The Epidemiology of Presenile Alzheimer's Disease in Scotland (1974 - 1988): Diagnosis, Incidence Rate and Natural History.

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Declaration

The original work presented was undertaken while a member of the Dementia Research Group based at the Royal Edinburgh Hospital, Edinburgh. Professor Lawrence J. Whalley supervised the study and Cecilia McQuade assisted in data collection from psychiatric hospitals. Brenda Thomas assisted in data collection from the Registrar General. I trained and supervised both observers, collected two-thirds of the psychiatric hospital data, all general hospital data, all neurology outpatient data, all neuropathology data and analysed the data. This thesis was written entirely by myself.

Part of the work was presented successfully for the Diploma in Epidemiology (awarded by the Faculty of Public Health, St Andrews Square, London). A copy of the manuscript entitled "Alzheimer's Disease in Scotland (1974 - 1988)" is enclosed together with copies of original papers that have been published (detailed below).

Publications and manuscripts based on this thesis

Whalley LJ and McGonigal G. Aetiology and Genetics of Alzheimer's Disease. In: The Psychiatry of Old Age, Copeland JRM, Abou-Saleh MT and Blazer D (eds). John Wiley & Sons, 1993.

McGonigal G, McQuade C, Thomas B and Whalley LJ. Survival in Presenile Alzheimer's and Multi-infarct Dementias. Neuroepidemiology 1992;11:121-126.

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Summary

Objectives - To evaluate clinical criteria to diagnose Alzheimer's disease and to describe the epidemiology of presenile Alzheimer's disease in Scotland from 1974 to 1988.

Design - Retrospective review of hospital records of patients aged less than 73 years admitted to psychiatric hospital with various diagnoses of dementia. Diagnoses were classified by National Institute of Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association Criteria (NINCDS-ADRDA) and the Hachinski score. Accuracy of diagnosis was assessed by reference to the neuropathological diagnosis in those who underwent postmortem examination. Completeness of the study sample was evaluated by scrutiny of selected neurology outpatient and general hospital records.

Setting - All general psychiatric hospitals in Scotland.

Subjects - All patients with onset of dementia aged 40 - 64 years inclusive.

Main outcome measures - Probable, broad and definite Alzheimer's disease, sex of patient, age at onset, age at presentation, date of death, place of death.

Results - 5874 psychiatric hospital records, 129 neurology outpatient records, 89 records from non-psychiatric hospitals and 61 neuropathology records were examined. A discriminant function analysis, which entered the clinical criteria as variables, was performed and the diagnostic accuracy of the clinical criteria was compared before and after the analysis. NINCDS-ADRDA criteria had a diagnostic

accuracy of 72% (specificity 88%, sensitivity 61%) compared to 77% (specificity 80%, sensitivity 75%) after analysis. NINCDS-ADRDA criteria together with a Hachinski score had an accuracy of 72% (specificity 61%, sensitivity 88%) compared to 83.6% (specificity 76%, sensitivity 89%) after analysis. Variables of highest discriminating value were the Hachinski score, presence of coexistent neurological disease and presence of coexistent systemic disease.

317 patients met criteria for probable Alzheimer's disease and 569 met criteria for broad Alzheimer's disease. Minimal incidences per 100 000 population aged 60-64 years were 22.6 (95% confidence interval, 20.2 to 25.2) and 40.5 (38.9 to 42.3) per 100 000 for probable and broad Alzheimer's disease. In the 1981 census year the annual incidence of probable Alzheimer's disease was 1.6 (1.0 to 2.6). Female gender was associated with a higher incidence of probable and broad Alzheimer's disease.

The five year survival rate for probable Alzheimer's disease was 51.2% decreasing to 17.3% at ten years. Females survived 1.3 times longer than males (95% confidence interval 1.04 to 1.61). Place of death, age at presentation and year of presentation did not significantly affect survival duration. There was no evidence of increased survival in those patients with probable Alzheimer's disease over the time period from 1974 to 1988.

Conclusions - Current clinical criteria used to diagnose Alzheimer's disease are limited and can be substantially improved. Female gender is positively associated with the development of Alzheimer's disease before age 65 years. Female patients with a clinical diagnosis of probable Alzheimer's disease live longer than male patients with the same diagnosis.

Section 1: Literature review

The literature on Alzheimer's disease is vast and the following review is necessarily selective but acts as an introduction to the original work reported. The review concentrates on three main areas which are most relevant to the thesis. Firstly, practical methodological considerations of disease definition and study sample choice will be discussed. Secondly, the basic epidemography of Alzheimer's disease will be described. Finally, the aetiology of the illness will be reviewed with known and proposed risk factors detailed.

