of risk factors.

There are difficulties involved in the neat application of criteria to the group. It appears that without resource to neuropathological confirmation, the most reliable (although not always accurate) definitions, are often the clinical based ones, see Gustafson and Nilsson (1982). Thus, clinically based diagnostic criteria, in the absence of pathological confirmation, are useful as a guide. They are not significantly enhanced by the application of a computerised algorithm, which could at first sight, appear to be a more objective approach. For example, using cut-off values based on the CAMCOG interview, has not been found to enhance the accuracy in applying criteria, (personal communication with the Cambridge MRC Multi-centre study).

The resulting group of cases available for the study, was a heterogeneous one, in terms of clinically defined risk factors, and also because of the different stages of the illness that the cases were investigated at.

Notes on the Assessment Battery.

The necessary instruction on each test was obtained, and the pilot study provided the opportunity to try out possible alternatives for the cognitive testing. For example, Raven's Coloured Progressive Matrices had been a suggested item, but was found very inappropriate in the pilot.

Several points arose from the experience of the interviews, which will be discussed here. By looking at the drawbacks of the assessment, data which is less objective can be identified.

Many of the group were at the severe end of the spectrum, and so would be scoring at the lowest values possible, for example on everyday activities and cognitive ability. Hence any deterioration at the second assessment would not be measureable, using these instruments.

The subjective nature of some of the questions also became apparent. Many points become open to interpretation, because communication is impaired in dementia. The perspective of the carer tended to bias the results. Also, the differences between ward and home-based perspectives became apparent. For example, what would be noticeably disturbing behaviour at night to a spouse, may be unobtrusive to a night nurse. The most objective questionnaires which could be used to assess change, were: the CAPE; CAMCOG; and neurological examination.

Various parts of the battery overlapped with others, providing the opportunity for a check of internal consistency in the informant. Reliability was a critical factor in obtaining good data.

The estimation of the duration of symptoms, in the historically orientated questionnaires, was a difficult area to ensure accuracy, and inconsistencies were likely to have occurred in certain cases.

The individual parts of the battery are discussed below:

The informant interview, CAMDEX H.

This is primarily a diagnostic tool, and the questions about functioning in everyday activity, were not so helpful in severely advanced cases, where the subject was scoring at the worst level at the first assessment. It was more useful when a subject was in the early stages of the illness, rather than in long-term care. This section was not very sensitive to different degrees of change, and so was not of great value at the follow-up.

The CAPE-BRS.

This was completed by the main carer, either in the home or ward. It seemed to be able to quantify the behavioural problems in each case. However, it was not free from bias introduced due to the rater's perception and interpretation of the subject's behaviour. One interesting effect was noticed at follow-up, in cases who had undeniably declined, that the rater would feel the subject to be less confused and more easily understandable. Two possible explanations for this are given. First, if the subject was in long-term care, the staff could have felt that the longer they had got to know the person, the more they could communicate with them. Second, sometimes with deterioration, the more agitated elements of behaviour were lost and the subject could have appeared more compliant.

The Cornell Depression Rating Scale.

During the data collection for the study, it became apparent that this scale was not incorporated into the assessment easily. The data from it was rather patchy and has therefore not been of particular value in the analysis. The description of the number of individual cases on anti-depressants, is given instead.

The MOUSEPAD assessment.

The interdependent nature of some of the items on this questionnaire, became apparent with its use. An example is, if restlessness at night was present, then the question regarding night time wandering would be much more likely to be present, and vice versa. A belief of someone else in the house, would also perhaps correspond with a visual hallucination and lead to the subject conversing with the imagined figure, apparently experiencing auditory hallucinations. In general a report of delusions and hallucinations, requires a high degree of effective communication on the part of the subject.

Factors such as whether the subject was in care, or on medication, and the stage of the illness, also influenced the results.

In long-term care, the subject is unable to leave if the ward is locked, and their food supply is regulated. Intervention following a wandering episode at home, would be likely to result in the door being locked, so further opportunities would be reduced. Sedation may reduce overactivity, or settle disturbed sleep.

Symptoms that were rapidly fluctuant or intermittent were not easily identified by this instrument. Lewy Body dementia is characterised by such fluctuations, see McKeith et al (1994).

As the illness progresses, and verbal ability is reduced, so verbal aggression would diminish. Many aspects requiring motivation, would likewise reduce with time. The interview takes a historical perspective to cover this, but perhaps fails to highlight the external factors which may influence the results. In this way, it may not only be the natural progression of the illness which is described.

Neurological Examination.

The presence of an abnormal gait could have been due to a number of different factors, not necessarily due to dementia. There was not normative data available on such items, which lessens the value of such information. Treatment with anti-psychotics and other health problems unrelated to the neurological system or dementia, could produce immobility or reduce the potential value of using the Webster scale. A subject who becomes immobile would score lower overall on the Webster scale, because the items would be unrateable, but could in fact have been significantly more Parkinsonian.

Cognitive Testing.

The variability in performance between the first and second assessments would have to be taken into account and would be described in the normative data available on this test. Subjects scoring <5 at the first assessment, were not re-tested.

Hints were taken from the messages written, for

example "I am tired" could be a clue to the subject getting annoyed, and recognition of this could enable the successful completion of the test. The use of patience and encouragement also helped completion. The writing of the subject's name allowed a sample of writing to be recorded, in some cases where it was impossible to write a sentence.

The Carer Stress Index.

The Carer Stress Index (CSI), has several drawbacks, which became apparent during its use.

Some of the questions are awkwardly phrased and seemed to invite negative responses. For example, in defining emotional adjustment in the family over the subject's illness, the instrument describes an 'argument'. The definition of financial strain also seemed unclear, and there were a variety of ways in which indirect financial disadvantage could result from the illness (see Appendix: Carers).

In interpreting this data, it would also be important to consider the relevance of the CSI, in terms of where the subject was when the CSI was completed, how long ago they were cared for at home, if historical, and the likely severity at that time. The mental wellbeing of the informant was also noted. When relevant, the duration of time between entry into long-term care and the second assessment (or death), was a measure of the time ago that the subject was cared for at home.

It became apparent that the perception of stress varied from one case to the next, and factors other than the subject's illness, such as the carer's tolerance, were of relevance. This theme is developed in the Appendix: Carers.

Subsequent phases of the study.

As was expected, once the contact was in progress, there was attrition of cases for reasons given in the Results. Patience was taken to try to trace each case and obtain consent. The response from all people contacted and approached was generally extremely helpful and cooperative. The interviews and

examinations appeared to be of an appropriate length and nature to avoid distress.

As the visits got underway it became important to keep arranging the next set of visits, to maintain the momentum of the study. The files with all relevant documentation were prepared in batches. The study diary is outlined below:

Outline of Study.

Stage of Study	Start	Finish	Numbers seen
Planning phase	Sept '93	Dec '93	-
Phase 1 (Pilot).	21/1/94	24/2/94	(1-24)15
Phase 2	19/4/94	4/6/94	(25-88)
Phase 3	7/6/94	26/8/94	(89-179)
Phase 4	20/9/94	20/12/94	(180-290)
2nd Assessments	April 1995	February 1996	
Sorting phase	March 1996	August 1996	

Method: VII. Genetic Analysis.

Blood Sample Collection.

At the first assessment 40 mls of blood was taken from each of the subjects, when possible. This was occasionally difficult when the subject was very disturbed, and was not always possible. Five samples were not taken, in four cases as the subject was not cooperative. One subject, without relatives, was in long-term care, and consent was felt to be inappropriate. In several cases, less than the 40 mls was taken. The use of anaesthetic patches was not found to be particularly helpful. A paper by Richards et al (1993), described DNA preparation from buccal swabs or brushes, which could potentially avoid the need for blood samples in this group of patients.

Having taken the blood, it was divided into four Ethylenediamine tetra-acetic acid (EDTA) tubes, each of which was labelled with the patient's study number and date of birth. Within the next few hours, at most within the next 24 hours, the tubes were taken to the Western General Hospital, Human Genetics Unit, where storage space had kindly been given in the freezer, kept at minus seventy degrees centigrade. before this, a further separate blood storage number was also added to each subject's individual set of tubes. In the freezer itself, the bloods were kept in a series of labelled boxes, to enable easy access and safe keeping. The blood was stored here until the DNA extraction in the summer of 1995.

Control samples.

A control population was not a feature of the basic study but was of crucial importance for the genetic analysis. A group with similar sex and age distribution, of similar ethnic background, but otherwise essentially random, was required. These features would influence the distribution of other pathology such as cardiovascular disease and the distribution of genetic alleles.

It also became apparent that it would be necessary to do a basic check for any cognitive impairment of the control sample. The Mini Mental State Examination (MMSE), was chosen for this purpose and scores below 23/30 taken to be indicative of impairment. Certain other questions were asked to each control case, such as any family history of a dementing illness. The consent form and data sheet, are given in the Appendix: Protocol.

The Church of Scotland Annual General Assembly Meeting was held in Edinburgh in the Spring of 1995, and the organisers very kindly allowed the approach of members for the purpose of blood collection. Other members of the department generously gave their time to help in the two days of intensive control sample acquisition. Prior to this, ten control cases had been collected from spouses of the study subjects.

Details of the age and sex distribution of the dementia and control samples, is not given here. This data is incorporated into the Genetic Results.

Of 122 dementia samples stored in the freezer, one was mislaid, and one case, already excluded, had Huntington's Chorea. A total of 120 dementia samples were therefore available for DNA preparation from the dementia group. 119 cases were analysed for all three loci.

Of the 165 control samples, 152 had all the three loci analysed.

Extraction of DNA from the Blood Samples.

In the summer of 1995, the DNA preparation was completed. Most resulting DNA samples, had a concentration of 50-200 ng/microlitre. The quality of the DNA was assessed, to ensure it was undegraded, RNA free and PCRable.

The protocol for this is given overleaf:

DNA Extraction Process.

For each 10 mls blood collected in EDTA tube.

Step 1. For cell lysis, add 30 ml buffer of
ammonium chloride (115mM)
potassium hydrogen carbonate (10mM)
EDTA (0.1mM)

Spin at 2.2 krpm for 10 minutes at 4°C, pour off supernatant.

Step 2. Resuspend pellet in 10ml of SET:
sodium chloride (75mM)
EDTA (25mM)
Tris buffer (30mM)

Spin at 2.2 krpm for 10 minutes at 4°C, pour off supernatant.
Repeat twice. Resuspend in 4.5ml SET.

Step 3. Protease K treatment.

Make to 0.1% sodium dodecylsulphate
and add 25µl of 20 µg/µl protease K

Incubate at 37 °C for 2 hours.

Step 4. For organic extraction, add 10 ml of
phenyl (1) : chloroform (1)

Mix and spin at 2.2 krpm for 10 minutes at room temperature,
recover water phase. Repeat twice.

Step 5. Add

sodium acetate (3M) one tenth volume.
ethanol, two and a half volumes.

Mix and spin at 2.2 krpm for 10 minutes at 4°C, recover water
phase. Repeat twice.

Step 6. Resuspend pellet in 0.5 ml buffer

Tris (10mM) : EDTA (1mM), at pH 7.5.

Genetic Testing.

The Candidate Gene Approach.

In the molecular study of a disease, the genetic defect must be located, identified and the defects characterised. This requires the gene to be assigned a position or linked, the locus defined and then the molecular pathology of the aberrant protein described.

The linkage approach requires the collection of families with multiply affected members, in which the phenotype and mode of inheritance are defined. The determination of the gene position is by random searching or the candidate gene or region approach. The flanking markers are found by multipoint mapping and international collaboration.

Once a gene is identified, it can be amplified and analysed using the technique of Polymerase Chain Reaction (PCR) on microtitre plates.

The dementia samples for the current study came from a group of non-related individuals, with sporadically occurring presenile-onset dementia, with a diverse range of aetiologies. This was not therefore amenable to the linkage approach, nor particularly to the association approach (for example between siblings and markers). The genes already known to be relevant in the familial forms of the disease were not of primary interest here. Genes known to be risk factors and other reported candidates, were of greater potential interest to study in relation to this group.

In collaboration with Dr. Anthony Brookes, at the Western General Hospital, Human Genetics Unit, decisions were made as to the testing which would be suitable in the initial analysis of the sample. The alleles chosen for typing were: APOE; ACT; and VLDL-R.

The resource of the extracted DNA obviously remains for future approaches, for example the testing of novel candidate genes. The genes chosen and other novel candidate genes,

especially with relevance to Alzheimer's Disease, are discussed in the Introduction: Genetics chapter.

The genetic analysis began in January 1996. The protocols are given below.

Apolipoprotein-E Genotyping (ϵ 2 /3 /4).

Assay.

A 227 bp fragment of the APOE gene coding sequence is PCR amplified. The sequences of two polymorphic base positions is detected by cleavage with HhaI restriction enzyme (whose sites are altered by these polymorphisms) and agarose gel electrophoresis.

Primers.

As published by Wenham et al (1991), here called Wen 3' and Wen 5'.

PCR. (25 μ l volume).

genomic DNA	80ng
Primer Wen 3'	150ng
Primer Wen 5'	150ng
10 x PCR Buffer (Perkin Elmer Cetus)	2.5 μ l
Dimethylsulphoxide (denaturant)	2.5 μ l
dATP, dTTP, dCTP, dGTP Nucleotides	0.2mM (each).
Taq (Perkin Elmer Cetus)	0.75 units
Water	to 25 μ l

PCR cycling conditions.

Perkin Elmer Cetus, 9600 machine

(96°C50"), (60°C30"), (72°C30"), 1 cycle
 (96°C15"), (60°C30"), (72°C30"), 17 cycle
 (96°C15"), (60°C30"), (72°C1:30"), 18 cycle.

Ethanol Precipitation.

100% Ethanol	2.5 X volume.
2M sodium acetate	0.1 X volume.

Mix, place at -20°C for 1 hour, spin in microfuge 15 minutes,
 leave at room temperature to dry.

Hhal Digestion.

10 X HHal restriction buffer	2 μ l.
0.1M Spermidine	1 μ l.
Hhal restriction enzyme	4 units.
Water	to 20 μ l.

37°C for 2 hours.

Electrophoresis.

Run on a 4% low melting temperature agarose gel in TAE buffer
 (40mM tris/acetate, 1 mM ethylene-diamine-tetraacetic acid, pH
 7.6).

Diagnostic allele sizes.

ϵ 2, 91 bp, 81 bp.
 ϵ 3, 91 bp, 48 bp.
 ϵ 4, 72 bp, 48 bp.

α 1-antichymotrypsin (ACT) Genotyping (T/A) Assay.Assay.

A 135 bp fragment of the ACT gene spanning the signal peptide is PCR amplified. The sequence of a polymorphic base position is detected by cleavage with BstNI restriction enzyme (whose site is altered by this polymorphism) and agarose gel electrophoresis. The base polymorphism codes for either a threonine (T) or an alanine (A) amino acid.

Primers.

NOT as previously published (those of Kamboh et al 1995), did not work).

ACT-F 5'- GCTTTTCAGAGTTGAGAATGG -3'
 ACT-R 3'- CTTGGTTCTCGTGGGTCAGAT -5'

(N.B. G is a C in the ACT gene but was altered to prevent forming an extra BstNI site in the PCR product.)

PCR. (25 μ l volume).

genomic DNA	80ng
Primer ACT-F	150ng
Primer ACT-R	150ng
10 x PCR Buffer (Perkin Elmer Cetus)	2.5 μ l
Dimethylsulphoxide (denaturant)	2.5 μ l
dATP, dTTP, dCTP, dGTP Nucleotides	0.2mM (each).
Taq (Perkin Elmer Cetus)	0.75 units
Water	to 25 μ l

PCR cycling conditions.

Perkin Elmer Cetus, 9600 machine

(96°C50"), (53°C30"), (72°C30"), 1 cycle
 (96°C15"), (53°C30"), (72°C30"), 17 cycle
 (96°C15"), (53°C30"), (72°C1:30"), 18 cycle.

Ethanol Precipitation.

100% Ethanol	2.5 X volume.
2M sodium acetate	0.1 X volume.

Mix, place at -20°C for 1 hour, spin in microfuge 15 minutes,
 leave at room temperature to dry.

BstNI Digestion.

10 X BstNI restriction buffer	2µl.
0.1M Spermidine	1 µl.
BstNI restriction enzyme	4 units.
Water	to 20µl.

37°C for 2 hours.

Electrophoresis.

Run on a 3% low melting temperature agarose gel in TAE buffer
 (40mM tris/acetate, 1 mM ethylene-diamine-tetraacetic acid, pH
 7.6).

Diagnostic allele sizes.

A (Ala) - 96 bp.
 T (Thr) - 135 bp.

Very-Low-Density-Lipoprotein Receptor (VLDL-R) microsatellite Genotyping Assay.

Assay.

A fragment of the VLDL-R gene 5'UTR is PCR amplified containing a (CGG)_n sequence (tri-nucleotide repeat). The number 'n' varies and defines this polymorphism. Product sizes are determined by denaturing polyacrylamide gel electrophoresis and fluorescence detection of the PCR product labelled at one primers 5' end (using ABI automatic sequencing gel apparatus).

Primers.

As published by Okuizumi et al (1991). Here called 'VLDL-F' and 'VLDL-R', with the former labelled at its 5' end with a FAM fluorescent moiety.

PCR. (25 µl volume).

genomic DNA	80ng
Primer VLDL-F	150ng
Primer VLDL-R	150ng
10 x PCR Buffer (Perkin Elmer Cetus)	2.5µl
Dimethylsulphoxide (denaturant)	2.5µl
dATP, dTTP, dCTP, dGTP Nucleotides	0.2mM (each).
Taq (Perkin Elmer Cetus)	0.75 units
Water	to 25µl

PCR cycling conditions.

Perkin Elmer Cetus, 9600 machine

(96°C50"), (60°C30"), (72°C30"), 1 cycle
 (96°C15"), (60°C30"), (72°C30"), 17 cycle
 (96°C15"), (60°C30"), (72°C1:30"), 18 cycle.

Electrophoresis.

Products diluted 1/20 in water and 2 μ l run on an ABI 373 automatic sequencing /genotyping device to determine allele sizes.

Diagnostic allele sizes.

Range from 94 bp (n=4) to 115 bp (n=11).

The results of the genetic analysis are in the Results.

Method: VIII. Statistics.

Aim of the statistical analysis.

The group of people with early-onset dementia, were not compared with a control sample for the clinical part of the data collection. For certain parts of the data collection, normative data exists, such as for the CAMDEX interview schedule. However, for the genetic tests, a control group was used.

The overall significance and applicability of any results from the study must also be seen in the context of the biases introduced in the sample selection, and these are discussed more fully in the Discussion. Furthermore, the sample used consists of individuals all at different stages of their illness.

At the outset it became apparent that although the sample size was reasonable, by the time the different subgroups (i.e. the different diagnostic categories) were being analysed, numbers would become small, especially when missing data is considered.

Rather than the study starting with a formal hypothesis to be tested, the approach was that of exploratory data analysis. A description has been given for the group as a whole, and the different DSM3R groups, both for the first and second assessment, for some of the different variables.

The populations studied were based on the DSM3R groups: Alzheimer's; Multi-infarct; Alcohol-related; and a group of those cases in overlapping categories. This combination group is also referred to as the Mixed group. The only one overlap not representing a combination with Alzheimer's, is one case, between Alcohol and Multi-infarct dementia. But the term 'combined' group is used in a slightly different context in the genetics results.

The data collected, determines the value of the results, and the more objective the data the more solid are the conclusions that can be drawn from the work. As already

mentioned, the most objective parts of the battery, for the measurement of change, were the CAPE, CAMCOG and neurological examination. One-way analysis of variance was used for the CAPE and CAMCOG in phase I of the study to compare group means in the four diagnostic categories. This method is described below.

Using data from the first assessment (phase I) and the second assessment (phase II) of the study, the DSM3R groups were analysed again using one-way analysis of variance to determine whether there were differences in the extent of change across the diagnostic groups. This and the analysis of the neurological data are discussed in greater detail in the Measures of Change section.

Using the CAPE, CAMCOG and neurological data from both phases of the study, multiple linear regression analysis was used to determine a relationship between the change scores (improvement or deterioration) and age at onset, sex, duration of illness, presence of a family history and diagnostic category. From this, predictors (for example of deterioration), could then be identified.

The analysis of the genetic results is given in the Results section. Possibilities for future directions for the data analysis are given in the Discussion.

One-way analysis of variance.

One-way analysis of variance has been used in Phase I of the study to determine whether the observed differences in the group means (for each sub-score of the CAPE and CAMCOG assessments) can be attributed to sampling variability among sample means or whether the four groups come from populations with different means.

The statistical technique is used to test the null hypothesis H_0 : all four group means are equal. The assumption is that equal variances of the four groups is necessary for valid use of this test.

The F-test statistic is an estimate of the variability in the population based on (i) how much the observations vary within each group and (ii) how much the group means vary among themselves. If group means are equal in the population, then it would be expected that (i) and (ii) are approximately equal. As the F-statistic is a ratio of (i) and (ii), it would then be close to the value one. The significance level p is calculated by comparing the F-value obtained with the F-distribution.

A statistically significant F-value tells you only that the population means are significantly different and gives no information as to the pattern of differences.

Therefore the Bonferroni test is used to compare pairs of means by adjusting the significance level to account for multiple comparisons. From the Bonferroni test, statistically significant differences between pairs of group means are shown.

This method was repeated when comparing the mean of the differences of the CAPE and CAMCOG assessment scores between each diagnostic group from Phase I to Phase II.

Measures of Change.

One-Way Analysis of Variance.

The next stage of the analysis was to look for differences between the two phases, to establish the degree of change (improvement or decline), compared between the four groups for the CAPE and CAMCOG assessments. This was achieved by comparing the means of the differences between the two phases using one-way analysis of variance.

The first assessment scores were subtracted from the second, therefore a resulting positive score would indicate the second assessment score was higher and a negative score that the second assessment score was lower. Each individual subscore has to be interpreted individually. In the CAPE, deterioration is represented by an increase in scores (positive differences), whereas for the CAMCOG, deterioration is represented by a decrease in scores (negative differences).

Chi-square.

For the analysis of the Neurological data, the X^2 test was used to determine whether the diagnostic group was independent of whether a change occurred between assessments.

Kruskal-Wallis one-way analysis of variance.

A total change score between assessments was constructed for each individual, for both the Neurological examination and the Webster scale. Using these scores the Kruskal-Wallis one-way analysis of variance was used to test for differences in changes between the four diagnostic groups.

The Kruskal-Wallis test is a distribution free test and used as an alternative to one-way analysis of variance, with the actual values of the data replaced by ranks.

Multiple Linear Regression Analysis.

Linear regression was used for the CAPE-BRS assessment (physical disability, apathy, communication difficulties, social disruption and CAPE total), the total CAMCOG assessment and the neurological examinations (neurological examination and Webster scale) to examine the relationship between the change scores and a set of independent variables. The independent variables used were: diagnostic group; age at referral (diagnosis); sex; duration of illness; and whether cases had a family history of the illness.

From this analysis the best model was determined for each change score in each of the assessment sub-groups. Care must be taken in the interpretation, and each category analysed separately. For example, a negative change score in the CAPE assessment indicates an overall improvement going from phase I to phase II. A negative change score in the CAMCOG, suggests a deterioration at phase II.

This analysis allows the identification of associations (or predictors) of decline.

Results.

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Ascertainment of the study sample.

290 cases were identified for the study, and the different sources as to where they came from, are shown here:

Table (1).

<u>Survey.</u>	<u>Total Cases.</u>	<u>Yes.</u>	<u>No.</u>	<u>No Trace.</u>
<u>Case Note Surveys.</u>	398 (72 %)	214	168	16
<u>Neurology Records.</u>	51 (9 %)	15	16	20
<u>Word of Mouth.</u>	34 (6 %)	34	0	0
<u>West Lothian.</u>	31 (6 %)	13	11	7
<u>Alcohol Related Survey.</u>	43 (7 %)	14	13	16
<u>Total</u>	557 (100 %)	290 (52 %)	208 (37 %)	59 (11 %)

Having inspected the case notes, the reasons why 208 cases were not included were as follows:

Table (2).