DEFINITION OF ALZHEIMER'S DISEASE

The paucity of consistent epidemiology data on Alzheimer's disease is largely explicable by difficulty in its antemortem diagnosis. The definition of Alzheimer's disease as a clinical, neuropathological or neurochemical entity is complex and controversial. However, a valid definition is a prerequisite for research in the illness and, therefore, a logical starting point in a review of the literature.

(a) Clinical definition of Alzheimer's disease.

The clinical diagnosis of Alzheimer's disease remains presumptive until confirmed by neuropathological examination. Definite Alzheimer's disease is a neuropathological diagnosis requiring the demonstration of specific neurohistological features (McKhann et al, 1984), but no universally accepted neuropathological criteria for this diagnosis exist (Khachaturian, 1985,Tierney et al, 1988). There are two further concerns. Firstly, in clinical practice and medical research neuropathological validation of diagnosis is rarely possible because cerebral biopsy in the absence of an effective treatment is considered unethical. Secondly, neurohistological features of the disease can be present in clinically nondemented elderly people. This diagnostic difficulty has important repercussions and it was not uncommon for clinical diagnostic error rates in Alzheimer's disease research to approach 50 percent (Garcia et al, 1981). Uniform clinical diagnostic criteria for the disease are needed and several have been proposed.

To facilitate epidemiological research, clinical criteria have been described to define the illness. Two comparable, but broad, definitions for Alzheimer's disease have been accepted (DSM-III-R and ICD 9) and several compatible clinical criteria described (Eisdorfer and Cohen, 1980, McKhann et al, 1984). Of these, clinical

criteria proposed by the Work Group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease Association (NINCDS-ADRDA) to diagnose possible, probable and definite Alzheimer's disease have been readily accepted (McKhann et al, 1984). The criteria for probable Alzheimer's disease are widely used in therapeutic and epidemiological research to define the disease in study populations. They have been validated in neuropathological studies and consistently have a diagnostic accuracy rate over 80% (Burns et al, 1990, Martin et al, 1987). However, the results of these studies are flawed because investigators rarely report neuropathological criteria used to define Alzheimer's disease and, importantly, their interpretation of the clinical criteria (Tierney et al, 1988). The clinical criteria are subjective, flexible, subject to interobserver variation and are not unambiguously defined (Kukull 1990(a and b)). The Work Group suggested that the criteria were tentative and could be improved by critical examination.

(b) Neuropathology of Alzheimer's disease.

There have been advances in understanding the neuropathology of Alzheimer's disease, particularly at a neurohistological and a neurochemical level. The neuropathological changes in Alzheimer's disease overlap with neurophysiological ageing processes. This causes difficulty in reaching a consensus as to what constitutes 'definite' Alzheimer's disease. Neurohistological and neurochemical changes considered characteristic of Alzheimer's disease are presented.

(i) Neurohistology.

In 1906 Alois Alzheimer reported his observations on a 51 year old woman who was at the insane asylum in Frankfurt Main (Alzheimer A, 1906). At post-mortem, he described her atrophic brain without macroscopic abnormality.

Microscopically neurofibrils, neuronal death and miliary foci were reported scattered throughout the entire cortex. Arteriosclerotic changes in large blood vessels and neovascularisation were also recorded. Since then the presence of a distinct disease process has been broadly accepted, though the degree of neuropathological change (along with clinical features) necessary to confirm its existence is debated.

Morphological changes of cerebral atrophy, neuronal cell loss, neurofibrillary tangles and neuritic plaques are established features of Alzheimer's disease (Terry and Katzman, 1983, Brun, 1985). Neurofibrillary tangles arise within neurones as submicroscopic filamentus structures wound round each other as a "paired helical filament" (Crowther and Wischik, 1985). Neuritic or senile plaques comprise degenerating nerve terminals with amyloid protein and aluminosilicate at their core (paired helical filaments can also accumulate in these plaques) (Wisniewski and Terry, 1970, Katzman, 1986, Candy et al 1986). Cerebrovascular amyloid within blood vessels in the meninges, cerebral cortex and hippocampus and granulovacuolar inclusion bodies, particularly in hippocampal neurones, are recognised neurohistological features of Alzheimer's disease (Vinters and Gilbert 1983, Ball, 1977, Ball et al, 1983). The topography of all these lesions is not strict nor pathognomonic of the disease (Ulrich and Stahelin, 1984, Tomlinson et al, 1968).