<u>Survey.</u>	<u>Total Not Included</u>	<u>Wrong Diagnosis</u>	<u>Death.</u>	<u>Too old/ Pre 1988.</u>	<u>Out of Area.</u>
<u>Case Note Surveys.</u>	168	101	57	8	2
<u>Neuro-Records.</u>	16	8	2	6	0
<u>Word of Mouth.</u>	0	0	0	0	0
<u>West Lothian.</u>	11	4	7	0	0
<u>Alcohol Related Survey.</u>	13	3	7	2	1
<u>Total.</u>	208 (100%)	116 (56 %)	73 * (35 %)	16 (8 %)	3 (1 %)

* Detail, not included here, is available on the 73 who died.

Contact was then made with the general practitioners and responsible consultants of the 290 cases identified.

From the initial clinical case note diagnosis, the 290 cases were made up of:

Table (3).

<u>Type of Diagnosis.</u>	<u>Number of Subjects.</u>	<u>% of Subjects.</u>
Uncertain type/ Atypical/ Mixed	75	25 %
Possible	60	21 %
Alzheimer's	49	17 %
Alcohol	44	15 %
Multi-Infarct	32	11 %
Huntington's Chorea	15	5 %
Head Injury	5	2 %
Down's	5	2 %
Rare *	3	1 %
Subcortical	2	1 %
Total	290	100 %

* The three rare cases were: Steele-Richardson Syndrome (SRO), or Progressive Supranuclear Palsy (PSP); Myotonic Dystrophy (MD); and Hereditary Spastic Paraparesis (HSP), see: Rother et al, 1976; Went et al, 1964; Bruyn et al, 1964; and Frey et al, 1972.

The case of MD had deceased, and the family of the case with SRO, refused entry to the study. The case of HSP was included.

If it was acceptable to the doctors concerned, then contact was made with the families.

Of the 290 cases, 164 were not seen, and the reasons for this are shown below. It was also decided at this stage not to include cases of Huntington's Chorea, Down's Syndrome, and major head injury.

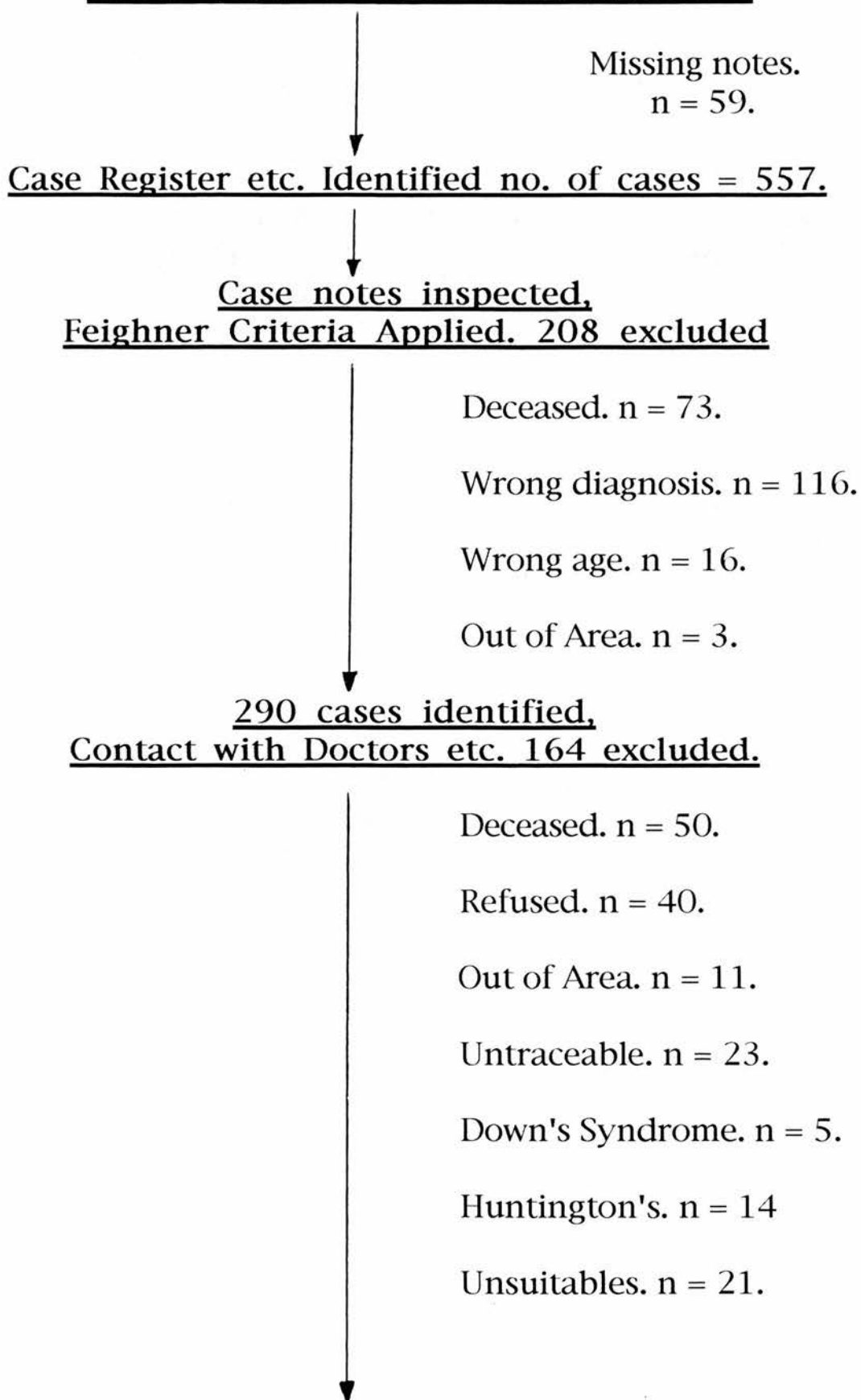
Table (4). Reasons For Case Non-Inclusion.

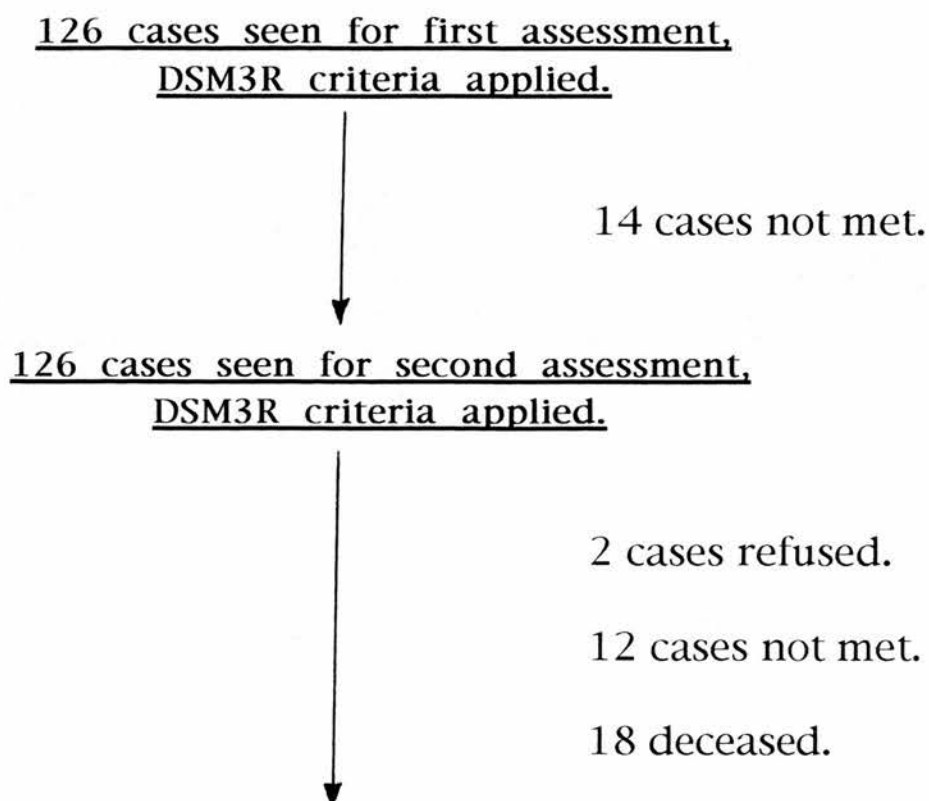
<u>Reason</u>	<u>Number of Cases</u>	<u>% of Total</u>
Deceased	50	30 %
Refused	40	24 %
Untraced	23	14 %
Unsuitable	21	13 %
Huntington's Chorea	14	9 %
Area	11	7 %
Down's Syndrome	5	3 %
Total	164	100 %

Of the cases who had deceased, the case note diagnostic grouping was as follows: Alzheimer's, 9; Multi-infarct, 12; Possibles, 5; Alcohol-related, 9; Not known, 8; Alzheimer's and Alcohol, 1; Alzheimer's and Multi-infarct, 1; Alcohol and Multi-infarct, 1; Parkinson's, 2; Myotonic Dystrophy ,1; and Huntington's Chorea, 1.

The reasons for unsuitability were: No progressive cognitive decline,10; Head injuries (including subarachnoid haemorrhage, drug overdose and asphyxia), 5; Depression, 3; Infarct, 1; Reversible alcohol-related, 1; and Learning disability, 1.

Flow Chart of Ascertainment.





126 cases were seen at the first assessment for the study and of these 112 met the DSM3R criteria for dementia (89 %).

The 14 cases (11 %) not meeting the DSM3R criteria were re-assessed at the second assessment. Detail not provided here documents which parts of the criteria were not met for these cases.

Table (5). Case Inclusion.

	<u>Excluded</u>	<u>Included</u> (Meeting DSM3R criteria)	<u>Possible</u> (Not meeting DSM3R criteria)
<u>Number of Cases</u>	164	112	14
<u>% of Total</u>	57 %	38 %	5 %

Therefore, 126 cases were seen for assessment.

The results of applying the DSM3R and McKhann criteria to the group of 112 are shown below:

Table (6). McKhann Criteria Applied to Cases Of DSM3R Dementia Seen.

<u>McKhann Criteria</u>	<u>Number of Cases</u>	<u>% of Total</u>
<u>Not Met</u>	32	29 %
<u>Met</u>	80	71 %
<u>Total</u>	112	100 %

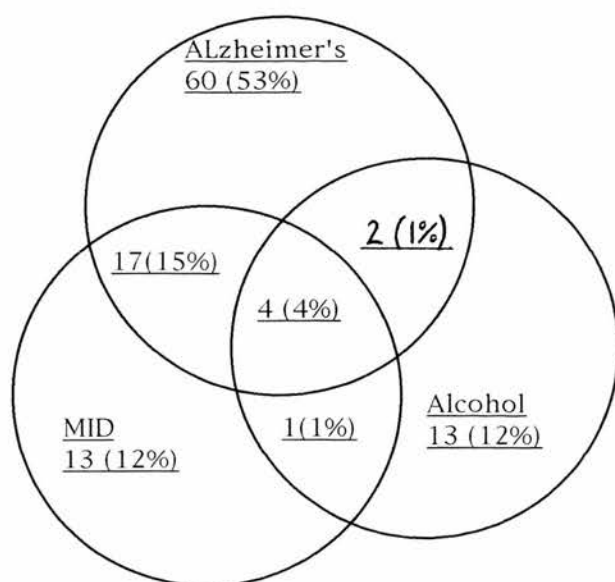
Of those meeting the McKhann criteria, 48 were probable and 32 possible, respectively 43% and 29% of the total, n=112.

14 of the McKhann +ve group did not have adequate investigations done, according to the case notes.

Table (7). DSM3R Criteria Applied to 112 Cases Of Dementia Seen.

<u>DSM3R Type.</u>	<u>Alzheimer's.</u>	<u>Multi-Infarct.</u>	<u>Alcohol.</u>
<u>Alzheimer's.</u>	60 (53%)	17 (15%)	2 (1%)
<u>Multi -Infarct.</u>		13 (12%)	1 (1%)
<u>Alcohol.</u>			13 (12%)

This is also displayed as a Venn Diagram:



With $n = 4$ (4%) overlapping all 3 groups, and $n = 2$ not fitting DSM3R categories. These latter two cases are known as rare types or 'other', one case due to a combination of risks and the other due to Hereditary Spastic Paraparesis.

Equating the DSM3R Alzheimer group
and McKhann group.

DSM3R Alzheimer	= 60
DSM3R Alzheimer + other	= 23
Total	= <u>83</u>

McKhann probable	= 48
McKhann possible	= 32
Total	= <u>80</u>

There were 3 cases which did not meet the tighter McKhann criteria, two with cerebrovascular risk factors too strong to be excluded as the primary cause, and one where the alcohol and cerebrovascular risk factors were too great for Alzheimer's to be the likely primary pathology. Obviously though, a subjective element arises in the decision as to which pathology is primary. These issues are raised again in the Discussion.

Table (8). DSM3R Severity Rating At The First Assessment For 112 Cases.

<u>Severity Rating</u>	<u>Number Of Cases</u>	<u>% Of Cases.</u>
<u>Severe</u>	63	56 %
<u>Moderate</u>	36	32 %
<u>Mild</u>	13	12 %
<u>Total</u>	112	100 %

The issues of applying severity ratings is discussed elsewhere. The DSM3R ratings were used, rather than, for example, the scales of Hughes et al (1982) and Blessed et al (1968).

For the different DSM3R groups, the severity ratings at the first assessment were as follows.

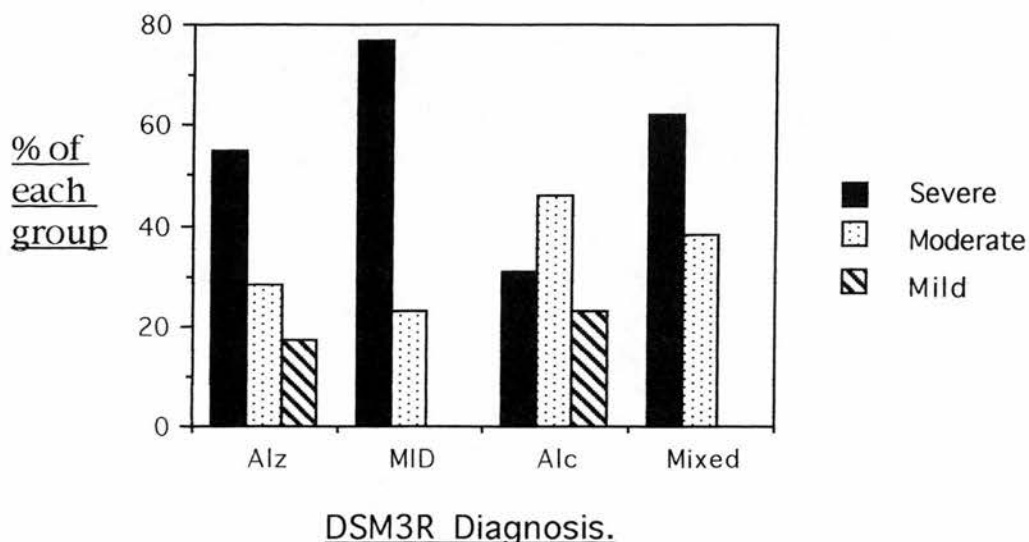
Table (9).

<u>DSM3R</u>	<u>Severe</u>	<u>Moderate</u>	<u>Mild</u>
<u>Alzheimer</u> (n=60)	33 (55%)	17 (28%)	10 (17%)
<u>Multi-infarct</u> (n=13)	10 (77%)	3 (23%)	0
<u>Alcohol</u> (n=13)	4 (31%)	6 (46%)	3 (23%)
<u>Mixed</u> (n=24)	15 (62%)	9 (38%)	0

This is displayed graphically below:

Figure (1).

Severity Rating at the first Assessment
According to DSM3R Diagnosis.



The following tables and figures all relate to a more detailed description of the 126 cases seen. This includes the 14 possible cases who were not excluded from the study, but kept in for the follow-up.

The general description of the group is not repeated in the Results following the 2nd assessment, therefore an opportunity to include the 2 cases who became DSM3R +ve by follow-up are included in some of the descriptions of the group divided according to DSM3R type. In these instances, n=114, rather than 126, and two of these cases are in the 'other' or non DSM3R specified group.

Sex.

For the total 126 cases seen:

53 Males, (42 %) : 73 Females (58 %).

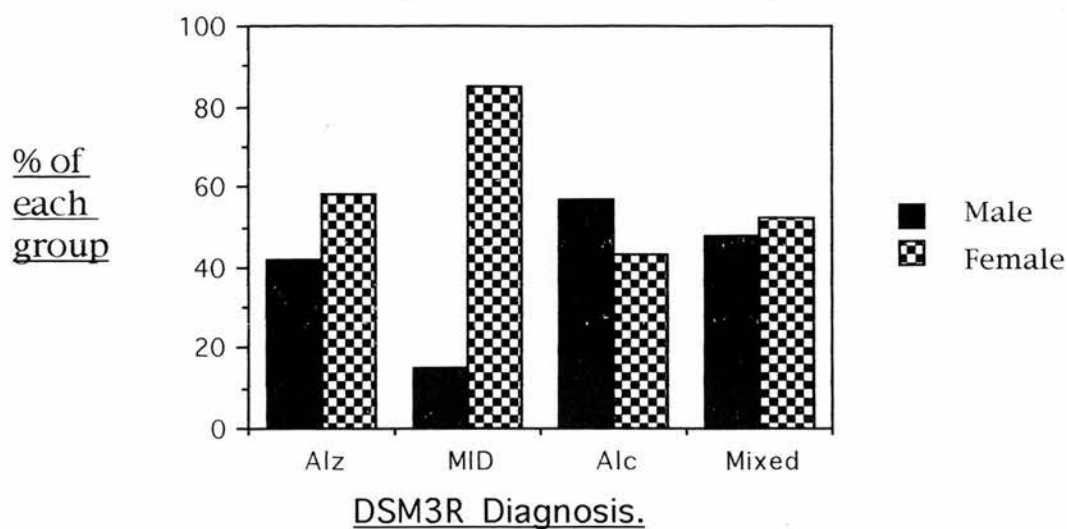
For the DSM3R +ve cases (n=114):

Table (10).

<u>DSM3R group.</u>	<u>Male</u>	<u>Female</u>
Alzheimer (60)	25 (42%)	35 (58%)
Multi-infarct (13)	2 (15%)	11 (85%)
Alcohol (14)	8 (57%)	6 (43%)
Mixed (25)	12 (48%)	13 (52%)

Figure (2).

Sex Distribution In The Study Sample,
According To DSM3R Diagnosis.



Age.

For the total 126 cases:

Average age at original referral = 58 years old.

Average age at first assessment = 62 years old.

For the DSM3R groups (n=114 at second assessment) :

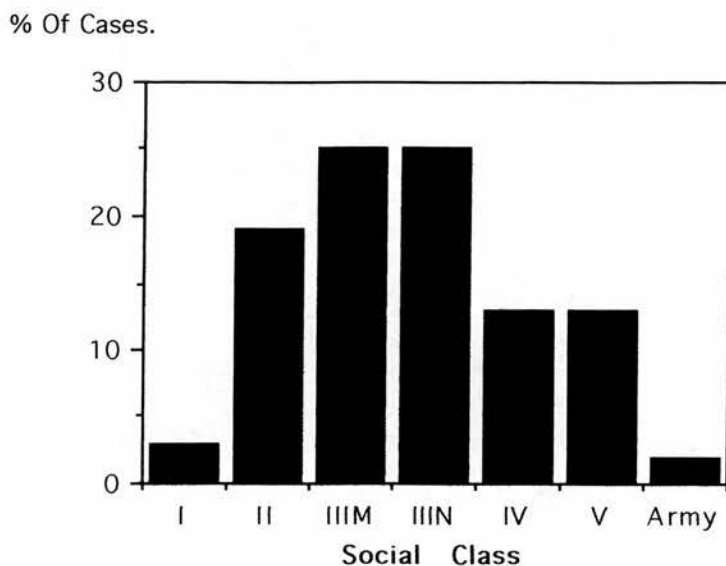
Table (11).

<u>DSM3R group</u>	<u>Age range at referral, years.</u>	<u>Age (mean) at referral, years.</u>
Alzheimer (60)	41-65	58
Multi-infarct (13)	57-65	62
Alcohol (14)	44-64	55
Mixed (25)	52-65	59

Socio-economic Group.

The socio-economic group (class I-V) distribution according to occupation of the 126 cases was as follows:

Figure (3).



Key to socio-economic group (class I-V), according to occupation.

(As defined by The Office Of Population Censuses and Surveys, HMSO 1980.)

I = Professional occupations

II = Intermediate occupations.

IIIN = Non-manual occupations.

IIIM = Manual occupations.

IV = Partly skilled

V = Unskilled

Army = Army personnel

**Table (12). Socio-Economic Group (Class I-V)
Distribution According To Occupation For The
DSM3R Groups:**

<u>DSM3R</u> <u>Group</u>	<u>Class</u> <u>I</u>	<u>II</u>	<u>IIIM</u>	<u>IIIN</u>	<u>IV</u>	<u>V</u>	<u>Army</u>	<u>Total</u>
<u>Alz</u>	3 (5%)	11 (18%)	16 (27%)	17 (28%)	7 (12%)	6 (10%)	0	60
<u>MID</u>	0	3 (23%)	2 (15%)	2 (15%)	4 (31%)	1 (8%)	1 (8%)	13
<u>Alc</u>	0	2 (14%)	6 (43%)	0	5 (36%)	1 (7%)	0	14
<u>Mixed</u>	1 (4%)	6 (24%)	4 (16%)	9 (36%)	1 (4%)	3 (12%)	1 (4%)	25

Academic Achievement.

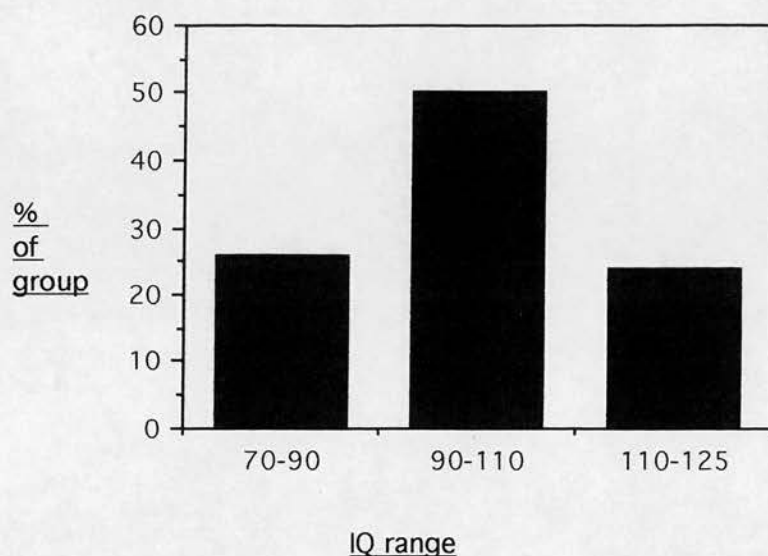
Known for 103 (= 82 %) of the sample

Table (13).

<u>Academic level.</u>	<u>Number Of Cases.</u>	<u>% Of Total.</u>
<u>Not Known.</u>	23	18 %
<u>Nil.</u>	59	47 %
<u>School Leaving Certificate.</u>	30	24 %
<u>Other School Exams.</u>	5	4 %
<u>University.</u>	9	7 %
<u>Total.</u>	126	100 %

Premorbid IQ

Only 58 (46 %) of the sample were able to complete the testing, as measured by the National Adult Reading Test (NART). For the 9 people who scored more than 40 errors on the NART, a Schonell reading test was given on the 2nd assessment, these results are not included.

Figure 4.Premorbid IQ of 58 cases , from the NART.

The mean premorbid IQ for the different DSM3R +ve cases (n = 114), were:

Alzheimer's (only 23 of 60 able to do test) = 103.

MID (only 3 of the 13 able to do test) = 94.

Alcohol (only 12 of 14 able to do test) = 94.

Mixed group (only 7 of 25 able to do test) = 94.

The differences between the groups, were not statistically significant.

Presenting Features.

The presentation was of: memory loss/ disorientation etc in 83 (66%) of the sample; mood/ personality change etc in 19 (15%) of the sample; other features etc in 24 (19%) of the sample.

Current Treatment.

No documentation as to past or current tacrine treatment was made.

At the first assessment,
30 (24%) of the sample were on neuroleptic medication.

At the second assessment, a more formal enquiry of
current anti-depressant treatment was made;
of the Alzheimer's group (n=60), 7 were on antidepressants (12%)
of the MID group (n=13), 2 were on antidepressants (15%)
of the Alcohol group (n=14), 1 was on antidepressants (7%)
of the Mixed group, (n=25), 5 were on antidepressants (20%)

Selected Risk Factors.

For the group as a whole,(n=126).

Table (14).

<u>Risk Factor</u>	<u>Definite Cases</u>	<u>% Of Total</u>
Previous stroke.	19	15 %
Hypertension.	33	26 %
Diabetes.	12	9 %
Head Injury.	22	17 %
Parkinson's Disease.	7	5 %
Alcohol.	26	21 %
Family history of dementia	39	31 %

Some of these have been described according to DSM3R group (n=114). In this, and subsequent tables describing the groups, the percentages in the horizontal rows, refer to the named DSM3R group.

Table (15). History of Previous Stroke.

<u>Dementia Type.</u>	<u>Yes</u>	<u>No</u>	<u>Not known</u>
<u>Alzheimer's</u> n=60	2 (3%)	53	5
<u>MID</u> n=13	9 (69%)	3	1
<u>Alcohol</u> n=14	2 (14%)	11	1
<u>Mixed</u> n=25	6 (24%)	13	6

Table (16). History of, or current hypertension.

<u>Dementia Type.</u>	<u>Yes</u>	<u>No</u>	<u>Not known</u>
<u>Alzheimer's</u> n=60	7 (12%)	49	4
<u>MID</u> n=13	8 (61%)	5	0
<u>Alcohol</u> n=14	2 (14%)	11	1
<u>Mixed</u> n=25	14 (56%)	11	0

Table (17). Previous Head Injury.

<u>Dementia Type.</u>	<u>Yes</u>	<u>No</u>	<u>Not known</u>
<u>Alzheimer's</u> n=60	5 (8%)	48	7
<u>MID</u> n=13	2 (15%)	10	1
<u>Alcohol</u> n=14	4 (28%)	9	1
<u>Mixed</u> n=25	6 (24%)	16	3

Table (18). History of Parkinson's Disease.

<u>Dementia Type.</u>	<u>Yes</u>	<u>No</u>	<u>Not known</u>
<u>Alzheimer's</u> n=60	5 (8%)	55	0
<u>MID</u> n=13	0	12	1
<u>Alcohol</u> n=14	1 (7%)	13	0
<u>Mixed</u> n=25	1 (4%)	23	1

More detailed information is available on the cases with a recorded family history.

Table (19). Family History, according to DSM3R groups.

<u>DSM3R group.</u>	<u>Alzheimer (n=60)</u>	<u>Multi-infarct (n=13)</u>	<u>Alcohol (n=14)</u>	<u>Mixed (n=25)</u>
Family history of dementia	22 (37%)	4 (31%)	2 (14%)	9 (36%)
Family history of Down's Syndrome	2 (3%)	0	0	3 (12%)
Family history of Parkinsons Disease	6 (10%)	0	1 (7%)	3 (12%)

The following are the family histories, of cardiovascular risk factors, for the DSM3R groups:

Table (20).

<u>Family History of:</u>	<u>Alzheimer (n=60)</u>	<u>Multi-infarct (n=13)</u>	<u>Alcohol (n=14)</u>	<u>Mixed (n=25)</u>
<u>Myocardial Infarction.</u>	30 (50%)	6 (46%)	6 (43%)	11 (44%)
<u>High Blood Pressure.</u>	15 (25%)	4 (31%)	3 (21%)	5 (20%)
<u>Stroke.</u>	22 (37%)	7 (54%)	3 (21%)	8 (32%)

None of the differences in family history, reach statistical significance.

The duration of the illness is difficult to accurately define, as discussed in the Introduction: Epidemiological Issues. Two measures are given here:

The First:

Table (21). Years Between First Contact With The Services and First Assessment For The Study.

<u>Years</u>	<u>Number Of Cases</u>	<u>% Of Total</u>
0 to 1	8	6 %
1 to 2	14	11 %
2 to 3	29	23 %
3 or more.	75	60 %
Total	126	100 %

The Second:

From the behavioural questionnaire, the relative's estimate of the duration of the dementia was enquired into:

Figure (5).

Duration Of Symptoms, in Years, for the Total Group:

3 cases (2%) of the 126, had a duration of unknown duration.

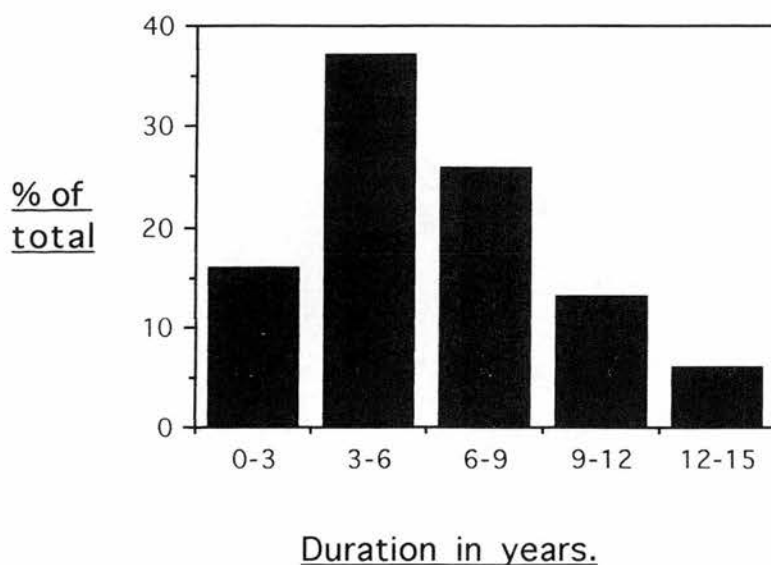


Table (22).

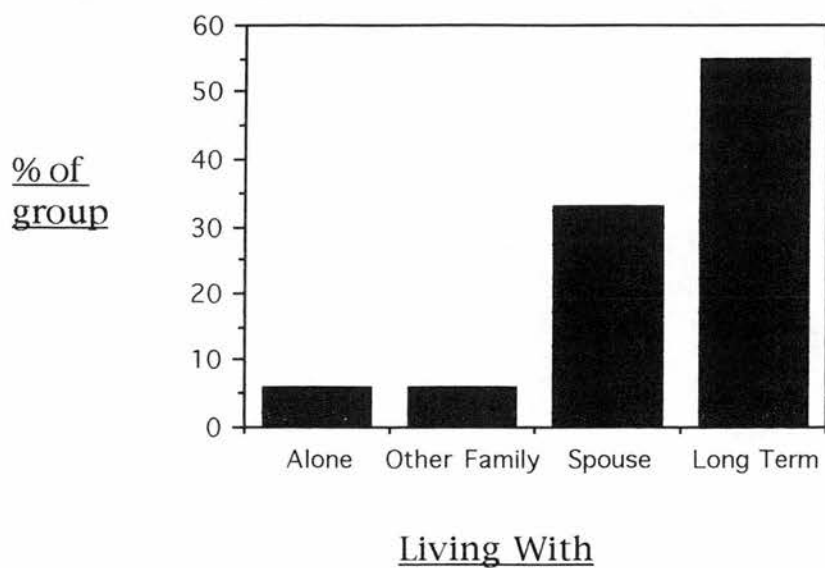
Duration Of Symptoms for the DSM3R Groups:

<u>DSM3R group</u>	<u>Range of duration, months</u>	<u>Mean duration, months and years.</u>
Alzheimer	11-156	75 (6.3 years)
Multi-infarct	36-96	69 (5.8 years)
Alcohol	12-120	55 (4.6 years)
Mixed	12-144	77 (6.4 years)

Data from the first assessment provided information as to the whereabouts of the sample and the relatives involved:

Figure (6).

Where Subjects Living, And With Whom.



From the MOUSEPAD behavioural and psychopathological questionnaire, symptoms of non-cognitive disturbance were recorded:

Delusions.

The total number of cases of the 126 seen, with a delusional belief recorded at some stage of the illness was 45 (**36%**), the most common types are shown in the following table:

Table (23).

Delusional Belief	Number Of cases	% Of Total
Something being stolen	19	15 %
Something being hidden	18	14 %
Someone else being in the house	16	13 %

For the DSM3R groups, n=114, the distribution of delusions is as follows:

Table (24).

<u>DSM3R Group</u>	<u>Delusions</u>
Alzheimer (n=60)	26 (43%)
Multi-infarct (n=13)	5 (38%)
Alcohol (n=14)	1 (7%)
Mixed (n=25)	11 (44%)

Hallucinations.

The total number of cases of the 126 seen, with any of the types of auditory hallucination enquired into, at some stage of the illness, was 11 (9%).

The total number of cases of the 126 seen, with any of the types of visual hallucination enquired into, at some stage of the illness, was 19 (15%).

Table (25).

<u>Hallucination</u>		<u>Number Of Cases</u>	<u>% Of Total</u>
Auditory	Voices	11	9 %
	VoicesUnknown	7	5 %
	Voices Understood	7	5 %
Visual	People	15	12 %
	PeopleUnknown	11	9 %
	People Known	9	7 %
	Animal	6	5 %

Table (26). For the different DSM3R groups:

<u>DSM3R Group</u>	<u>Auditory Hall.</u>	<u>Visual Hall.</u>
Alzheimer (n=60)	8 (13%)	9 (15%)
Multi-infarct (n=13)	0	2 (15%)
Alcohol (n=14)	0	0
Mixed (n=25)	2 (8%)	6 (24%)

Apart from the psychotic and affective symptomatology enquired into, other aspects of the non-cognitive changes in dementia was also documented from the behavioural questionnaire. Selected data from the MOUSEPAD is summarised below, for the group as a whole, (n=126).

Table (27).

<u>Behaviour</u>		<u>Number Of Cases</u>	<u>% Of Total</u>
Walking	More Active On Feet	44	35 %
	Following Another Around	48	38 %
Aggression	All forms	56	44 %
	Physical Against People	36	28 %
	Physical Against Objects	8	6 %
	Verbal	47	37 %

Eating behaviour

Eating more = 22 (17%)

Eating more quickly = 31 (25%)

Emotional lability

Outbursts of crying = 26 (21%)

Outbursts of laughing = 21 (17%)

Some of these items are also described by DSM3R grouping:

Table (28).

<u>Behaviour</u>	<u>Alzheimer</u> <u>(n=60)</u>	<u>Multi-</u> <u>Infarct</u> <u>(n=13)</u>	<u>Alcohol</u> <u>(n=14)</u>	<u>Mixed</u> <u>(n=25)</u>
<u>Walking</u> More active	25 (42%)	6 (46%)	1 (7%)	12 (48%)
<u>Walking</u> Following	29 (48%)	3 (23%)	1 (7%)	14 (56%)
<u>Eating</u> Quicker	16 (27%)	3 (23%)	3 (21%)	8 (32%)
<u>Eating</u> More	13 (22%)	3 (23%)	1 (7%)	4 (16%)
<u>Aggression,</u> all forms.	32 (53%)	5 (38%)	4 (28%)	12 (48%)

Neurological Examination Results.

Some selected items, for the group of 126, are shown below:

Table (29). Primitive reflexes:

<u>Reflex</u>	<u>No. out of 126</u>	<u>% of sample</u>
Hoffman	7	5
Grasp	23	18
Palmo-mental	2	1
Jaw	10	8
Snout	11	9
Glabellar	20	16
Sucking	5	4

This can also be described for the different DSM3R groups:

Table (30).

<u>Reflex</u>	<u>Alzheimer</u> (n=60)	<u>Multi-Infarct</u> (n=13)	<u>Alcohol</u> (n=14)	<u>Mixed</u> (n=25)
Hoffman	5 (8%)	0	0	1 (4%)
Grasp	14 (23%)	4 (31%)	0	5 (20%)
Palmo-Mental	0	1 (8%)	1 (7%)	0
Jaw	5 (8%)	1 (8%)	1 (7%)	3 (12%)
Snout	6 (10%)	1 (8%)	0	1 (4%)
Glabellar	8 (13%)	5 (38%)	3 (21%)	2 (8%)
Sucking	2 (3%)	1 (8%)	0	1 (4%)

The plantar reflexes for the DSM3R groups are as follows:

Table (31).

<u>Dementia Type</u>	<u>Left Planter</u>	<u>Right Planter</u>	<u>Both Plantars</u>	<u>Not known</u>
<u>Alzheimer (n=60)</u>	2 (3%)	2 (3%)	9 (15%)	14 (23%)
<u>Multi-infarct (n=13)</u>	1 (8%)	1(8%)	2 (15%)	3 (23%)
<u>Alcohol (n=14)</u>	0	0	2 (14%)	1 (7%)
<u>Mixed (n=25)</u>	2 (8%)	0	2 (8%)	5 (20%)

And the results for tone; myoclonus; abnormal movements, for the DSM3R groups:

Table (32).

	<u>Alzheimer (n=60)</u>	<u>Multi-infarct (n=13)</u>	<u>Alcohol (n=14)</u>	<u>Mixed (n=25)</u>
<u>Abnormal Tone.</u>	27 (45%)	6 (46%)	2 (14%)	8 (32%)
<u>Myoclonus</u>	6 (10%)	1 (8%)	0	1 (4%)
<u>Abnormal Movements.</u>	12 (20%)	2 (15%)	0	2 (8%)

The mean Webster scores were, for the: Alzheimer's group = 4; Multi-infarct group = 4; Alcohol group = 2 and the Mixed group = 2.

One-way Analysis of Variance.

As described in the Method: Statistics, one-way analysis of variance for the CAPE-BRS and CAMCOG, for the first assessment, was used to compare the group means in the four diagnostic categories.

At the end of this chapter, an Appendix gives the descriptive statistics for the CAPE and CAMCOG totals and subscores, for the first and the second assessments .

A summary of the findings from the first assessment (phase I), is given in table (33). Significance is at the 0.05 level.

From this table, the statistically significant differences in group mean scores occur between the Alcohol group, and at least one other group. This is true for the CAPE subscores of: Physical disability; Communication difficulty and Social disruption. In each case the Alcohol group is scoring significantly lower in the CAPE assessment compared to the other diagnostic groups.

Similarly for the CAMCOG statistically significant differences in group mean scores occur between the Alcohol group, and at least one other group for all subscores. However, the Alcohol group is scoring significantly higher than all other diagnostic groups.

The Alcohol group can therefore be distinguished in its profile from the other three groups.

Summary of Results, Phase I.Table (33).

<u>Description</u>	<u>F-Test</u>	<u>p-value</u>	<u>Differences</u>	<u>Significant Means.</u>
<u>CAPE:</u>				
Physical Disability Subscore	3.34	<0.05 (0.02)	Alc & Comb. Alc and MID.	4 vs 7.33 4 vs 7.69
Apathy Subscore	2.57	(0.06)		
Communication Difficulty Subscore	7.05	<0.001	Alc and Alc. Alc & Comb. Alc and MID.	0.31 vs 2.05 0.31 vs 2.33 0.31 vs 1.85
Social Disruption Subscore	3.17	<0.05 (0.03)	Alc & Comb.	0.85 vs 2.5
Total CAPE.	4.72	<0.01 (0.004)	Alc and Alc. Alc & Comb. Alc and MID.	10.38 vs 16.92 10.38 vs 20.08 10.38 vs 19.54

(Table 33 continued)

<u>CAMCOG</u>				
Total	6.89	<0.001	Alc and Alz. Alc and MID Alc & Comb.	57 vs 22.62 57 vs 18.15 57 vs 15.54
Orientation	3.91	0.01	Alc and Alz. Alc and MID Alc & Comb.	5 vs 2.33 5 vs 1.62 5 vs 1.63
Language	9.59	<0.001	Alc and Alz. Alc and MID Alc & Comb.	21.77vs7.63 21.77vs7.23 21.77vs5.88
Memory	5.65	<0.01	Alc and Alz. Alc and MID. Alc & Comb.	10.31vs4.23 10.31vs3.38 10.31vs2.58
Remote	4.96	<0.01	Alc and Alz. Alc & Comb.	3 vs 1.15 3 vs 0.79
Recent	3.69	0.01	Alc and Alz. Alc and MID. Alc & Comb.	1.69 vs 0.70 1.69 vs 0.38 1.69 vs 0.50
Learning	4.88	<0.01	Alc and Alz. Alc and MID. Alc & Comb.	5.62 vs 2.38 5.62 vs 1.77 5.62 vs 1.29
Attention	8.46	<0.001	Alc and Alz. Alc and MID Alc & Comb.	3.62 vs 1.00 3.62 vs 0.08 3.62 vs 0.67
Praxis	5.98	<0.001	Alc and Alz. Alc and MID Alc & Comb.	7 vs 2.95 7 vs 2.08 7 vs 1.75
Calculation	2.44	>0.05	-	
Abstract thinking	3.93	0.01	Alc and Alz Alc & Comb.	3.69 vs 1.42 3.69 vs 1.00
Perception	2.84	<0.05 (0.04)	Alc & Comb.	4.69 vs 1.67
MSE	6.91	<0.001	Alc and Alz. Alc and MID Alc & Comb.	16.69 vs 6.62 16.69 vs 5.08 16.69 vs 5.29

Results From The Second Assessment.

The descriptive analysis done for the first assessment was not repeated in full again after the second. The description from the 2nd assessment data uses new information, particularly about service needs. Whereas the CAMDEX H questionnaire was found not relevant at the 2nd assessment, the data sheet, CAPE, CAMCOG, MOUSEPAD and neurological examination were.

Meeting DSM3R Criteria.

Following the second assessment, two of the cases previously not meeting the DSM3R criteria for dementia, did so.

Total no. of cases =126.

No. DSM3R +ve =114.

12 cases remained in the possible group.

DSM3R Dementia Diagnosis.

One new case was in the Alzheimer's / Alcohol group, the other in the Alcohol group.

The DSM3R diagnosis for the 114 cases is shown below. As before, 2 cases (1%), were 'other' dementia types and 4 cases (4%) were in the group overlapping all three.

Table (34).

<u>DSM3R Type.</u>	<u>Alzheimer's.</u>	<u>Multi-Infarct.</u>	<u>Alcohol.</u>
<u>Alzheimer's</u>	60 (53%)	17 (15%)	3 (3%)
<u>Multi-Infarct</u>		13 (12%)	1 (1%)
<u>Alcohol</u>			14 (12%)

This is also shown as a Venn Diagram:

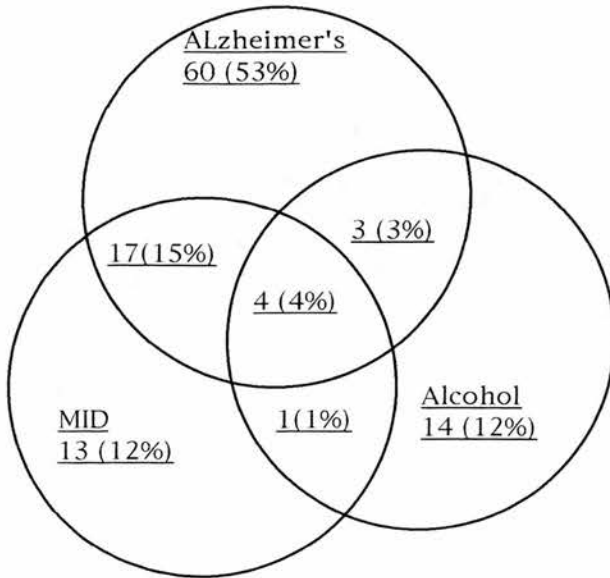


Table (35). DSM3R Severity Rating at the First and Second Assessments.

DSM3R Severity Rating.	Cases and % at 1st assessment, of 112.	Cases and % at 2nd assessment, of 114*.
Severe	63 (56%)	76 (67%)
Moderate	36 (32%)	26 (23%)
Mild	13 (12%)	11 (10%)

* (One case not known, as not re - assessed).

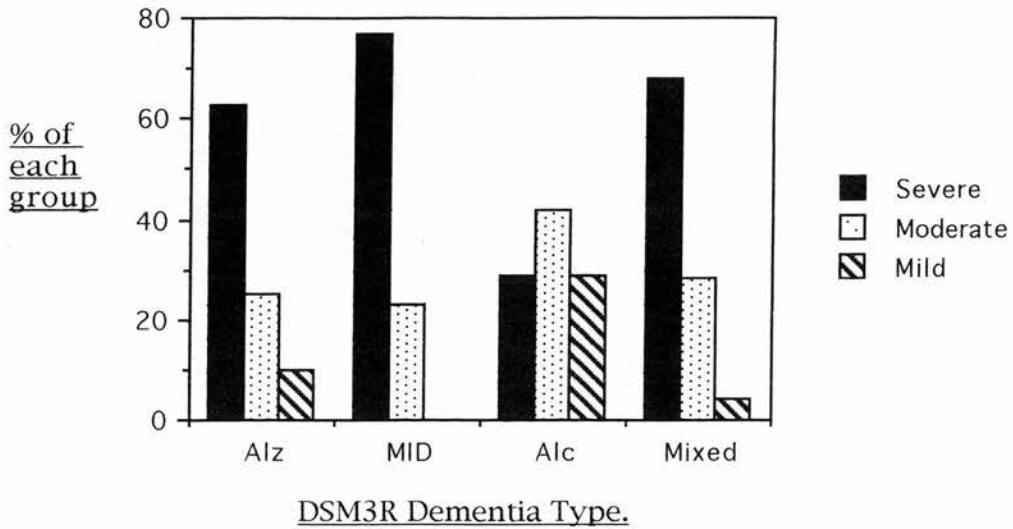
Looking at the different DSM3R groups, the distribution of the severity ratings at the second assessments, compared with those quoted for the first was as follows, (n=114).

Table (36).

<u>DSM3R Group</u>	<u>Severe</u>	<u>Moderate /Severe*</u>	<u>Moderate</u>	<u>Mild</u>	<u>Not Known</u>
<u>Alzheimer (n=60)</u>	38 (63%)	4 (7%)	11 (18%)	6 (10%)	1 (2%)
<u>Multi-infarct (n=13)</u>	10 (77%)	0	3 (23%)	0	0
<u>Alcohol (n=14)</u>	4 (29%)	0	6 (42%)	4 (29%)	0
<u>Mixed (n=25)</u>	17 (68%)	1 (4%)	6 (24%)	1 (4%)	0

* The Moderate/Severe group described an intermediate category of cases in the moderate rating at the severe end of the spectrum, who were often still at home (see Discussion).

The next graph shows the severity ratings for the different DSM3R groups at the 2nd assessment, which can be compared with the first assessment. For this graph, the Moderate/Severe cases are included in the Moderate category:

Figure (7).Severity Ratings for DSM3R Groups at 2nd Assessment.

In total 16 cases changed severity rating:

Table (37).

<u>Change</u>	<u>No. of Cases</u>
To mild	2
Mild to Moderate	2
Mild to Severe	1
Moderate to Severe	6
Moderate to Mod/Sev.	5

The distribution of these changes amongst the various DSM3R groups is as follows:

Table (38).

<u>DSM3R</u>	<u>Change in DSM3R Severity</u> (% Of total)
<u>Alzheimer (n=60)</u>	11 (18%)
<u>Multi-infarct (n=13)</u>	0
<u>Alcohol (n=14)</u>	1 (7%)
<u>Mixed (n=25)</u>	4 (16%)

The McKhann criteria for Alzheimer's Type Dementia were fulfilled as at the first assessment.

Table (39). Attrition after 2nd Assessments.

Reason	No. of Cases	%
Deceased	18	14
Refusal	2	2

Only two neuropathological post-mortem examinations were done. The results of these can be found in the individual case histories given in the appendix. The cases are ma2 and jh101. The findings were not used to retrospectively alter the individual's DSM3R grouping.

The time intervals for the second visits was between 12 and 15.4 months after the first.

Table (40). Profile of Services Used, by 126 cases at the second assessment.

N.B. These are not exclusive categories; those not in long-term care (LTC), may be receiving more than one service. Of the 50 not in LTC, 15 were receiving no services (30%). The data includes those who deceased in the follow-up.

<u>Service Used.</u>	<u>No. of Cases</u>	<u>% of 126.</u>
Long Term Care	76	60
Hospital	58	76
Nursing Home	18	24
Respite Care	12	10
Day Care	22	17
Hospital	9	41
Club	10	45
Both	3	14
Health Worker (district nurse / health visitor / social worker / community psychiatric nurse).	17	13
Home Care (home help / meals on wheels).	9	7
Sitter Service	7	5
Other (Supported accommodation, chiropody etc)	6	5

Table (41). Supports used by Relatives at 2nd Assessment.

Support	No. Cases	%
Alzheimer Group (e.g. Alzheimer's Scotland)	16	13
Carer Group	22	17
Other	3	2

Unknown in 3 cases (2 %).

Where the 126 Cases Were at 1st and 2nd Assessment.

The majority of the group of 126 cases were in LTC but a substantial number were cared for by a spouse (or other family) at home:

Table (42).

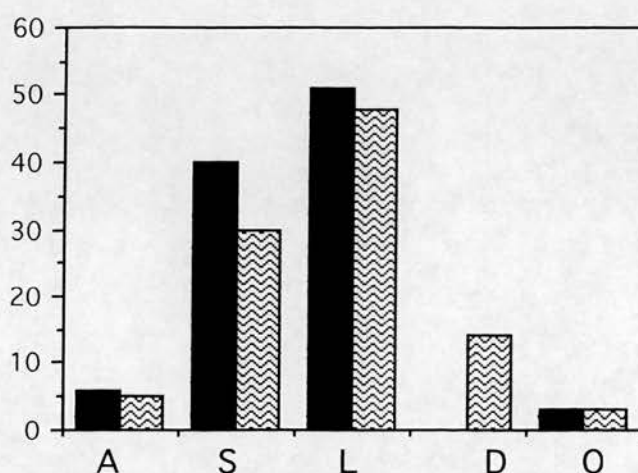
<u>Where</u>	<u>Assessment 1</u>	<u>Assessment 2</u>
Alone	8 (6%)	6 (5%)
Spouse or other	50 (40%)	37 (30%)
Long Term Care	64 (51%)	61* (48%)
Deceased	0	18 (14%)
Other (e.g. Supported accommodation)	4 (3%)	4 (3%)
Total	126	126

* Of the people in LTC at the second assessment, the 15 who died are not included but the 12 new cases admitted, are.

This is displayed graphically in Figure (8).

Figure (8).

Whereabouts of Cases at Both Assessments.



Key:



1st assessment

2nd assessment

A = alone

S = spouse or other

L = long term care

D = deceased

O = other

At the second assessment, 30 people with dementia, were currently at home, living with relatives. Of these, the severity distribution was: mild = 4; moderate = 24; severe = 1; (one case not reassessed). The carers were as follows: wife, 13; husband, 11; son, 3; daughter, 1; other combination of relatives, 2. The ages of the spouses was also collected as part of the initial data, but is not presented here.

Admission to Long-Term Care (LTC).

Of the 18 cases who deceased during the follow-up period, 15 died in LTC, two shortly after entry and 12 new cases had been admitted into LTC in the follow-up period.

Table (43). Time in Long-Term Care, since admission.

(figures include those deceased.) It is striking that about 50% of these subjects had been in LTC for more than 3 years .

Time in months	no =	%
< or = 12	12	15
12-24	11	15
24-36	15	20
36-48	6	8
48-60	11	15
60-72	4	5
72-84	9	12
84-96	4	5
96-108	2	3
108-120	1	1
120-132	0	0
>132	1	1
Total	76	100

Carer Stress Index.

95 relatives completed the questionnaire. The score distribution is shown here:

Table (44).

Score out of 15	No. Cases.out of 95	%
0-3	11	11
3-6	13	14
6-9	33	35
9-12	30	32
12-15	8	8
Total	95	100

Measures of Change.

The section on Measures of Change in the Method : Statistics, describes the comparison of the means of the differences between the two phases, using one-way analysis of variance.

The Phase II - Phase I results are given here:

Table (45).

<u>Description</u>	<u>F-test</u>	<u>p-value</u>	<u>Differences</u>	<u>Significant Means.</u>
<u>CAPE</u>				
Physical Disability Subscore	0.72	(0.5)	-	-
Apathy Subscore	1.25	(0.3)	-	-
Communication Difficulty Subscore	0.49	(0.7)	-	-
Social Disruption Subscore	1.98	(0.12)	-	-
Total	1.52	(0.21)	-	-

Table (45) continued.

<u>CAMCOG</u>				
Total	3.27	<0.05 (0.03)	Alc and Alz.	6 vs -7.10
Orientation	1.88	(0.14)	-	
Language	0.95	(0.42)	-	
Memory	3.11	<0.05 (0.03)	Alc and Alz. Alc and MID.	1.8 vs -0.88 1.8 vs -1.45
Remote	1.28	(0.29)	-	
Recent	1.61	(0.19)	-	
Learning	3.23	<0.05 (0.03)	Alc and MID.	1.30 vs -1.0
Attention	3.43	<0.05 (0.02)	Alc and Alz.	1.1 vs -.031
Praxis	2.73	0.05	*	
Calculation	2.41	(0.07)	-	
Abstract thinking	2.86	<0.05 (0.04)	Alc and Alz.	0.70 vs -0.52
Perception	3.06	<0.05 (0.03)	Alc and Alz.	1.1 vs -0.67
MSE	2.11	(0.10)		

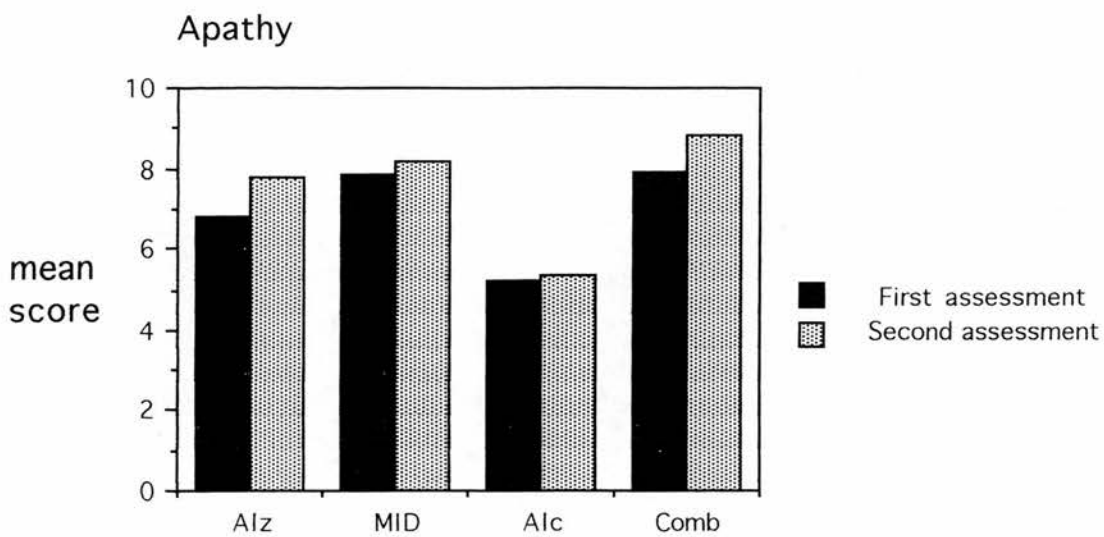
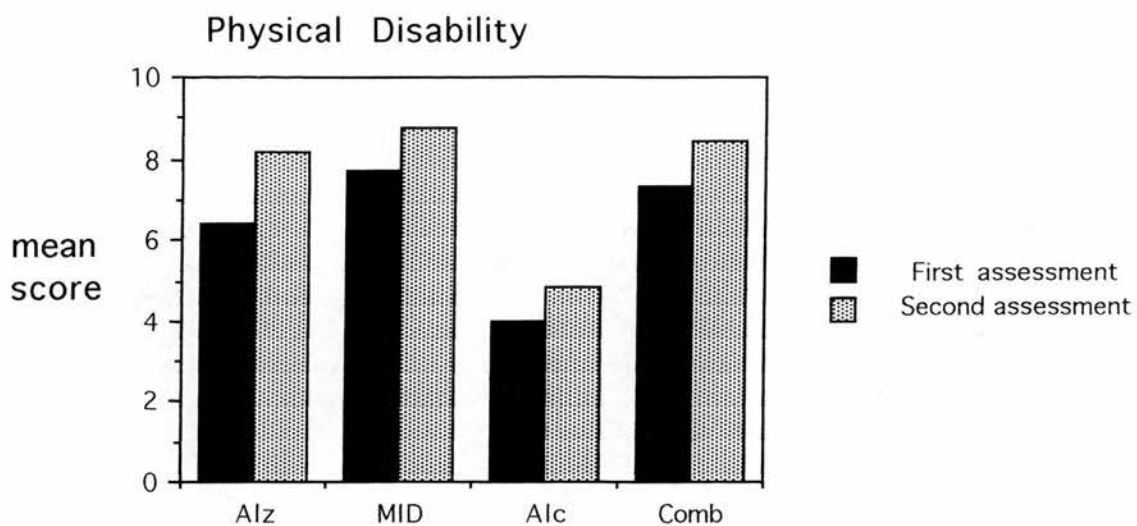
* = No statistically significant results, after adjusting for multiple testing.

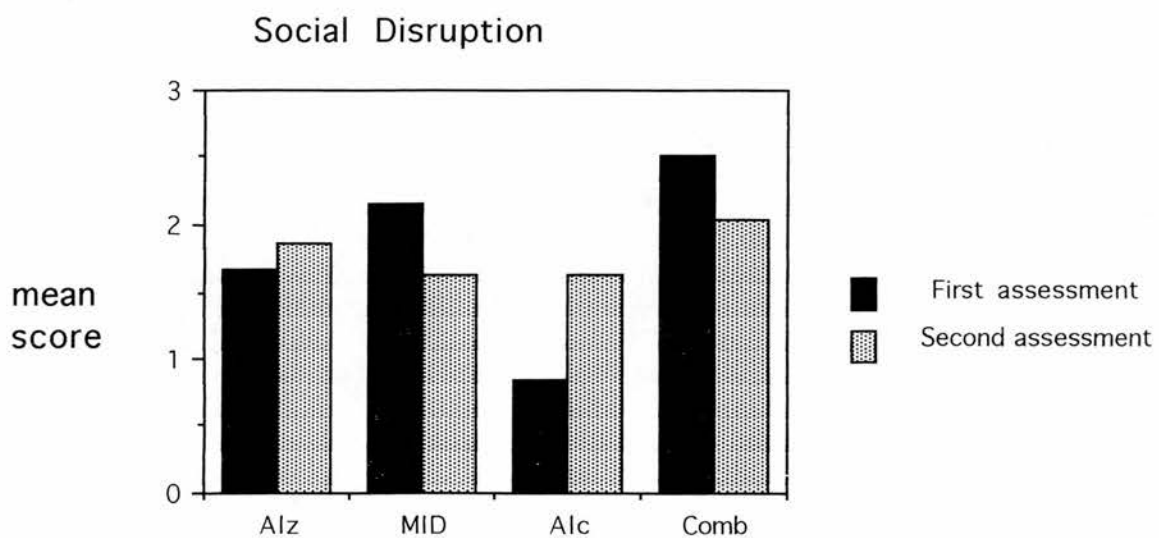
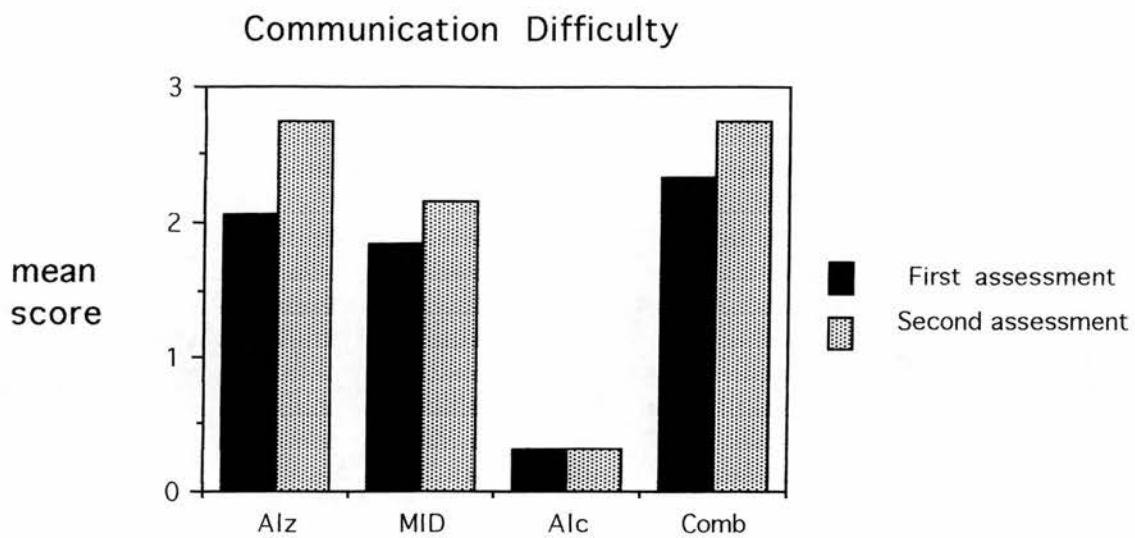
The only significant difference shown, in the change of the mean scores between the phases, was that of the Alcohol group and

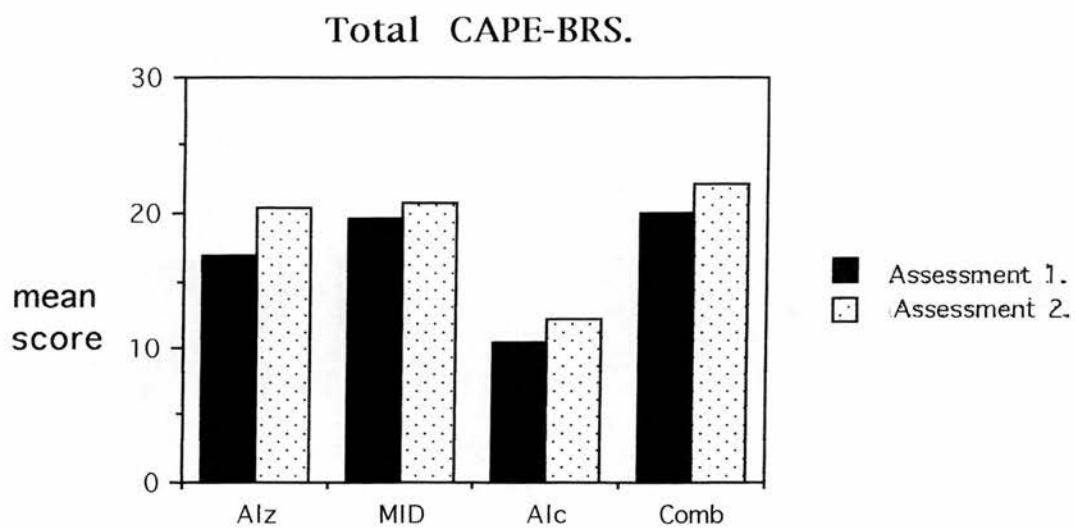
1) the Alzheimer's group, for the CAMCOG total and subscores of: memory; attention; abstract thinking; and perception.

2) the MID group, for the CAMCOG subscores of memory and learning.

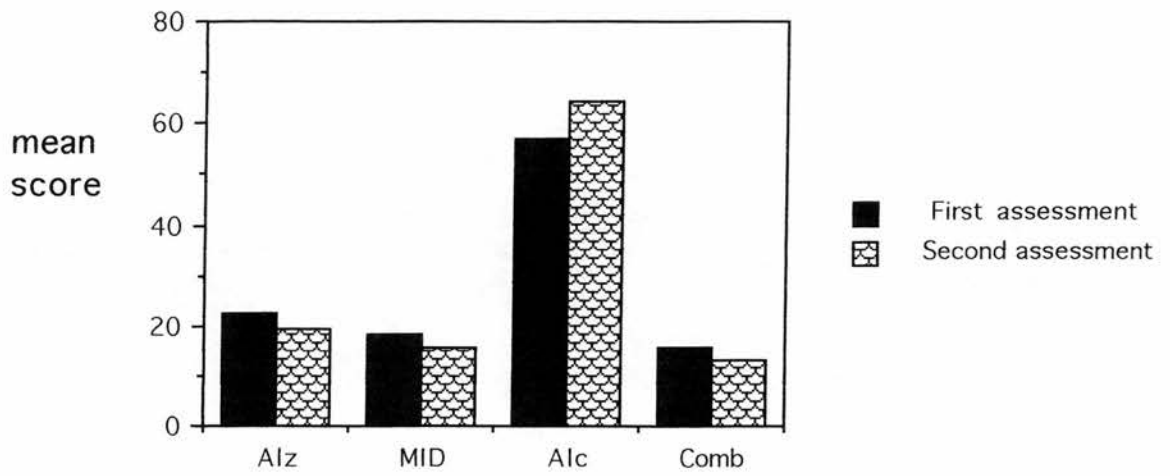
The Results Appendix already mentioned, has details of the descriptive statistics for the CAPE and CAMCOG subscores, for the first and second assessments. The following figures (9-26) display the mean scores, for phase I and phase II, by diagnostic group, and show the Alcohol group to be improving by the second assessment, in the instances mentioned above.



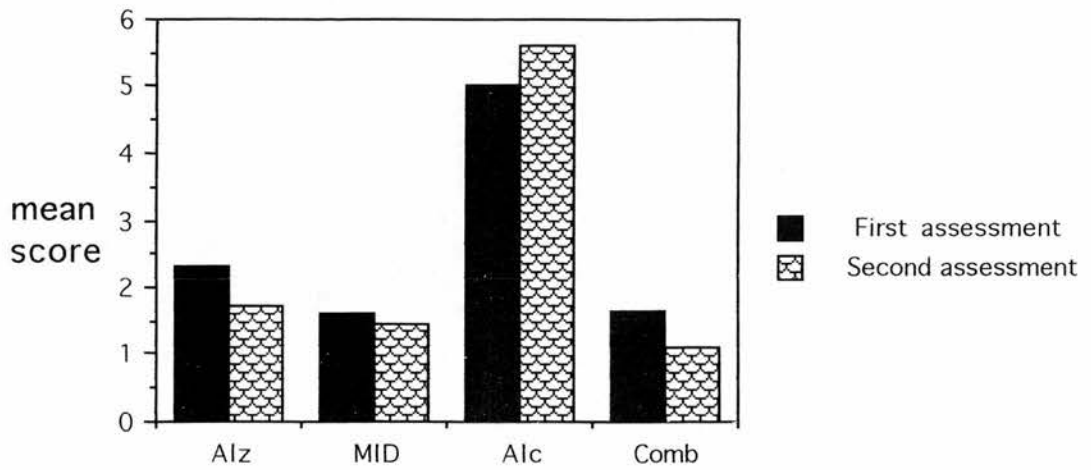




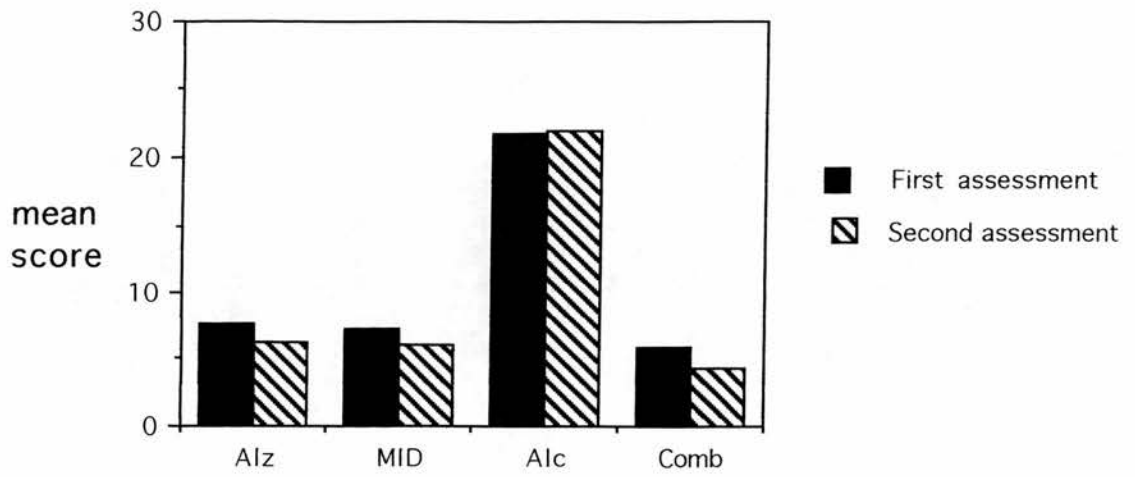
CAMCOG Total



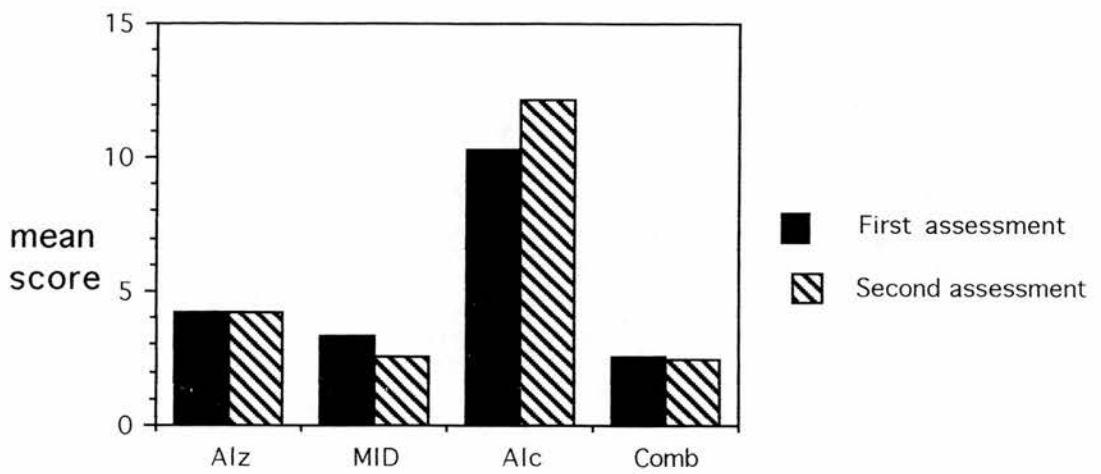
Orientation.



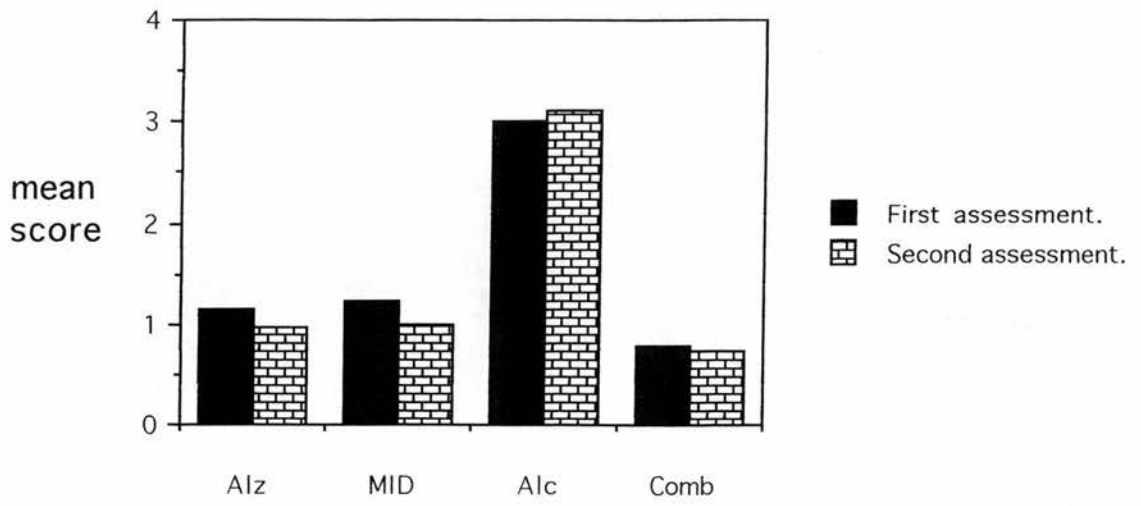
Language



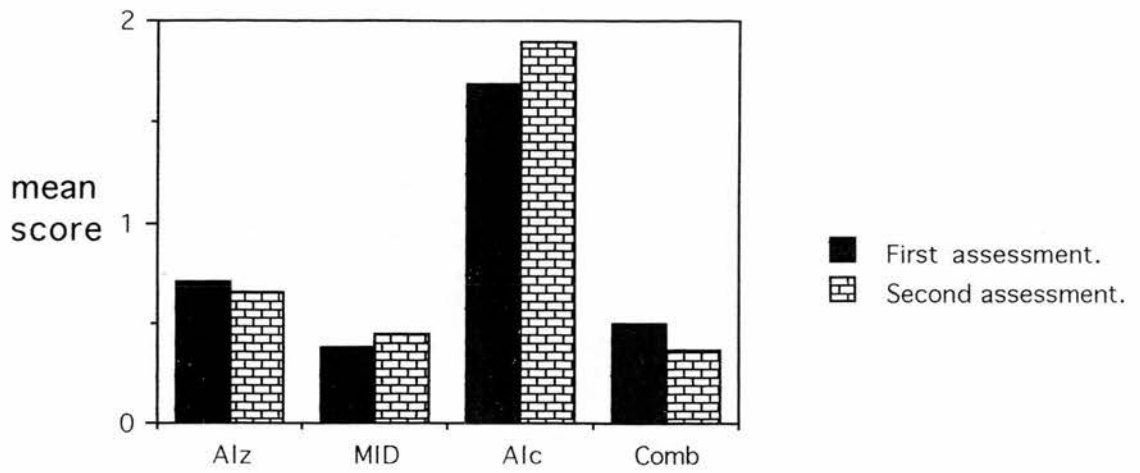
Memory



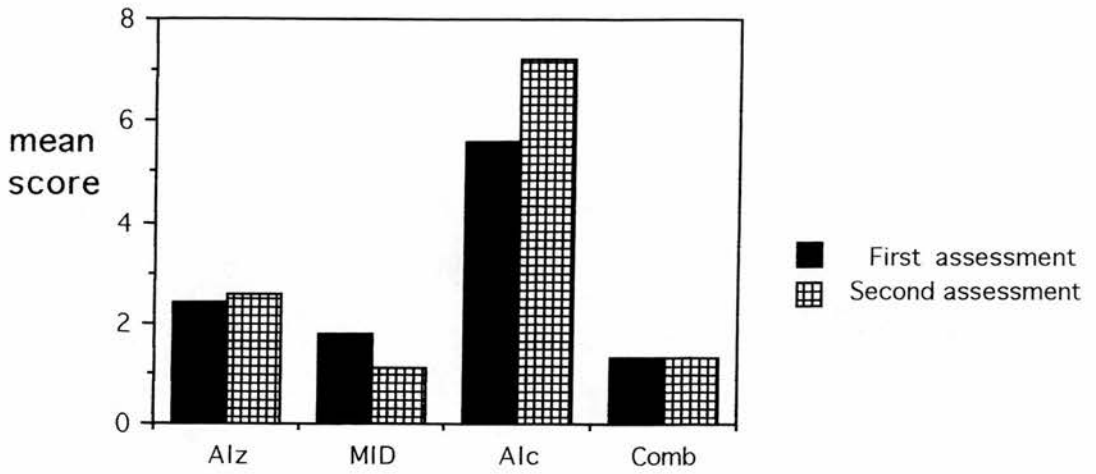
Remote memory.



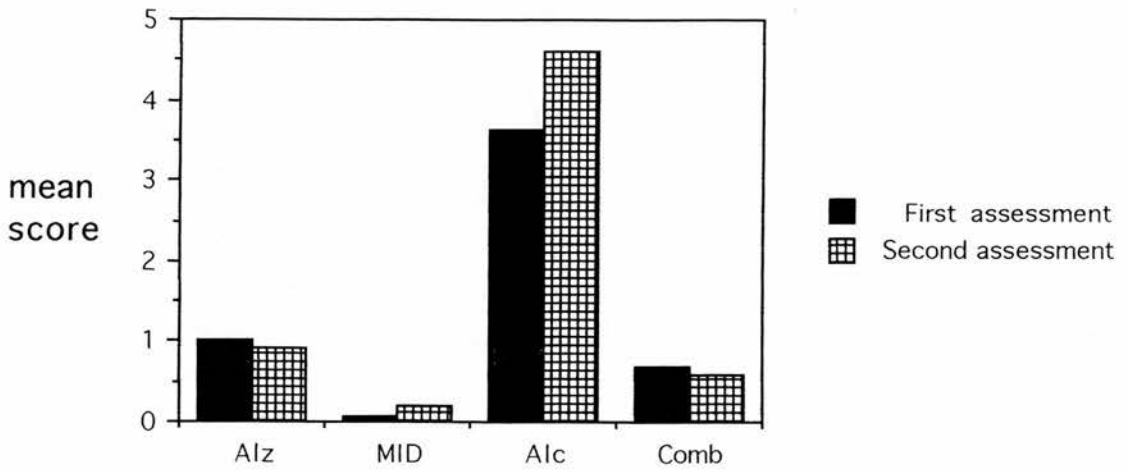
Recent Memory.



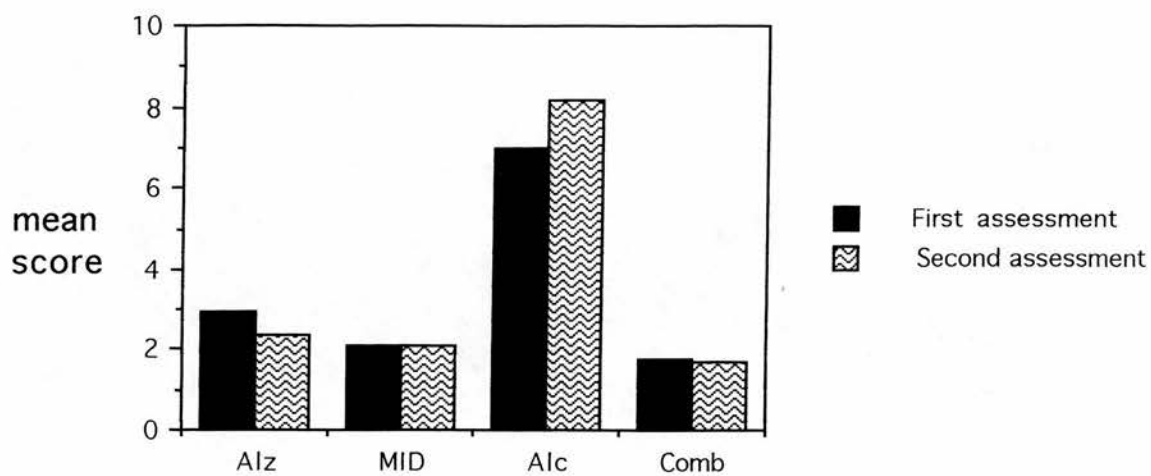
Learning.



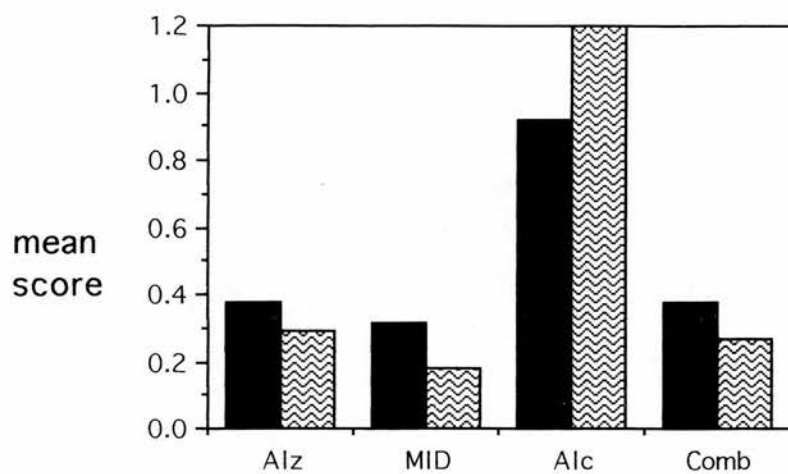
Attention.

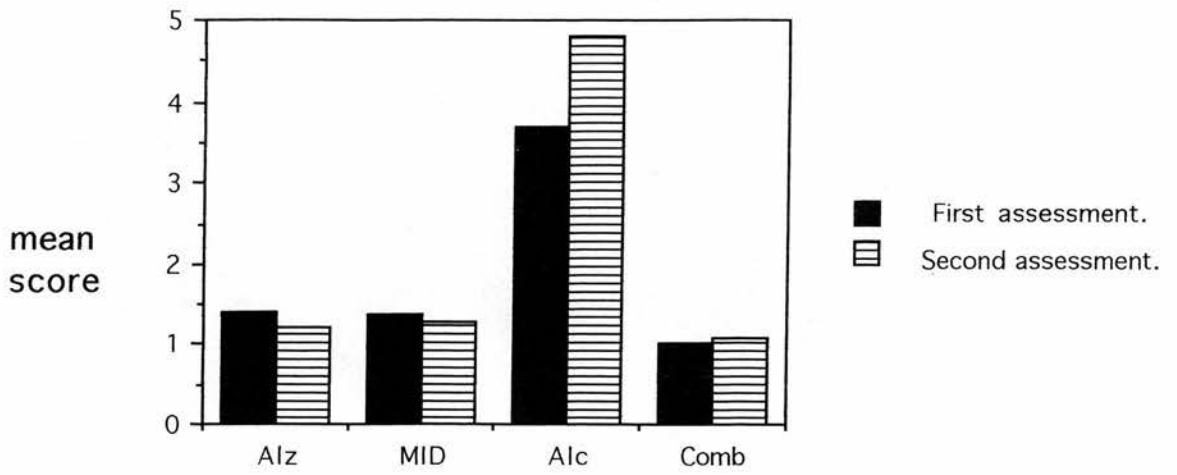
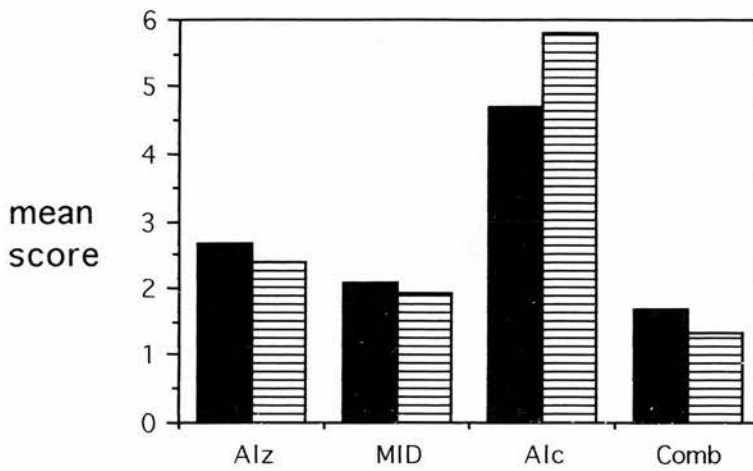


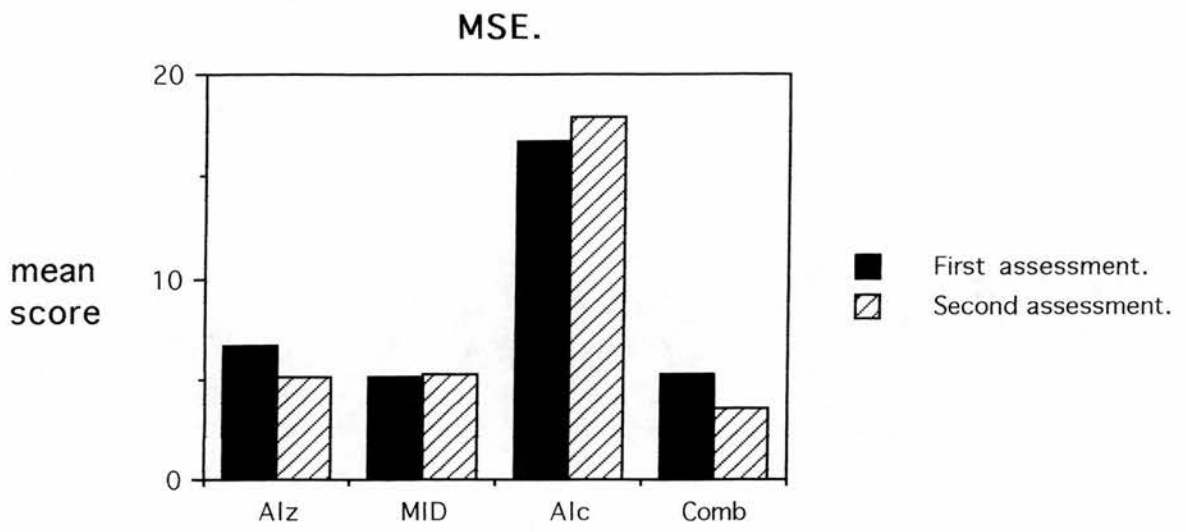
Praxis.



Calculation.



Abstract thinking.**Perception.**



In addition, the Neurological examination and Webster scale data, were analysed, to detect changes from the first assessment to the second, for the four groups. It became apparent when inspecting individual questions that when changes did occur their direction were similar over diagnostic groups and no clear pattern emerged.

The following tables summarise both the Neurological and Webster scale data to display where changes occur. These combine all sections of the questionnaire. The X^2 test was used to determine whether the diagnostic group was independent of whether a change occurred between assessments.

Table (46). Numbers of patients changing in at least one subgroup between the first neurological assessment and the second.

	<u>No change.</u>	<u>Change.</u>	<u>Total.</u>
<u>Alzheimer</u>	29	31	60
<u>MID</u>	4	9	13
<u>Alcohol</u>	9	4	13
<u>Combination</u>	8	16	24
<u>Total</u>	50	60	110

$X^2_{,3} = 5.72, p = 0.13.$

Table (47). Numbers of patients changing in at least one subgroup between the first Webster scale assessment and the second.

	<u>No change.</u>	<u>Change.</u>	<u>Total.</u>
<u>Alzheimer</u>	29	31	60
<u>MID</u>	4	9	13
<u>Alcohol</u>	10	3	13
<u>Combination</u>	11	13	24
<u>Total</u>	54	56	110

$$X^2_{,3} = 5.89, p = 0.12.$$

In both examinations, the X^2 statistic shows that when a change occurs it is independent of diagnostic group.

From the Kruskal-Wallis one-way analysis of variance for the total neurological change score, a $X^2_{,3} = 9.65$, ($p = 0.02$) indicates a statistically significant difference in the change score between the four groups. (MID mean rank 30.29, Combination mean rank 56.23.)

From the Kruskal-Wallis one-way analysis of variance for the total Webster scale change score, a $X^2_{,3} = 4.83$, ($p = 0.18$) indicates no evidence of differences in changes between the four groups.

Results of Multiple Linear Regression Analysis.

Table (48) shows the model which best describes the data. Included are the regression coefficients, standard error in parenthesis and the significance level of the independent variables.

For the CAMCOG total and the Neurological total (N score), statistically significant differences were observed between diagnostic groups. In each case the group means, F-value and significance levels are shown (see table 49).

Table (48).

	DSM3R Groups	Age	Sex	Duration	Family History	Constant
<u>CAPE</u> Total.		0.17 (0.085) p=0.04.				-7.49 (5.022) p=0.14
Physical Disability.		0.07 (0.034) p=0.04		-0.01 (0.0040) p=0.02.		-2.04 (1.996) p=0.31
Apathy						
Communication.		0.04 (0.017) p=0.02				-1.99 (0.992) p=0.05
Social Disruption.						
<u>CAMCOG</u> Total.	see below			0.10 (0.031) p=0.002		-15.06 (2.972) p=0.000
<u>N score</u>	see below					0.77 (0.214) p=0.001
<u>W score</u>		0.14 (0.060) p=0.02				-7.30 (3.550) p=0.04

Table (49).

CAMCOG Total	<u>Group Means</u>			
	<u>Alz</u>	<u>MID</u>	<u>Alc</u>	<u>Comb</u>
	-7.10	-5.82	5.67	-3.59
	F=3.84, df=3 p=0.012			
N score	<u>Group Means</u>			
	<u>Alz</u>	<u>MID</u>	<u>Alc</u>	<u>Comb</u>
	0.77	-0.58	0.10	1.32
	F=4.83 df=3 p=0.004			

The table shows for the CAPE subscores of physical disability, communication and the CAPE total, that age at diagnosis is a statistically significant factor in explaining the change score between phases. Since the sign of the regression coefficient is positive in all cases, this indicates an increase in the change score, i.e. a deterioration as age at diagnosis increases. However, the opposite effect is seen for the physical disability subscore and duration of illness. As duration of illness increases, the CAPE subscore reduces and hence an improvement is detected. These findings, and others from this table, are discussed in the next chapter.

Genetic Results.

Analysis Of Genotype Frequencies At The APOE, VDRL-R and ACT Loci In Dementia Patients.

Description of data.

Genotype data on the three loci were received on 119 dementia patients and 152 non-demented controls. For the dementia patients, additional data were recorded on: DSM3R diagnosis; sex; age at referral; whether familial or not; duration of illness; severity rating at first and second assessments. Of the 119 dementia patients, 59 were classified by the DSM3R diagnosis as 'Pure' Alzheimer's, 22 as 'Mixed' Alzheimer's (Alzheimer's together with Alcohol-related or Multi-infarct dementia), and 38 as non-Alzheimer's. The mean ages at referral of these three groups of dementia patients were very similar, both to each other - respectively 58.4, 59.6 and 55.9 - and to the mean age of the controls - 58.0. The corresponding proportions of males were respectively 40.7%, 45.5%, 39.5% and 62.5%. There was therefore a marked difference in sex ratio between patients and controls, but not between the three patient groups.

Tables G1-G13, give the genetics results and are in the Results: Appendix.

Analysis of APOE locus.

(In this part of the text, APOE ϵ 4, is symbolised by E4.)

Genotype frequencies.

Table (G1) gives the breakdown according to diagnostic grouping and genotype. Because the frequency of E2 was low, and because of the strong prior hypothesis concerning the role of E4, the genotypes were grouped (for the purposes of statistical testing) as homozygous E4, heterozygous E4 or non-E4 carrier (i.e.

having 2, 1, or 0, E4 alleles respectively). Also, in the initial analysis all 81 patients with an Alzheimer's diagnosis, whether 'Pure' or 'Mixed', were grouped together. They are specifically referred to in the genetics results as the 'Combined' Alzheimer's group. The overall chi-squared comparing the three groups (Alzheimer's, non-Alzheimer's and controls) was highly statistically significant ($X^2 = 19.1$, 4 d.f., $P = 0.00074$). However, of the pairwise comparisons, only that between the Alzheimer's and controls was significant ($X^2 = 19.5$, 2d.f., $P = 0.000059$), with an excess of E4 carriers in the patient group. The non-Alzheimer's group did not differ significantly (at the $P = 0.05$ level) from either of the other two.

The analysis was repeated with the four groupings: 'Pure' Alzheimer's, 'Mixed' Alzheimer's, non-Alzheimer's and controls. Here the overall chi-squared was again significant ($X^2 = 20.5$, 6 d.f., $P = 0.0022$). Pairwise comparisons showed that there were highly significant differences between the 'Pure' Alzheimer's and controls ($X^2 = 13.9$, 2 d.f., $P = 0.00095$), and between the 'Mixed' Alzheimer's and controls ($X^2 = 17.9$, 2 d.f., $P = 0.00013$), but not between the non-Alzheimer's and controls ($X^2 = 4.90$, 2 d.f., $P = 0.086$), nor between the 'Pure' and 'Mixed' Alzheimer's ($X^2 = 0.88$, 2 d.f., $P = 0.65$). (N.B. Some P-values quoted in this paragraph are unreliable, because of small numbers in some categories; however, the general conclusions are unaffected).

Analysis of allele frequencies.

Table (G2) is a breakdown of allele frequencies by patient grouping. Statistical tests gave broadly similar results to those comparing genotype frequencies. Thus, the overall chi-squared comparing the three groups ('Combined' Alzheimer's, non-Alzheimer's and controls) was highly significant ($X^2 = 21.2$, 4 d.f., $P = 0.00029$). However, of the pairwise comparisons only that between the Alzheimer's and controls was significant ($X^2 = 20.6$, 2 d.f., $P = 0.000033$), with an excess frequency of E4 in the

patient group. The non-Alzheimer's group did not differ significantly (at the $P = 0.05$ level) from either of the other two.

As in the case of the genotype frequencies, the analysis was repeated with the four patient groupings. Here the overall chi-squared was again significant ($X^2 = 23.4$, 6 d.f., $P = 0.00066$). Pairwise comparisons showed that there were highly significant differences between the 'Pure' Alzheimer's and controls ($X^2 = 14.4$, 2 d.f., $P = 0.00074$), and between the 'Mixed' Alzheimer's and controls ($X^2 = 14.7$, 2 d.f., $P = 0.00065$), but not between the non-Alzheimer's and controls ($X^2 = 3.27$, 2 d.f., $P = 0.19$), nor between the 'Pure' and 'Mixed' Alzheimer's ($X^2 = 2.35$, 2 d.f., $P = 0.31$). (As above, some P-values quoted in this paragraph are unreliable).

Hardy-Weinberg equilibrium.

Using the observed allele frequencies in the control group, the expected numbers of each genotype can be calculated, under the assumption that the population from which the controls were drawn is in Hardy-Weinberg equilibrium. The expected numbers of genotypes 2/2, 2/3, 2/4, 3/3, 3/4, 4/4 were respectively 1.0, 18.8, 4.1, 86.3, 37.7 and 4.1 (compare with observed numbers in Table G1). Small expected numbers for some genotypes make it unwise to apply standard tests of significance. However, since the observed and expected numbers differed by no more than 1, the fit appears to be very close. The main practical use of this result is that it justifies using expected rather than observed values in calculations of risk (see below), leading to estimates with lower standard errors.

Relative and attributable risks.

Table (G3) gives relative risk estimates for 'Combined' Alzheimer's, for various comparison groups and using both observed and Hardy-Weinberg expected numbers in the control categories. Table (G4) gives corresponding values for 'Pure' Alzheimer's. It can be seen that the estimates are all slightly higher for the 'Combined' than the 'Pure' group, and that the effect of using Hardy-Weinberg expected values was to reduce

the widths of the 95% confidence intervals (though by a rather small amount in most cases).

It is also possible to calculate the so-called 'population attributable risk'. This is an attempt to answer the question: if the risk in E4 carriers were reduced to the same level as in non-carriers, by how much would the population incidence of the disease be reduced? It is therefore a somewhat hypothetical concept, but nonetheless gives a measure of the impact of the E4 allele as a cause of Alzheimer's. The answers from the present data are 31.0% (95% C.L.: 11.4% -46.2%) for 'Combined ' Alzheimer's and 29.5% (95% C.L.: 6.8% - 46.7%) for 'Pure' Alzheimer's (these figures were derived using observed numbers in the controls; using Hardy-Weinberg expectations made little difference).

Characteristics of Alzheimer patients.

Analysis of the recorded characteristics of the Alzheimer patients, led to the following conclusions (unless otherwise stated the conclusions apply to both the 'Combined' and 'Pure' groups):

- (1) the sex ratio did not differ significantly between genotype groups (i.e. non-E4 carriers, E4 heterozygotes and E4 homozygotes);
- (2) there was a trend towards a higher proportion of familial cases with increasing numbers of E4 allele; the significance levels for the regression were 0.038 and 0.049 for the 'Combined' and 'Pure' groups respectively;
- (3) there were no significant differences between genotype groups in the severity at first or second assessment, or in the change between them;
- (4) there were no significant differences between genotype groups in the duration of illness (N.B. the standard deviations were extremely large);
- (5) there was a significant regression of age at referral on the number of E4 alleles; for the 'Combined' and 'Pure' groups the estimates were respectively +1.83 (SE 0.73) years and +2.03 (SE 0.88) for each additional E4 allele;

(6) the mean age at referral was lower for familial cases than for non-familial ones in each genotype group, but after adjusting for genotype, the multiple regressions including familiarity as a predictor, were not significant (at the $P = 0.05$ level); over all genotype groups combined, the mean difference was less than 1 year.

Analysis of VDRL-R locus.

Genotype frequencies.

More than 97% of alleles were identified at one of three loci (97, 106, 109). The remainder were at 115 (2.0%), 112 (0.4%) and 103 (0.2%). Since none of these 'minor' loci showed any interesting associations, they were pooled together with 109 for purposes of statistical analysis (Table G5). No significant differences were found between any of the groups ('Pure', 'Mixed', 'Combined', Non-Alzheimers and Controls). Because of the reported association with the 97-allele (Okuizumi et al 1995), the data were also analysed in terms of individuals with 0, 1 or 2, 97-alleles. Again, no significant differences were found. Table (G7) summarises the results.

Allele Frequencies.

No significant differences in allele frequencies were found between any of the groups (Table G6). When all alleles except for 97 were pooled, there was a single significant difference between the non-Alzheimer patients and controls ($X^2 = 4.93$, 1 d.f., $P = 0.026$). Table (G8) summarises the results.

Hardy-Weinberg equilibrium.

The expected distribution of control genotypes under the assumption of Hardy-Weinberg equilibrium was (in the order shown in Table G5): 14.8, 24.4, 40.9, 10.0, 33.6, 28.2. The observed distribution did not differ significantly from this ($X^2 = 1.94$, 3 d.f., $P = 0.58$).

Relative and attributable risk.

There seemed little point in calculating these for the VLDL-R locus, since no significant associations were found.

Characteristics of Alzheimer patients.

Similar analyses were carried out for the VLDL-R locus as for APOE. The only significant results were an increased level of recorded familiarity in patients with at least one 106-allele (68% vs. 31%, $X^2 = 7.42$, 1 d.f., $P = 0.0065$), and an increased proportion of the highest severity rating at first assessment in patients lacking a 97-allele (76% vs. 57%, $X^2 = 7.92$, 1 d.f., $P = 0.0049$). There was a similar, though less marked, effect in the severity rating at second assessment.

Analysis of ACT locus.

Genotype frequencies.

No significant differences in ACT genotype frequencies were found between any of the groups ('Pure', 'Mixed', 'Combined', Non-Alzheimers and Controls). See Tables (G9) and (G11).

Allele frequencies.

No significant differences in ACT allele frequencies were found between any of the groups. See Tables (G10) and (G12).

Hardy-Weinberg equilibrium.

The expected distribution of control genotypes under the assumption of Hardy-Weinberg equilibrium was: 35.54 (TT), 75.92 (AT), 40.54 (AA). The observed distribution differed significantly from this ($X^2 = 5.87$, 1 d.f., $P = 0.015$).

Relative and attributable risks.

As with the VDRL-R locus, there seemed little point in calculating these, since no significant associations were found.

Charateristics of Alzheimer patients.

Similar analyses were carried out as for VDRL-R and APOE. No significant results were found.

Further Comments.

In these analyses, each locus has been analysed independently. Also, the influence of covariates, such as sex, has been ignored. This may be unwise, since there was a gross disparity between the sex ratios of cases and controls. The best way to deal with these problems is to use logistic regression methods, which allow one to model the risk as a simultaneous function of all potentially predictive variables - in this case genotypes at all loci and sex.

Further Analysis Of Genotype Frequencies At The APOE, VDRL-R And ACT Loci In Dementia Patients: Results Of Logistic Regression.

Background and methods.

In the previous analysis, each locus was examined independently of all others as a possible risk factor for Alzheimer's disease. Also no account was taken of the large discrepancy in the sex ratio between cases and controls, which resulted largely from the method of sampling the latter. In order simultaneously to investigate the effects of all loci, and to allow for the biased sex ratio in the controls, logistic regression analysis can be used. This is a multiple regression procedure which models the logarithm of the odds ratio as a linear function of whatever predictor variables required. The model is:

$$\log \left[\frac{P}{1-P} \right] = B_0 + B_1 X_1 + B_2 X_2 + \dots$$

P denotes the probability of being affected.

$X_1 X_2$ represent predictor variables

$B_0 B_1 B_2$ are coefficients reflecting the influence of each predictor

The coefficients themselves are estimated, together with standard errors and correlations, using maximum likelihood. Furthermore, standard methods exist for judging whether the influence of any particular predictor is statistically significant (at say the $p=0.05$ level), either alone or in conjunction with other variables. By starting from a basic model with no predictor variables at all, then adding them one at a time according to their statistical significance and stopping when no more can be found, there is the possibility of building a model that explains the data with the smallest number of predictors. This is known as the 'forward selection' approach and, although it is not guaranteed to give an identical result to that obtained by other methods, it usually does.

The predictor variables used in the analysis are listed and defined in Table (G13). Note that two variables are defined for each allele. In each case, the first variable represents a contrast between non-carriers and carriers, while the second represents one between homozygous carriers and the rest (heterozygous carriers plus non-carriers). Although there are many different ways of defining contrasts, a maximum of only two can be included in any analysis, and any set of two will lead to the same final result.

Results.

As a check that the procedure was correctly implemented, a model was fitted with predictors APOE.1 and APOE.2 only. The relative risks were calculated from the estimated B-values and, as expected, were found to be identical to those obtained from the previous analysis. The confidence intervals were also identical.

All variables and their interactions were put into a 'forward selection' analysis with $p=0.05$ as the criterion for including predictors. For the pure Alzheimer data, only SEX ($p=0.0056$), APOE.2 ($p=0.0011$) and VDRL.106.1 ($p=0.0176$) were selected, while for the combined Alzheimer data, SEX ($p=0.0040$), APOE.1 ($p=0.051$), APOE.2 ($p=0.0036$) and VDRL.106.1 ($p=0.0185$)

were selected. The effect of APOE ϵ 4 was therefore highly significant, as previously, and the estimates of relative risk associated with them were very similar. In interpreting these results however, it must be borne in mind that the SEX variable in itself is uninformative - it simply adjusts for the bias in sampling the controls. In effect, it allows us to estimate a pooled risk for the two sexes from data on each sex separately. What is important is that there were no significant interactions between SEX and any other variable i.e. there was no evidence that any of the risks differed significantly between the sexes. The coefficient of VLDLR.106.1 was positive, indicating a protective effect in those carrying at least one copy of this allele. Interestingly, the effect was not significant, or only marginally so, when this variable was considered on its own. This explains why it was not detected by the previous analysis, and illustrates the usefulness of the logistic regression approach. However, the effect was considerably smaller than that in APOE ϵ 4 homozygotes; the relative risk for 106-non-carriers to carriers was estimated as 2.33 (95% C.I. 1.16-4.67) for pure Alzheimer's and 2.11 (95% C.I. 1.13-3.92) for the combined Alzheimer group.

Results: Appendix.

(all tables in this section numbered independently from the rest of the chapter)

Descriptive Statistics for CAPE and CAMCOG by group.

I. CAPE-BRS:

An increase in these scores indicates a deterioration.

i) Physical Disability.

	Assessment I.					Assessment II.				
	n	mean	SD	Min	Max	n	mean	SD	Min	Max
Alz	60	6.40	3.68	0	12	59*	8.14	4.60	0	31
MID	13	7.69	2.90	2	11	13	8.77	2.80	3	11
Alc	13	4.00	2.97	0	8	13	4.85	3.63	0	11
Comb	24	7.33	3.16	2	12	24	8.46	2.47	3	12

* One Alzheimer case was not reassessed as the family refused the second visit.

The analysis was done using those cases who were DSM3R +ve at the first assessment, i.e. excluding the 2 cases who became so at the second assessment.

These points apply to all the following tables.

ii). Apathy.

	Assessment I.					Assessment II.				
	n	mean	SD	Min	Max	n	mean	SD	Min	Max
Alz	60	6.80	3.37	0	10	59	7.75	3.00	0	10
MID	13	7.85	2.27	2	10	13	8.15	1.95	3	10
Alc	13	5.23	3.22	0	10	13	5.38	3.33	0	10
Comb	24	7.92	2.47	2	10	24	8.83	1.74	4	10

iii). Communication.

	Assessment I.					Assessment II.				
	n	mean	SD	Min	Max	n	mean	SD	Min	Max
Alz	60	2.05	1.47	0	4	59	2.75	3.01	0	23
MID	13	1.85	1.52	0	4	13	2.15	1.63	0	4
Alc	13	0.31	0.48	0	1	13	0.31	0.63	0	2
Comb	24	2.33	1.27	0	4	24	2.75	1.26	0	4

iv). Social Disruption.

	Assessment I.					Assessment II.				
	n	mean	SD	Min	Max	n	mean	SD	Min	Max
Alz	60	1.67	1.69	0	6	59	1.86	1.81	0	6
MID	13	2.15	1.99	0	5	13	1.62	1.61	0	4
Alc	13	0.85	1.28	0	4	13	1.62	1.71	0	4
Comb	24	2.50	1.56	1	5	24	2.04	1.49	1	5

v). Total score.

	Assessment I.					Assessment II.				
	n	mean	SD	Min	Max	n	mean	SD	Min	Max
Alz	60	16.92	8.58	0	30	59	20.49	8.82	0	43
MID	13	19.54	7.09	4	28	13	20.69	6.25	6	28
Alc	13	10.38	6.78	1	18	13	12.15	7.57	0	24
Comb	24	20.08	6.88	5	29	24	22.08	4.69	9	29

II. CAMCOG.

A decrease in these scores indicates a deterioration.

i). Total.

	Assessment I.					Assessment II.				
	n	mean	SD	Min	Max	n*	mean	SD	Min	Max
Alz	60	22.62	30.90	0	94	48	19.35	31.14	0	98
MID	13	18.15	19.92	0	48	11	15.64	16.19	3	44
Alc	13	57.00	21.84	19	85	10	64.40	25.11	4	90
Comb	24	15.54	27.33	0	96	22	12.82	27.13	0	97

* The second assessment of the CAMCOG was not done in 19 cases, 18 who died and 1 who was refused. This applies to all the following tables.

ii). Orientation.

	Assessment I.					Assessment II.				
	n	mean	SD	Min	Max	n	mean	SD	Min	Max
Alz	60	2.33	3.41	0	10	48	1.73	3.06	0	10
MID	13	1.62	2.10	0	5	11	1.45	1.57	0	4
Alc	13	5.00	2.48	2	9	10	5.60	3.24	0	10
Comb	24	1.63	2.83	0	10	22	1.09	2.54	0	10

iii). Language.

	Assessment I.					Assessment II.				
	n	mean	SD	Min	Max	n	mean	SD	Min	Max
Alz	60	7.63	10.09	0	29	48	6.33	9.73	0	28
MID	13	7.23	7.82	0	18	11	6.00	6.10	0	18
Alc	13	21.77	6.80	7	29	10	22.00	6.85	4	27
Comb	24	5.88	9.19	0	29	22	4.36	8.81	0	27

iv). Memory.

	Assessment I.					Assessment II.				
	n	mean	SD	Min	Max	n	mean	SD	Min	Max
Alz	60	4.23	6.30	0	21	48	4.17	6.97	0	26
MID	13	3.38	3.69	0	8	11	2.55	2.70	0	7
Alc	13	10.31	4.53	3	17	10	12.20	5.38	0	18
Comb	24	2.58	5.39	0	21	22	2.41	5.70	0	24

v). Remote.

	Assessment I.					Assessment II.				
	n	mean	SD	Min	Max	n	mean	SD	Min	Max
Alz	60	1.15	1.82	0	5	48	0.96	1.65	0	6
MID	13	1.23	1.42	0	3	11	1.00	1.10	0	3
Alc	13	3.00	1.63	1	6	10	3.10	2.02	0	6
Comb	24	0.79	1.74	0	6	22	0.73	1.78	0	6

vi). Recent.

	Assessment I.					Assessment II.				
	n	mean	SD	Min	Max	n	mean	SD	Min	Max
Alz	60	0.70	1.29	0	4	48	0.65	1.19	0	4
MID	13	0.38	0.51	0	1	11	0.45	0.52	0	1
Alc	13	1.69	1.11	0	3	10	1.90	1.10	0	4
Comb	24	0.50	1.06	0	4	22	0.36	0.95	0	4

vii). Learning.

	Assessment I.					Assessment II.				
	n	mean	SD	Min	Max	n	mean	SD	Min	Max
Alz	60	2.38	3.89	0	14	48	2.56	4.54	0	17
MID	13	1.77	1.88	0	4	11	1.09	1.38	0	4
Alc	13	5.62	2.81	1	9	10	7.20	3.68	0	12
Comb	24	1.29	2.90	0	11	22	1.32	3.21	0	14

viii). Attention.

	Assessment I.					Assessment II.				
	n	mean	SD	Min	Max	n	mean	SD	Min	Max
Alz	60	1.00	2.03	0	7	48	0.92	2.08	0	7
MID	13	0.08	0.28	0	1	11	0.18	0.60	0	2
Alc	13	3.62	2.66	0	7	10	4.60	2.50	0	7
Comb	24	0.67	1.99	0	7	22	0.59	1.56	0	5

ix). Praxis.

	Assessment I.					Assessment II.				
	n	mean	SD	Min	Max	n	mean	SD	Min	Max
Alz	60	2.95	4.03	0	12	48	2.33	3.84	0	12
MID	13	2.08	2.53	0	7	11	2.09	2.21	0	6
Alc	13	7.00	3.96	0	12	10	8.20	3.43	0	12
Comb	24	1.75	3.57	0	12	22	1.68	3.47	0	12

x). Calculation.

	Assessment I.					Assessment II.				
	n	mean	SD	Min	Max	n	mean	SD	Min	Max
Alz	60	0.38	0.72	0	2	48	0.29	0.62	0	2
MID	13	0.31	0.48	0	1	11	0.18	0.40	0	1
Alc	13	0.92	0.76	0	2	10	1.20	1.03	0	2
Comb	24	0.38	0.71	0	2	22	0.27	0.70	0	2

xi). Abstract thinking.

	Assessment I.					Assessment II.				
	n	mean	SD	Min	Max	n	mean	SD	Min	Max
Alz	60	1.42	2.47	0	8	48	1.21	2.42	0	8
MID	13	1.38	2.14	0	6	11	1.27	2.00	0	5
Alc	13	3.69	2.66	0	8	10	4.80	2.82	0	8
Comb	24	1.00	2.23	0	7	22	1.09	2.60	0	8

xii). Perception.

	Assessment I.					Assessment II.				
	n	mean	SD	Min	Max	n	mean	SD	Min	Max
Alz	60	2.67	3.41	0	10	48	2.38	3.59	0	10
MID	13	2.08	2.50	0	6	11	1.91	2.07	0	5
Alc	13	4.69	2.21	0	7	10	5.80	2.97	0	10
Comb	24	1.67	2.91	0	9	22	1.32	2.70	0	9

xiii). MSE.

	Assessment I.					Assessment II.				
	n	mean	SD	Min	Max	n	mean	SD	Min	Max
Alz	60	6.62	8.70	0	29	48	5.08	7.63	0	27
MID	13	5.08	5.36	0	13	11	5.18	5.06	0	14
Alc	13	16.69	6.38	5	25	10	17.90	7.43	2	27
Comb	24	5.29	8.14	0	29	22	3.55	7.63	0	28

Genetic Tables.

Table (G1).

Numbers of cases by DSM3R patient grouping and APOE ϵ 4 genotype.

	2/2	2/3	2/4	3/3	3/4	4/4	Total
'Pure' Alz	0	3	1	27	19	9	59
'Mixed' Alz	0	3	0	6	8	5	22
Non-Alz	2	3	0	18	11	4*	38
Control	1	18	5	87	37	4	152
Total	3	27	6	138	75	22	271

* One MID, 2 Alcohol and one 'other', case cf82.

For the McKhann grouping, 75% of the McKhann +ve group, have the 4/4 allele combination.

Table (G2).

APOE ϵ 4 allele frequencies by patient grouping.

	E2	E3	E4	Total
'Pure' Alz	4	76	38	118
'Mixed' Alz	3	23	18	44
Non-Alz	7	50	19	76
Controls	25	229	50	304
Total	39	378	125	542

Table (G3)Relative risk estimates for 'Combined' Alzheimer's.

	using observed numbers			using H-W expectation		
	R.risk	lower	upper	R.risk	lower	upper
E4 homo/ non-E4	9.51.	2.95	30.66	9.27	3.92	21.92
E4 hetero/ non-E4	1.81	0.99	3.31	1.82	1.03	3.23
E4 carr/ non-E4 ca	2.48	1.42	4.33	2.49	1.44	4.30
E4 homo/ rest	7.73	2.45	24.37	7.52	3.46	16.34

E4 homo/non-E4 = E4 homozygotes/non-E4 carriers.

E4 hetero/non-E4 = E4 heterozygotes/non-E4 carriers.

E4 carr/non-E4 ca = E4 carriers/non-E4 carriers.

E4 homo/rest = E4 homozygotes/rest.

Table (G4)Relative risk estimates for 'Pure' Alzheimer's.

	using observed numbers			using H-W expectation		
	R.risk	lower	upper	R.risk	lower	upper
E4 homo/ non-E4	7.95	2.29	27.63	7.74	2.96	20.24
E4 hetero/ non-E4	1.68	0.86	3.28	1.69	0.89	3.22
E4 carr/ non-E4 ca	2.23	1.20	4.13	2.24	1.22	4.11
E4 homo/ rest	6.66	1.96	22.57	6.48	2.69	15.62

Table (G5).Numbers of cases by patient grouping and VLDL-R genotype.

	97/97	97/106	97/X	106/ 106	106/X	X/X	Total
'Pure' Alz	8	4	22	3	10	12	59
'Mixed' Alz	5	2	6	1	6	2	22
Non-Alz	9	5	11	2	9	2	38
Control	17	21	40	9	39	26	152
Total	39	32	79	15	64	42	271

X includes alleles 103, 109, 112 and 115.

Table (G6). VLDL-R allele frequencies by patient grouping.

	97	106	X	Total
'Pure'Alz	42	20	56	118
'Mixed'Alz	18	10	16	44
Non-Alz	34	18	24	76
Controls	95	78	131	304
Total	189	126	227	542

X includes alleles 103, 109, 112 and 115.

Table (G7). Tests of significance for differences in VLDL-R genotype frequencies between groups.

Comparing	6 classes			3 classes		
	X**2	DF	P	X**2	DF	P
All groups	14.13	15	0.52	6.64	6	0.36
'Pure'vs 'Mixed'	3.47	5	0.63	1.07	2	0.58
'Pure'vs Controls	5.41	5	0.37	0.72	2	0.70
'Mixed'v Controls	3.21	5	0.67	2.34	2	0.31
Non-Alz vs. Controls	6.52	5	0.26	4.89	2	0.087
'Comb'.v Controls	4.95	5	0.42	1.53	2	0.47

Notes: For the 6-class analysis, alleles 103, 109, 112 and 115 were pooled. For the 3-class analysis, all alleles except 97 were pooled. Many of the P-values are approximate because of small numbers in some categories.

Table (G8). Tests of significance for differences in VDRL-R allele frequencies between groups.

Comparing	3 classes			2 classes		
	X**2	DF	P	X**2	DF	P
All groups	9.76	6	0.14	5.75	3	0.12
'Pure'vs 'Mixed'	1.71	2	0.43	0.39	1	0.53
'Pure'vs Controls	3.64	2	0.16	0.73	1	0.39
'Mixed'v Controls	1.65	2	0.44	1.64	1	0.20
Non-Alz vs. Controls	5.33	2	0.070	4.93	1	0.026
'Comb'.v Controls	3.43	2	0.18	1.59	1	0.21

Notes: For the 3-class analysis, alleles 103, 109, 112 and 115 were pooled. For the 2-class analysis, all alleles except 97 were pooled.

Table (G9). Numbers of cases by patient grouping and ACT genotype.

	TT	AT	AA	Total
'Pure'Alz	15	30	14	59
'Mixed'Alz	8	9	5	22
Non-Alz	15	14	9	38
Controls	43	61	48	152
Total	81	114	76	271

X includes alleles 103, 109, 112 and 115.

Table (G10). ACT allele frequencies by patient grouping.

	T	A	Total
'Pure'Alz	60	58	118
'Mixed'Alz	25	19	44
Non-Alz	44	32	76
Controls	147	157	304
Total	276	266	542

X includes alleles 103, 109, 112 and 115.

Table (G11). Tests of significance for differences in ACT genotype frequencies between groups.

Comparison	χ^2	DF	P
All groups	5.02	6	0.54
'Pure' vs 'Mixed'	1.01	2	0.31
'Pure' vs Controls	2.15	2	0.34
'Mixed' vs Controls	0.93	2	0.63
Non-Alz vs Controls	1.96	2	0.38
'Comb'.vs Controls	2.00	2	0.37

Table (G12). Tests of significance for differences in ACT allele frequencies between groups.

Comparison	X**2	DF	P
All groups	2.89	3	0.41
'Pure' vs 'Mixed'	0.25	1	0.62
'Pure' vs Controls	0.12	1	0.73
'Mixed' vs Controls	0.79	1	0.37
Non-Alz vs Controls	1.85	1	0.17
'Comb'.vs Controls	0.56	1	0.45

Table (G13).

Definition of variables used in logistic regression analysis.

<u>Variable</u>	<u>Definition</u>
<u>SEX</u>	= -1 if m = +1 if f
<u>APOE.1.</u>	= 1 if #of ε4-alleles is 0 = 0 if #of ε4-alleles is 1 = 0 if #of ε4-alleles is 2
<u>APOE.2</u>	= 0 if #of ε4-alleles is 0 = 0 if #of ε4-alleles is 1 = 1 if #of ε4-alleles is 2
<u>VLDLR.0.97.1</u>	= 1 if #of 97-alleles is 0 = 0 if #of 97-alleles is 1 = 0 if #of 97-alleles is 2
<u>VLDLR.0.97.2</u>	= 0 if #of 97-alleles is 0 = 0 if #of 97-alleles is 1 = 1 if #of 97-alleles is 2
<u>VLDLR.106.1</u>	= 1 if #of 106-alleles is 0 = 0 if #of 106-alleles is 1 = 0 if #of 106-alleles is 2
<u>VLDLR.106.2</u>	= 0 if #of 106-alleles is 0 = 0 if #of 106-alleles is 1 = 1 if #of 106-alleles is 2
<u>VLDLR.109.1</u>	= 1 if #of 103+109+112+115-alleles is 0 = 0 if #of 103+109+112+115-alleles is 1 = 0 if #of 103+109+112+115-alleles is 2
<u>VLDLR.109.2</u>	= 0 if #of 103+109+112+115-alleles is 0 = 0 if #of 103+109+112+115-alleles is 1 = 1 if #of 103+109+112+115-alleles is 2
<u>ACT.E.1</u>	= 1 if #of T-alleles is 0 = 0 if #of T-alleles is 1 = 0 if #of T-alleles is 2
<u>ACT.E.2</u>	= 0 if #of T-alleles is 0 = 0 if #of T-alleles is 1 = 1 if #of T-alleles is 2

Discussion.

Introduction.

From such a wide-ranging set of data and possible analysis, what are the useful points to raise and discuss in this section? The results have included the identification, and clinical and genetic description, of the study group. Measurement of change, and the identification of associations with it, have also been attempted.

There are various aspects of the design of this study, both good and bad, which can be commented upon. It is also possible to compare the results in the context of other studies, but much of the work stands alone, without the possibility of comparison.

Arising from the discussion will be indications of data analysis and research ideas that can be pursued in the future, based on this piece of work.

Discussion of the Study Ascertainment.

Where the cases were from.

During the course of the study, planning for a service to provide for the population of people with younger-onset dementia has become of interest locally. For such planning, epidemiological data is required, to provide a guide as to the number of expected cases in the region. Can the data obtained in this study help in this? The answer is yes, but only with a clear awareness of the biases introduced in the study. These biases will be discussed here. The Introduction: Epidemiological Issues introduced some of these points but not specifically with respect to the study. An approach to provide epidemiological data is discussed, at the end of this section on the ascertainment.

The aim of the study, was to identify and describe a population of live cases of presenile dementia in the Lothian area. The use of the Lothian Psychiatric Case Register (LPCR), enabled an efficient starting point for the identification of cases, but only

included those people who had been referred to the service. For this reason, the neurology case records were also investigated. However, it is likely that this case finding method was not entirely comprehensive, although these would have been the most likely referral specialities. In order to ascertain all cases, all individual general practitioners and residential units would also have had to have been approached.

Cases of Down's Syndrome-related dementia were not included in the study. They would not have been recorded in the LPCR, unless requiring a separate psychiatric referral. No cases of AIDS-related dementia were identified for the study, and this was in part due to the separate service for the AIDS-related cases, based at the City Hospital. Only 15 cases of Huntington's Disease were found from the search, whereas it is likely that a far greater number of cases exist, but are not found by the ascertainment method used.

Another group of cases who would be hard to identify, would be people with chronic psychiatric illness, in long-term care, who go on to develop dementia. Cases of Alcohol-related dementia would be a difficult group to trace, unless they were severely affected and under the care of the National Health Service.

Issues about the accuracy and completeness of the Scottish Mental Health inpatient data, are discussed by McGonigal et al (1992a). They review the limitations of the data obtained from this computerised record of patients admitted and discharged from, or who died in Scottish Mental Hospitals. 93% of cases were identified under a variety of different diagnostic codes, 17% of the cases were not identified and 23% were wrongly classified. Methods of retrospective study, using death certification, have been found to under-report the cases of dementia, see Morgan and Clarke (1995), and Newens et al, (1993b).

When looking at Neurology Records, the cases included for the study clearly stated dementia. However, in the cases of Parkinson's Disease, where a dementing process could have been

a part of, but not necessarily the overriding feature of the illness, cases may not have been identified. It would be necessary to review all such cases for more precise epidemiological figures. This study only included the cases with an established diagnosis of dementia.

Inclusion of Alcohol-related Cases.

The inclusion of cases of Alcohol-related diagnoses will be discussed here. The identification of heavy alcohol consumption as a risk factor, will often preclude the inclusion of an individual to a sample of more purely defined cases of, for example, Alzheimer's Disease. However, it would appear that of all individuals who drink heavily, only some go on to develop a definite and irreversible cognitive impairment, possibly of a declining nature. The pathology of alcohol-related damage and other aetiologies, may often co-exist and even act to aggravate each other. Also, the overlap between Korsakoff's Psychosis and Alcohol-related dementia is unclear, see Lishman (1986). The criteria for Korsakoff's Psychosis have been described by Deary et al (1991), but the data available on the investigations done on this group, was often incomplete, and the diagnosis had been assumed.

The analysis has revealed this group to have a distinct pattern of symptoms and pattern of decline. Whether the condition would continue to improve, remain the same, or deteriorate over time and the effect of continued drinking, would require a longer period of follow-up. As discussed, the accurate documentation of the amounts of alcohol previously consumed is difficult.

Saunders et al (1991), looked at the relationship between drinking history and current psychiatric morbidity. Explaining the relationship between alcohol and dementia, presents problems. Investigation to examine the risk factors for SDAT, have failed to identify alcohol as a significant risk factor. But as already stated, in general, these studies select and investigate what is presumed to be a single diagnostic entity.

They therefore employ inclusion criteria specifying the absence of indicators of past or present alcohol abuse. Here, they found heavy drinking as a risk factor for depression and dementia in elderly men. They suggest that maybe a higher proportion of cases of dementia are alcoholic than was previously suspected. This however does not account for the delay in onset of detectable cognitive deficit following cessation of heavy alcohol intake. It may be that chronic alcohol intake may cause premature ageing of the brain.

Case Note Diagnosis.

Series such as that of Tomlinson et al (1970), have provided percentages of the different dementia types found at post-mortem in their series. It is of interest to look at the case note diagnoses of the sample. The most interesting feature of this, is the 25% of cases who have a case note diagnosis of atypical, mixed or uncertain type dementia. This appears to be a more commonly used category than for an elderly population. It may reflect the greater degree of uncertainty in diagnosis, at presentation of these conditions.

It may be hypothesized that the Lothian study would show a greater percentage of alcohol-related cases than would a more rural area, and perhaps geographically reveal a higher incidence than other parts of the U.K. with correspondingly lower drinking rates.

Case Non-Inclusion.

Cases found to have deceased on inspection of the notes, were excluded. Another bias which the study has, is that the cases of younger-onset dementia seen, are likely to be less rapidly declining than cases which would have declined more quickly and died. Taking the sampling period further back than 1988 found that most cases were deceased, so the sampling frame of 1988 to the end of 1993 was kept.

Further biases introduced into the sample, were at the stage of exclusion of cases of Huntington's Chorea, Down's

Syndrome, and major head injury, before the cases were contacted. Examples of head trauma were following: a road traffic accident; subarachnoid haemorrhage; or hypoxia as a result of overdose. In these situations there was a defined and recognisable insult precipitating the disorder. In Huntington's Chorea, the underlying genetic mechanism has already been discovered, see Introduction: Genetics. This group of subjects was also felt to be sufficiently different in presentation to be less suitable for the study. Cognitive decline is not a primary element, and the neurological and physical problems would not have been adequately assessed by the test battery chosen. In the pilot study, one case of Huntington's was included but was later excluded from the study.

Down's Syndrome cases likewise had a clear chromosomal cause for their dementia, and furthermore, there would be difficulties in testing this group of people using the instruments chosen for this study. It is difficult to establish the evidence for cognitive decline in the situation where there is premorbid impairment, see Royston et al (1994). The need to plan a service for younger people with cognitive impairment, including such groups, is discussed in the Introduction: Epidemiological Issues.

It would also be of interest to know more about the cases in which permission was not granted to participate in the study, either by the General Practitioner or the family. It could be that the families most under stress, felt unable to cooperate, so that some severely disturbed cases were not included. This would introduce a bias, by not including the more disturbed cases. The proportion of cases at home, or in long-term care, who were refused for the study, would also be of interest.

The cases found to be unsuitable, are commented upon in the Results. The majority of these were found to be cases of non-progressive cognitive decline, but only a longer-term follow-up of such cases would effectively exclude them. The other main group was of non-progressive damage due to head injury.

Can the figures be used to estimate the number of cases of presenile dementia in Lothian?

The nature of a case finding study such as this, is that it has led to a large number of exclusions (431 out of 557 potential cases). A total of 123 cases were found to have deceased, which does not include an estimate from the missing cases. When looking at the other 299 exclusions, a large proportion have been excluded for reasons pertinent only to the study itself (e.g. cases refused, 40; untraceables, 23; Down's Syndrome and Huntington's Chorea, 19; Unsuitables, 21). A large number of these, could be legitimate cases, and should be included (or account taken of them) for the purpose of calculating prevalence rates. The other major source of exclusions can be generally classified under false positives (e.g. wrong diagnosis, 116; wrong age, 16; out of area, 14). This study has not however been able to detect false negatives - those who had the right diagnosis but were wrongly coded, those who were in the right age group but wrongly recorded etc. The study is therefore biased toward excluding false positives but not including false negatives.

As has already been mentioned, a hospital study, by its nature, is biased towards identification of the more severe end of the spectrum of any disease. People with mild or moderate symptoms, who do not go to their GPs or are not referred by their GPs to the specialist services, or who are misdiagnosed, are not included. Furthermore, certain types of dementia have not been included: cases of related to head injury, Aids, Huntington's and Down's are either positively excluded or underestimated.

Although the criteria used for inclusion and exclusion of cases in this study are directed toward achieving the aims of this particular study, its findings have to be modified to reach an estimate of all cases of presenile dementia in Lothian.

Calculating the Incidence Rate.

To compare the Lothian incidence rate with those found elsewhere, the people who were 65 years old at the time of diagnosis would have to be excluded.

An estimate of the number of cases that were not included but were likely to have been cases is needed. One way to do this would be calculate the percentage of the definite dementia group from the total seen, and apply this percentage to the group of cases who had died, refused and were untraced. This could be done for the categories in the DSM3R groupings and the McKhann groupings. The incidence rates could be calculated using the Census data for the Lothian Region (1991). Annual incidence would be estimated by dividing by 6, since the years 1988 - 1993 provide 6 years of data.

Calculating the Prevalence Rate.

To compare the Lothian point prevalence figure with those found elsewhere, the people who had reached the age of 65 would have to be excluded. For these figures, none of the deaths of included individuals should have occurred before the end of the ascertainment period (31/12/93).

After the First Assessment.

The data set for this study is extremely large, and selected areas are discussed here.

Diagnosis Application.

This has already been discussed in the chapter on Method: Contact. The issue as to the subjective nature of clinically defined criteria, has been raised. It is interesting to see how well the APOE allele typing corresponds to the Alzheimer's group, as defined by the DSM3R criteria.

For the most clear distinction between the various aetiologies seen for the study, the DSM3R groupings have been used. As mentioned previously, the inclusion of overlap groups allowed for cases in which the known risk factors were sufficiently strong to weigh equally in the final diagnosis. By the second assessment there were 24 cases who overlapped between Alzheimer's and other DSM3R diagnostic groups. As stated, only one case overlapped between groups not involving Alzheimer's

(the Alcohol/Multi-infarct group). As alcohol represents a risk factor for cerebrovascular disease, and possibly also for Multi-infarct dementia, it would not have been surprising to find more overlap between these two groups, see Fisman et al (1996).

As described in the Results, the DSM3R and McKhann groups are equated. The McKhann criteria state that the diagnosis of Alzheimer's Disease can only be made: "*in the presence of a second systemic or brain disorder not considered to be the primary cause*", but this requires some subjective judgement as to the primary cause. For this reason, three cases met the DSM3R Alzheimer's criteria, but not the McKhann probable criteria, and three cases were in the DSM3R Alzheimer's plus other group, but not the McKhann group. The McKhann criteria are stricter than the DSM3R criteria. It should however be noted, that some individuals classified in this way, had not had complete investigations recorded.

It is likely that the majority of the case note diagnoses of uncertain, atypical or mixed aetiology, infact become classified in the DSM3R Alzheimer group. Application of the DSM3R criteria for Alzheimer's Disease is likely to include several other forms of presenile dementia. For example, if Lewy Body type dementia in the elderly does represent the second commonest cause of dementia, it will be likely to be represented here by DSM3R Alzheimer's Disease. Frontal type dementias have also been said to be commoner amongst the presenile dementia population, and only specific criteria could distinguish these from the umbrella heading of Alzheimer's Disease as used here. The application of these other criteria to the data set would be of future interest.

The accurate application of the diagnostic criteria was a difficult part of the study process, and of crucial importance. It also provides a base-line, so that cases of cognitive impairment, not fulfilling the dementia criteria, are excluded. Investigating who of this possible group go on to develop dementia, would require a study with longer follow-up.

It is interesting to note that the cases which did not meet the criteria for dementia when seen for the study, had been

clinically diagnosed as having the condition at some stage previously. Hence the change is not only in the direction of becoming demented.

Severity Rating.

The DSM3R severity criteria are based on rather general description, depending on the level of independence of the individual. This means that the severity rating will not only depend on the individual's level of functioning, but also on the physical setting of their care. There is a subjective element to the application of such criteria.

The changes in severity over the year between assessments provides a crude measure of the decline. It was necessary to consider a group intermediate to the moderate and severe categories, that of moderate-severe. This was for the individuals who although still at home and perhaps not receiving the same level of nursing care as in hospital, were never the less extremely impaired and significantly declined from the first visit.

Risk Factors.

The study is not a true epidemiological one, comparing a group of early-onset dementia cases with a non-demented cohort. However, it is possible to comment in a descriptive way, on a range of risk factors looked at.

Sex Differences.

McGonigal et al (1993), suggest that female sex is associated with presenile Alzheimer's Disease. This finding was challenged as an artefact in letters following the publication.

The results in the study show that there are more females than males in all categories but the DSM3R Alcohol-related group.

Age of Onset.

The difficulty in the objective measurement of this has been discussed in the Introduction: Epidemiological Issues. The

age at referral for diagnosis provides a standard which is used as an alternative to the age of onset, in some parts of the analysis.

In the genetic studies by Mullan et al (1993), it was found that age of onset demarcated aetiological subtypes of familial Alzheimer's Disease. The early-onset forms they found, conformed to autosomal dominant patterns of inheritance, whereas later-onset forms appeared more complex. They suggested that early-onset Alzheimer's Disease could be subdivided by genetic aetiology, with which the age of onset correlated. This is also shown in figure (6) of the Introduction: Genetics.

The average age at referral, in years, in this study for cases of Alzheimer's was 58; Mixed Alzheimer's, 59; MID, 62; and Alcohol-related, 55.

In the analysis of the APOE results, there was a significant regression of age at referral on the number of APOE ϵ 4 alleles, in the Alzheimer group. It is also an important variable to consider in looking for heterogeneity, and was investigated as a predictor of decline. It has been demonstrated to be statistically significant in explaining the change of scores in some assessments between the phases. Deterioration (in the CAPE-BRS total and physical disability and communication difficulty subscores, and the Webster score), was associated with an older age at referral. But this may be due to the fact that cases of Alcohol-related dementia (with the pattern of less deterioration) had a younger average age at referral.

Socio-Economic Group (Class).

The distribution of socio-economic group (class I-V) within the group, compared with that of the population, is of interest because of the possible link between deprivation, and the subsequent development of dementia.

In the study by Whalley et al (1995a & b), looking at the epidemiology of presenile Alzheimer's dementia in Scotland, the group reported that socio-economic deprivation was related to vascular dementia. This would predict that people in the lower socio-economic groups (classes IV and V) would be more prone to vascular problems and secondary dementia associated with this.

There were no marked differences apparent in the study group, but there was a higher percentage of individuals in socio-economic group class IV, in the MID and Alcohol-related DSM3R groups.

Education and Premorbid Intelligence.

The possible protective effect of education and premorbid intelligence on the subsequent development of dementia, is a debated issue. It is reviewed by Katzman (1993).

Work done with older subjects, has found no association between early educational achievement and a protective effect with respect to Alzheimer's Disease, see Katzman et al (1989). Fratiglioni et al (1991), revealed differences between educational levels in total prevalence ratios for dementia, but not with respect to the diagnosis of Alzheimer's Disease. Ott et al (1995), looked at the association between education in Alzheimer's Disease and vascular dementia, and found an inverse dose-response relationship between education and dementia, in particular for Alzheimer's Disease. This association was not explained by cardiovascular disease co-morbidity.

Extending the theme further, the beneficial effect of continued mental stimulation is possibly able to act as a protective factor. Orrell and Sahakian (1995), concluded that although more research is needed in this area, there may be truth in the statement "use it or lose it".

The IQ distribution, in subjects in this study, when calculated from the small number of subjects able to do the NART, showed a normal distribution. There was not a significant difference between the mean IQ of the DSM3R groups.

Down's Syndrome

Heston and Mastri (1977), initially reported an increased occurrence of Down's Syndrome (DS), among the relatives of individuals with Alzheimer's Disease. Sadovnick et al (1994), studied the rate of Down's Syndrome among 578 offspring of 206 women with Alzheimer's Disease. The data did not suggest that women who subsequently developed Alzheimer's Disease had a higher (or lower) rate of Down's Syndrome offspring than expected. However, Schupf et al (1994), showed familial aggregation of dementia among mothers of adults with Down's Syndrome, supporting the hypothesis of a shared genetic susceptibility to DS and AD.

Tanzi (1996b), reviews the presence of a specific amyloid β -protein in the brains of Down's syndrome patients, suggesting a common aetiological pathway for the development of Alzheimer Disease-related neuropathology. Molecular aspects of the links between AD and DS are given in the chapter Introduction: Genetics.

The study enquired in the CAMDEX H interview with the informant, into the presence of relatives with Down's Syndrome or mental handicap. There was no significant difference between the DSM3R groups for this.

Stress.

Orrell and O'Dwyer (1995), explore if stress, or an abnormal stress control system is involved in the genesis or exacerbation of Alzheimer's Disease. There is insufficient evidence to make a case for this yet. Several families wondered about this as a potential aetiological factor for their relatives with dementia. No objective measure was available from the study data to test this hypothesis.

Head Injury.

Head injury has been demonstrated to be a risk factor for the development of Alzheimer's Disease. Mortimer et al (1985), conducted a case controlled study to look at the frequency of prior head injury assessed in 78 patients with DAT and 124 matched controls. They found head injury to be a possible aetiological factor in the development of Alzheimer's Disease. Mayeux et al (1993), investigated head injury as a risk factor for Alzheimer's Disease among community dwelling elderly persons and found severe head injury to be associated with the disease. Roberts et al (1994), discuss the implications for the pathogenesis of Alzheimer's Disease, of β -amyloid protein deposition in the brain after severe head injury. The area is reviewed by Roses and Saunders (1995). The influence of the APOE ϵ 4 genotype on the outcome following head injury, has been discussed in the Introduction: Genetics.

By DSM3R group, the percentages of the Alzheimer, Multi-infarct, Alcohol-related and Mixed groups, with a history of head injury, were respectively 8%, 15%, 28% and 24%.

Blood Pressure.

Although hypertension is a risk factor for cerebrovascular disease, no definite link has been established between hypertension and impaired cognitive function. Hypotension has even been claimed to be a risk factor for the development of dementia. How the process of hypertension could cause dementia, is still unconfirmed. White matter lesions prevalent in late-onset Alzheimer's Disease may represent vascular lesions which act by disconnecting subcortical from cortical association pathways. The deposition of β -amyloid has been shown in animal models to interact with endothelial cells causing vascular constriction. Superoxide-mediated endothelial damage may also be related to this process. See Martyn (1996).

Skoog et al (1996), found that hypertension predicted both Alzheimer's Disease and Multi-infarct dementia.

The terms of exclusion from the McKhann Criteria are that *"no other condition that could account for the progressive deficits in memory and cognition should be present"*. This necessarily excludes vascular lesions as a cause, but this may seriously prejudice thinking about aetiology, at a time when vascular mechanisms are found to possibly contribute to the development of Alzheimer's Disease.

The percentages of the DSM3R groups, Alzheimer's, Multi-infarct, Alcohol-related and Mixed, with a history of, or current hypertension, were respectively 12%, 61%, 14% and 56%.

Family History.

In the chapter Introduction: Genetics, the familial occurrence of Alzheimer's Disease has been discussed, and the presence of a family history noted to be found in about 30-50 % of cases, in series studied.

In a study by Hofman et al (1989), of 198 people with Alzheimer's Disease, diagnosed before the age of 70 years, 48% had at least one first-degree relative with dementia, as compared with 19% of controls. They found familial aggregation of Alzheimer's Disease and also evidence for familial aggregation of Alzheimer's Disease with Parkinson's Disease. This latter point was especially the case for men with earlier-onset of Alzheimer's Disease. It was suggested that this may point to a joint aetiology of these diseases.

Van Duijn et al (1993), studied the age at onset and transmission patterns of Alzheimer's Disease, in the families of the subjects described by Hofman et al (1989). These subjects had onset of symptoms before the age of 65 years and were diagnosed before the age of 70 years. Although the study confirmed that a dominant major gene is implicated in early-onset Alzheimer's Disease, the results suggest that other genetic or perhaps non-genetic factors may account for the disease in a considerable number of patients.

Korten et al (1993), assessed the risk of Alzheimer's Disease in first-degree relatives of cases with Alzheimer's Disease.

No evidence was found that a familial form of Alzheimer's Disease is more common in those with earlier-onset Alzheimer's Disease (before the age of 75 years), nor in those who display early, prominent features of aphasia or apraxia, nor that an Alzheimer's Disease gene maybe sex linked.

However, in another study by Li et al (1995), with 200 clinically diagnosed Alzheimer Disease cases, and 179 controls, the finding was different. They investigated the relationship between probands age at onset of Alzheimer's Disease, with the risk of primary progressive dementia in the probands' first-degree relatives. They found patients with an earlier age at onset of Alzheimer's Disease were more likely to have relatives with Alzheimer's Disease, than patients with a later age at onset of the disease. The study of Heston et al (1981), found a similar effect.

Silverman et al (1994), examined the possible age-related characteristics associated with a more familial variety of Alzheimer's Disease. They found that for relatives of probands with Alzheimer's Disease, while the lifetime risk of progressive dementia is greater than in the relatives of controls, the familial contribution to the risk, decreases with increasing age.

In this study, the report of a close relative, (in the majority of cases a first degree relative), having had a dementing illness, was given in 31% of the sample. No verification of such reports was possible, but it would be of interest as a further study to look in more detail at these cases and their families. Of those with a family history of dementia, for DSM3R Alzheimer's, this was 37% of the total, Mixed Alzheimers 36%, MID 31% and less for the Alcohol-related group. There were no statistically significant differences between the DSM3R groups for any of the family history features.

The variable of having a family history of dementia, was of interest in the genetic analysis, and was also investigated as a possible predictor of decline. No evidence was found that this is a predictor of change, but from the genetic results, there was a trend towards a higher proportion of familial cases with increasing numbers of APOE ϵ 4 alleles in Alzheimer cases.

Duration of Symptoms and Survival.

Linked to the patterns of decline, is the consideration of the overall duration of symptoms and survival time. The difficulty here, as with the estimation of illness onset, is having an objective starting point. Survival is not of particular relevance to this study as it did not aim to follow up cases to death, but will be briefly considered. Van Dijk et al (1991), reviewed the evidence on survival in dementia, and this is discussed by McGonigal et al (1992b), and Newens et al (1993a), for presenile dementia.

Another potential area of study, would be to investigate the study cases who died, and to see if the rates were as expected. The place and cause of death of individuals, identified at the stage of: case note assessment; contacting individuals; and during the follow-up period, could be investigated.

Duration of Illness.

In this sample, there are a group of subjects who appear to have a long-lasting illness. As mentioned, it may be that the sample selection has favoured the inclusion of these cases. Of those who were in long-term care, over 50% had been there for over 3 years.

The association of genetic type and illness duration was analysed, but no significant differences found between the DSM3R groups. Illness duration was also investigated as a predictor of decline. The data indicates (for cognitive testing) that a detectable deterioration is associated with a longer duration of illness. This is rather surprising, as clinically the subjects with long-standing illnesses were very impaired at both assessments. However, the opposite effect was seen for the CAPE-physical disability subscore, where there is a trend to improvement as the duration of the illness increases. Clearly, this also, does not fit clinically. No explanation is apparent for these findings, which may be the result of artefact.

Non-Cognitive Symptoms.

The literature in this area refers to Alzheimer's Disease, and in general does not specifically study a presenile group. In the following section, psychopathological, affective, behavioural and neurological symptoms will be discussed. A review of the findings in other studies will be given, and those of this study mentioned. The background to the testing in these areas is given in the Method: Battery, which provides an introduction to the following discussion.

Psychopathological Symptoms.

Ballard and Oyebode (1995c), have reviewed the area of psychotic symptoms in patients with dementia. The majority of studies have found a prevalence of psychotic symptoms in excess of 60%, and those with dementia of moderate severity having the highest prevalence.

In a study by Ballard et al (1995a), 124 patients referred to an old age psychiatry service and memory clinic with dementia were studied. 66.9% were found to have at least one psychotic symptom. 35% had at least one visual hallucination, 12.9% had at least one auditory hallucination, 48.4% had at least one delusional belief and 29% had at least one delusional misinterpretation.

Patterson et al (1990), studied a series of 34 patients with Alzheimer's Disease, and 21 spousal control subjects and enquired into noncognitive behavioural symptoms in the week previously. In the dementia group, delusional or paranoid features were present in 38%, and hallucinations in 18%.

Jabeen et al (1992), studied the case notes of 37 patients neuropathologically confirmed with Alzheimer's Disease, for non-cognitive features during the illness. 11% had exhibited delusions, 6% misidentification syndrome, 14% non-delusional but paranoid thinking, 14% visual hallucinations, and 3% auditory hallucinations. Possible explanations for the wide variation in reported rates of psychotic symptoms in Alzheimer's Disease in the literature, are discussed.

Migliorelli et al (1995), studied 103 patients with probable Alzheimer's disease and found a rate of 20% DSM3R delusional disorder, the most frequent being paranoid, 71%; hypochondriacal, 67%; Capgras syndrome, 29%; house misidentification, 29%; grandiose, 29%. Of these subjects, 76% had three or more delusions simultaneously. They found no significant association with age, education and age of onset. The type and severity of other impairments, such as myoclonus, were similar for AD patients with and without delusions. However, the AD patients with delusions had higher mania and anosognosia scores, (that is, the patient was less aware of their cognitive and emotional deficits).

Associations have been reported for psychotic phenomena with a number of other variables, such as older age of onset, race, a longer course of illness, lower levels of education, and gender. Ballard et al (1995b), demonstrated differences in associations for visual hallucinations and delusions, and found sensory impairments were associated with both. Delusions were associated with deafness. Visual impairments were associated with visual hallucination. Older age was associated with delusions and later age of onset was associated with visual hallucinations. The authors suggest that grouping the psychotic symptoms as one entity may mask important differences.

Work on the psychotic symptomatology found in Lewy Body Dementia by McKeith et al (1992), found 47.6% of patients to have visual hallucinations, 19% to have auditory hallucinations and 57% to have delusions. However, the sample size was small and the instruments used to detect the phenomena not structured.

In the series of papers by Burns et al (1990b), disorders of thought content (delusions and persecutory ideation), perception, mood and behaviour, were described in 178 patients with Alzheimer's Disease. In studying disorders of thought content, they found delusions had occurred in 16% of the sample since the onset of the illness. Simple delusions of theft and suspicion were the most common types. Cognitive function at the

entry to the study, and cognitive deterioration over the next 12 months, was not influenced by the presence of disorders of thought content. Their finding was of a lower rate of disorder of thought content than previously published - presumably because of the methodology and sample used. The rates of disorders of perception are also reviewed. The reported range of frequency for hallucinations is from 3 - 49%. Such differences may be due to variations in the populations studied, the method of case ascertainment, the presence or absence of symptoms, and the periods of time to which the rates refer. The authors found disorders of perception occurred commonly in Alzheimer's Disease. The study found visual hallucinations in 13% and auditory hallucinations in 10%. Misidentification syndromes were found in 30% - these were associated with a younger age and younger age at onset of the illness, and proportionally more men than women were affected. There was a reduced 30-month mortality in this group. Subjects with hallucinations had a greater deterioration in cognitive function at the 12-month follow-up.

Rubin (1992), reviews delusions as part of Alzheimer's Disease, and the relationship of them to the stage and progression of the illness. Methodological issues, involving research design and assessment tools are addressed, and the advantages of studying delusions at several levels are discussed, ranging from psychological to neuroanatomical.

The results using the method described for this study, found for the DSM3R Alzheimer's Disease group, at some stage of the illness, 43% had delusions; 15% visual hallucinations and 13% auditory hallucinations. The study provides data on DSM3R MID and Alcohol-related group, so far unreported on.

Affective Symptoms.

As mentioned, the data obtained from the Cornell Scale for Depression in Dementia in this study, was not felt to be reliable. The assessment of mood will not be a detailed area for discussion, but will be briefly covered.

Sunderland et al (1988), states that depressive symptoms frequently accompany dementia and states that the estimates have ranged as high as between 30 - 50%. Ballard et al (1996), described a one year follow-up study of depression in dementia sufferers and indicated that the annual incidence rate for major depression was 10.6% and for minor depression was 29.8%. Some subjects had a mild persistent form akin to dysthymia, and depression in vascular dementia appeared to be persistent. Whereas most cases of depression in dementia resolved in 3 months, 20% experienced symptoms for 6 months or longer.

In the study by Cummings et al (1995), no relation was found between the patient's depression and dementia severity, self awareness of cognitive deficits (memory self-rating scale) or mood of carer. Delusional patients had higher scores on mood rating scales than non-delusional patients. The study by Weiner et al (1994), confirmed the low prevalence and incidence of major depression in Alzheimer's Disease, as found by other investigators. They suggested that Alzheimer's Disease does not predispose to major depression as diagnosed according to the DSM3R criteria.

At the second assessment for the study, the subjects on antidepressant treatment in the DSM3R groups, Alzheimer's, Multi-infarct, Alcohol-related and Mixed, were respectively 12%, 15%, 7% and 20%.

Behavioural Symptoms.

In the study of Burns et al (1990b), in the group of 178 patients with Alzheimer's Disease, aggression was present in 20%, wandering in 19%, binge-eating in 10%, hyperorality in 6%, urinary incontinence in 48% and sexual disinhibition in 7%. Behavioural abnormalities were greater in those with more severe dementia. Features of the Kluver-Bucy syndrome were commonly seen.

In the study by Patterson et al (1990), mentioned above, activity disturbance was recorded for 44% of the group. Ryden

(1988), studied the aggressive behaviour of people with dementia in the community, using an aggression scale. The results of a pilot survey of caregivers revealed aggressive behaviour in 65% of 183 subjects, weekly or more in 31% and daily in 16%. Verbal and physical aggression were the most prevalent, at 50% and 46% respectively and sexual aggression less frequently at 18%. Aggression was significantly related to the degree of cognitive impairment and past history of aggression, not to diagnosis nor drugs.

The distressing aspects of these symptoms to the carers can only be imagined. The high levels of morbidity in these areas are reported in the Results, and are also illustrated in the Appendix: Case Studies and Appendix: Carers. The data collected, illustrates that whereas most attention has been directed to Alzheimer's Disease, these symptoms are also occurring in other dementia types too.

For comparison, in this study, some of the behavioural problems displayed at some stage of the illness, by the Alzheimer group are given here: overactivity, 42%; following behaviour, 48%; and all forms of aggression, 53%.

Neurological Signs.

Involvement of the extrapyramidal system is a common finding in Alzheimer's Disease, Funkenstein et al (1993). The work found a strong association between a diagnosis of Alzheimer's Disease and changes in the neurologic examination, especially those suggesting extrapyramidal dysfunction, frontal release signs and impaired alternating motor sequences.

Pearce (1974), examined 65 patients referred to a neurology unit with organic dementia, 86% of whom were presenile cases. He found extrapyramidal features in 40 cases, mainly of akinesia, and mild dyspraxia of the arms and gait, and also primitive reflexes.

The relationship between extrapyramidal signs and cognitive function, in patients with moderate to severe AD, was investigated by Richards et al (1995). They studied 137 patients

and found the presence of extrapyramidal signs (EPS) in AD was associated with a distinct neuropsychological profile, suggestive of the additive effect of frontostriatal degeneration. There was no significant difference in the functional capacity between patients with and without EPS. These findings support the hypothesis that EPS represent a parallel independent pathology superimposed over the classical features of AD, rather than providing a marker for global AD severity.

Molsa et al (1984), studied 143 patients with AD. Only 8% were free of EPS. The commonest signs were: rigidity and hypokinesia. Resting tremor was rare, and 17% had dyskinesia, mostly orofacial.

In the paper by Burns et al (1991b), on neurological signs in Alzheimer's Disease, the reported frequencies of various neurological signs from previous studies is given. The frequency of: the snout reflex occurring in about 20%; grasp reflex, 10-17%; palmomentar reflex, 10-47%; myoclonus, 8%; and extrapyramidal signs, 60%. For their study of the group of 178 AD patients, the neurological assessment revealed a snout reflex in 41%, extrapyramidal features in 12%, drug induced extrapyramidal signs in 3%, myoclonus in 5% and a history of epileptic fits in 3%. A grasp reflex and extrapyramidal symptoms and signs were associated with severe cognitive impairment, and extrapyramidal signs and primitive reflexes were associated with a higher mortality.

The Results section describes some of the neurological findings. To compare with some of the studies mentioned, for the Alzheimer group, the frequency at the first assessment of: the snout reflex was 10%; grasp reflex, 23%; and myoclonus, 10%. From the analysis of change, for the total neurological change score, there was a statistically significant difference between the four DSM3R groups. This does not distinguish the Alcohol-related cases from the others, and indicates that the Multi-infarct group tends to improve. This does not fit clinically with the findings, and may be an artefact of the analysis.

After the Second Assessment.

Information on the services provided for and used by the subjects and their carers, was collected. Some of these findings are discussed more fully in the Appendix: Carers. The data from the second assessment was also used to measure change. From the statistical comparison between the DSM3R groups after the first and second assessments, using the CAPE-BRS and CAMCOG, the Alcohol group appears to be distinct from the others.

Measuring Deterioration.

Prospective longitudinal studies have assessed the rate of cognitive decline in Alzheimer's Disease, and have attempted to identify variables that affect the rate or pattern of deterioration. Reliable prediction of the rate of deterioration in AD is important for the patient, the family, and the treating physician as well as for health-planning authorities. To demonstrate that subgroups of AD patients have different rates of deterioration, also has implications for neuropathological and aetiological heterogeneity. However, Stern et al (1990), have commented that functional loss in AD is difficult to measure or predict.

Teri et al (1990), studied cognitive deterioration in AD, and found the rate of decline quite variable on an individual basis, according to various health and behavioural factors. Alcohol abuse, additional neurological disease and agitation, were significantly related to the rate of decline. Van Belle et al (1990), commented on the reliability of estimates of changes in mental status test performance in SDAT and found it depended primarily on the length of time of observation, not the number of observations made. Green et al (1993), studied the functional decline in AD in a longitudinal study, with evaluations every six months. 104 patients with McKhann probable AD were followed up over an average of 31 months, using a physical self-maintenance scale, and an instrumental activities of daily living scale. Rogosa et al (1982), consider the statistical and psychometric properties of measures of individual change, in the

sphere of the behavioural sciences. They examine the measures of change for data with more than two observations on each individual.

Other considerations of assessing change over time in the study.

It is worth considering the meaning of the score totals, for example, with the CAPE, the higher the score, the greater the overall behavioural disturbance. In the case of a person who is declining rapidly, the behavioural problems may be actually decreasing as the docility and inability to respond increase. The change that is best reflected is of increasing disturbance rather than increasing disability and this may not therefore be a good reflection of overall decline.

Describing the changes in various symptoms with time is also possible from a more detailed analysis of the information from the MOUSEPAD. In a cruder way, the CAMDEX H interview, asks the carer to describe the pattern of decline since the onset of the illness.

Questions to ask of the data include, does the description of a step-wise decline, presumed to be a feature of MID, hold true for the group studied here? Difficulties with this are that if the steps are very steep the slope of decline may appear smooth. Infections and other accidents can precipitate steps, rather than them being intrinsic to the illness itself. Another area enquired into was the fluctuating nature of the symptoms. Fluctuations which occur as part of the clinical picture, for example in Lewy Body Dementia, are difficult to substantiate, see McKeith et al (1994). This becomes especially hard to distinguish later on in the course of the illness, when the level of confusion is greater.

The individuals at base-line at the first assessment will have already undergone their deterioration, whether rapid or slow. Therefore the rates of decline measured, will depend in part, on the stage of the illness of the individuals. The only way to really examine the different decline patterns would be to begin a study, where the individuals were at the same point of the illness (the start), and measure the changes from there.

The most suitable way to measure the changes that had occurred between the two assessments was considered. This could very crudely be seen by looking at who of the group had had a severity change during the follow-up period, and describing the characteristics of this group. But a more sensitive measure was also required. As described, the most objective parts of the assessment battery were the CAPE-BRS, CAMCOG and neurological examination. These could provide a profile for the individuals assessed on both occasions, of the behavioural, cognitive and neurological features. The statistical methods used to measure change, have already been described.

Does Heterogeneity exist?

There are different dementia types, based on aetiological risk factors (such as Alcohol-related and vascular), and on distinct clinical presentations (such as for Pick's Disease or Lewy Body dementia). Within Alzheimer's Disease, do further subtypes exist? Do these have distinct patterns of decline? if so, can predictors be identified?

Subtypes could be based on certain clinical features or clusters of these such as: neuropsychological profile; neurological profile; psychotic features; and behavioural disturbances. Risk factors, such as family history, have also been examined as subtype indicators.

Heterogeneity Based on Age of Onset.

Are these potential subtypes based on age of onset? Overall, it is unclear from the evidence whether clinically separable subgroups of patients exist, and the relation of age to disease subtypes is poorly defined.

Rossor et al (1984), reviewed the neurochemical characteristics of early and late onset types of AD, and found that the older type had relatively pure Ach deficiency in the temporal lobe and hippocampus. The younger type had more widespread and severe changes.

Rubin et al (1993), found a similar pattern of psychopathology in younger and more elderly persons with AD, supporting the suggestion that these changes are the direct effects of the illness on the central nervous system.

Stern et al (1992), studied 111 subjects with probable AD, and the deterioration on the Blessed Test. They found that age of onset had no significant effect on the rate of decline.

Evidence for the existence of subgroups within Alzheimer's in terms of neurocognitive profile, is shown by the work of: Jorm (1985); Filley et al (1986); and Seltzer and Sherwin (1983). This last paper, indicates that younger Alzheimer patients have greater levels of language disorder. Becker (1988), demonstrated that early-onset cases had greater syntactic problems. Other reports are of early-onset dementia having: a more pronounced aphasia (Seltzer and Sherwin 1983); and a more severe non-dominant hemisphere dysfunction (Loring and Lorgen 1985).

Even differences in fingerprint pattern have been reported between early- and late-onset cases, see Seltzer and Sherwin (1986). But such reports of differences between the two types, are not consistently found. There is also a hypothesis that the early-onset form of dementia is more aggressive, or rapidly declining, with shorter survival time, than the older-onset form.

Barclay et al (1985), investigated factors associated with duration of survival in Alzheimer's Disease. Factors associated with decreased duration of survival in Alzheimer's Disease include: male sex, presenile onset and an increased severity of behavioural disturbance.

Loring and Lorgen (1985), found that patients who developed a degenerative dementia in their presenium, were more impaired than their senile counterparts, on age-adjusted measures of sustained concentration and mental tracking. The data supports the relative worsening of behavioural performance in presenile dementia of the Alzheimer type and is consistent with the literature describing a more rapid clinical course for this group of people.

Heyman et al (1987), looked at the clinical predictors of institutionalisation and death, in their study of 92 early-onset cases. They found language ability and cognitive function were predictors. The age of the patients had a significant modifying effect on these predictive factors, resulting in a greater risk of institutionalisation and death in younger patients with severe cognitive impairment as compared with older individuals with the same degree of dysfunction.

There is therefore some evidence that different subgroups of Alzheimer's Disease exist, based on symptoms or age of onset, with a faster decline in younger patients. This is not supported by the work of Grady et al (1987), where cerebral metabolism and cognitive performance in early- and late-onset Alzheimer Disease patients with the equivalent duration and severity of illness were studied.

In the study by Newens et al (1993a), the area is reviewed and it is concluded that recent data does not suggest that patients with presenile Alzheimer's Disease suffer a malignant course with short survival, compared with older patients, and do not support the view that there is an age related heterogeneity in Alzheimer's Disease.

As already mentioned, the data from this study suggests that deterioration within the presenile group, was associated with older age at original referral.

Heterogeneity Based on Other Clinical Features.

Myoclonus has been discussed as a potential predictor of rapid decline associated with Alzheimer's Disease. Chui et al (1985), in their study of 146 individuals with Alzheimer's Disease, found that independently of the duration of the illness, myoclonus and non-iatrogenic extrapyramidal disorder, were associated with greater severity of dementia. They also evaluated the possibility of other clinical subtypes, and found that early-onset dementia was significantly associated with more prevalent and severe language disorder. However, the familial risk could not be differentiated on the basis of age of onset or aphasia.

Folstein and Breitner (1981), and Breitner and Folstein (1984), have indicated from their studies, that familial cases have more apraxia and language disorder.

Mayeux et al (1985), studied 121 Alzheimer Disease cases and found those with myoclonus or extrapyramidal signs, had greater intellectual decline and functional impairment in their daily activities. The heterogeneity demonstrated that certain clinical manifestations may be useful in predicting outcome. Work by Stern et al (1990), indicated that extrapyramidal signs and psychosis, are powerful predictors of the rate of decline in basic self-care activities and cognition.

In the work by Heyman et al (1987), the significance of epileptic phenomena in Alzheimer's Disease, was felt to need the consideration of the severity of the dementia process. Chen et al (1991), looked at the development of extrapyramidal symptoms, myoclonus and psychosis in the course of Alzheimer's Disease and concluded that these features mark progression rather than indicate subtypes.

Forstl et al (1996), indicate that neuroimaging, neurophysiology and genetic risk markers maybe more important for early differential diagnosis, than prediction of the course of the illness. Cognitive performance may represent a better predictor of further course of intellectual and morphological changes in Alzheimer's Disease, than EEG alterations and brain atrophy.

The results from this study do not allow a comparison of older- and younger-onset forms of dementia, but may identify subgroups based on various features. The results have indicated the distinctions that can be made between the DSM3R groups.

From the one-way analysis of variance of the CAPE and CAMCOG data, the Alcohol group can be clearly distinguished from the other DSM3R groups, by its profile. In general, the subjects with Alcohol-related dementia in this study, had a less profound dementia. However, there were a higher proportion of mild severity cases in this group at the first assessment.

From the CAMCOG data, the Alcohol group can also be distinguished in its pattern of change, with some areas of assessment showing a trend to improvement over the follow-up period. Clearly, the nature and definition of Alcohol-related dementia needs scrutiny in order to make sense of the results.

The analysis of the changes in the neurological data has revealed differences between the four DSM3R groups, but not in a meaningful way.

From the multiple logistic regression analysis, family history and gender are not found to have any significant association with change. The findings with regard to diagnostic group, age at referral and illness duration have been discussed.

Genetic Results.

The results from the analysis for the three alleles, APOE, α -1 antichymotrypsin, and VLDL-R, and their interaction, have been summarised in the Results. Whereas the APOE allele has been well established as a genetic risk factor for Alzheimer's Disease, the other two loci have not.

APOE.

This confirms that the APOE ϵ 4/APOE ϵ 4 allele type is represented to a greater extent in the cases clinically defined as having Alzheimer's type dementia. The results confirm that there is a trend towards a higher proportion of familial cases with an increasing number of APOE ϵ 4 alleles, and demonstrates a significant regression of the age at referral, on the number of APOE ϵ 4 alleles. This is in keeping with reports from other work, see Introduction: Genetics.

VLDL-R.

There were a couple of findings of significance in the Alzheimer's group, which would need further investigation. There were increased levels of familiarity in subjects with at least one

106-allele, and an increased proportion of the highest severity ratings in those without a 97 allele.

ACT.

There was nil significant in the Alzheimer's group for this gene.

Interaction.

The logistic regression analysis suggests the possibility of a protective effect associated with the possession of the VLDL-R 106-allele. No substantiation was made of the report of Kamboh et al (1995), that the ACT genotype modifies the risk from APOE ϵ 4.

Future Directions For The Study.

As mentioned, not all the data analysis possible has been presented in this thesis, and other questions have arisen from it as a process of evolution. Some could be answered using the collected data and others would require additional studies, possibly using cases from the identified group.

Some of these points have been mentioned already, and are summarised here:

1. Using the data to make epidemiological estimates of the incidence and prevalence of early-onset dementia in the Lothian area.

2. Identification of distinct subgroup profiles

- using the DSM3R defined groups.
 - within the Alzheimer or mixed Alzheimer group
- by looking at the associations between some of the following, (with specified hypotheses):

Diagnosis.

Age at onset.

Illness duration.

9. A more detailed analysis of the presentations, and onset symptoms, (possibly with an additional interview), would be of interest. Comparing the presentation of an age- and sex-matched group with cases presenting with the new CJD-BSE variant, may be valuable.

10. Look at the details of the individuals from the control group who were APOE ϵ 4/APOE ϵ 4.

11. The possibility of scanning with MRI would provide extremely valuable information in study of early-onset dementia.

12. Comparison with a group of age- and sex-matched Down's cases with dementia.

13. Genetic testing

- looking at new candidate genes (perhaps even PrP analysis).

Conclusion.

This study provides a detailed and careful clinical description of a group of subjects with early-onset dementia. It is the first study of its kind, to look at dementias of various aetiologies, and attempt to compare them. There is no other literature to compare directly with it. The feature of having a second assessment, after a year, has meant that change can also be monitored.

The DSM3R Alcohol-related dementia group, appears to have a distinct profile from the CAPE-BRS and CAMCOG scores. In general, the dementia in this group seems to be less severe. The pattern of change in some cognitive assessments over the year, also appeared to have a distinct profile in this group. Over the follow-up period, the deterioration was minimal in the Alcohol-related group and there was even evidence of improvement in scores, compared with the other groups.

Other predictors of decline have been looked for, but no relevant themes have emerged.

The data collected has been analysed only in part, and will provide the basis of future work as outlined in the Discussion.

The genetic analysis confirmed the effect of the APOE ϵ 4 allele previously reported in Alzheimer's Disease. No substantial findings were apparent for the other two loci tested, but there was a suggestion of a possible protective effect associated with the possession of the VLDL-R 106-allele. As molecular advances are made, it remains an exciting prospect that the clinical differences in presentation, rate and pattern of progression, and demographic characteristics, may be explicable at the molecular level.

Some data concerning the services provided for, and used by this specific group of patients and their carers, in Lothian, had also been collected. This information can be shared with organisations, working to find funding for presenile dementia in the health service. The data will give a greater chance to plan appropriately for those involved in caring , and managing these illnesses.

End of Volume I.