The result is that no standard inclusion neuropathological criteria to diagnose definite Alzheimer's disease have been accepted. It is accepted that exclusion criteria for vascular dementia are required before the diagnosis of definite Alzheimer's disease can be reached, but again no criteria can be agreed (Tierney et al, 1988, Tomlinson et al, 1970, Molsa et al 1985). Such lack of agreement adversely affects clinical research. The diagnostic accuracy of clinical criteria may vary by approximately 10% depending on the neuropathological criteria used to confirm Alzheimer's disease (Tierney et al, 1988).

(ii) Neurochemistry.

The brains of people with Alzheimer's disease have a 40 - 90 percent decrease in activity of acetylcholine associated enzyme and choline acetyltransferase, ACE and CAT, in the cerebral cortex and hippocampus (Davies and Maloney, 1976, White et al, 1977). This deficit correlates with neuropathological changes and severity of dementia and is demonstrable in the first year of symptoms (Perry et al, 1978, Katzman, 1986). It is largely due to a loss of primary ascending presynaptic cholinergic neurones, but there is also a smaller loss of muscarinic postsynaptic M2 receptors (Davies and Verth, 1977, Mash et al, 1985).

This discovery led to the cholinergic hypothesis to explain memory impairment in Alzheimer's disease. The hypothesis postulated a connection between some of the cognitive impairments of the disease, especially memory, and a disturbance in presynaptic cholinergic transmission (Davidson, 1979, Perry, 1986). It could have heralded a treatment or even cure for the disease. However, although the cholinergic hypothesis has generally stood the test of time it has not led (so far) to an effective treatment (Perry, 1991). This is because the complete effects and interactions of the cholinergic system within the brain are more complex than originally thought. For example, trophic factors (e.g. nerve growth factor) maintain forebrain cholinergic neurones and can even 'rescue' them in ageing animal brains (Perry, 1990, Stromberg et al, 1990). Also, cholinergic deficits are not specific to Alzheimer's disease and have been described in physiological ageing and Parkinson's disease (McGeer et al, 1984, Perry, 1990(b)).

Other neurochemical changes are a feature of Alzheimer's disease, for example, a decrease in the concentration of cortical somatostatin, a peptide neurotransmitter (Davies et al, 1980, Rossor et al 1980, Arai et al, 1984). Other less consistent deficits have also been reported in Alzheimer disease, such as decreases in noradrenaline and serotonin levels within the brain but increased levels of

noradrenaline and its metabolites in the cerebrospinal fluid around the brain (Arai et al 1984, Raskind et al, 1984).

Summary.

Alzheimer's disease is a distinct pathological illness, however, its boundaries in terms of clinical features, neurohistological features and neurochemical changes merge with those physiological changes experienced with age. There are no pathognomonic features of Alzheimer's disease and this causes diagnostic difficulties which impedes epidemiological research. Improving clinical criteria to diagnose Alzheimer's disease for specific use in epidemiological research is a major objective of this thesis.

SAMPLING AND STUDY DESIGNS

Population sampling is a major concern which limits conclusions drawn from epidemiological research in Alzheimer's disease (Weiler, 1986). This arises because of the insidious nature of the illness and the variety of ways in which it can present to medical attention. This review critically appraises the main advantages and disadvantages of study designs used in previous epidemiological studies in Alzheimer's disease.

(a) Study samples.

(i) Community-based studies in Alzheimer's disease.

All, or a randomly chosen sample of people, within a defined geographical area have been studied (Rocca et al, 1990, Evans et al, 1989, Pfeffer et al, 1987). Typically, after screening for cognitive impairment in a geographically defined population, a sample that has possible dementia is ascertained and all, or a further random sub-sample, is studied. The main advantages and disadvantages of this selection process are outlined in Table A.

Table A. Main advantages and disadvantages of community-based screening for Alzheimer's disease.

ADVANTAGES	DISADVANTAGES
Useful in assessing local health care needs	Validity and reliability of screening test (? miss asymptomatic and mild cases)
Demographic data directly applicable	Large number of people need to be screened
Sample less dependent on availability of health care	People with dementia may be preferentially missed in survey

The use of community based studies within localised, defined geographical regions to investigate possible associations between environmental toxin exposure and the development of Alzheimer's disease are potentially flawed. Bias is introduced when conclusions drawn from small geographical ares are extrapolated to national populations if the effects of population migration, temporal and geographical variation in risk exposure, validity of diagnostic criteria or dynamic changes in health care.provision have not been considered as plausible explanations of results. Selection bias and difficulty generalising conclusions beyond the study area are major problems in community-based research.

(ii) Health service studies in Alzheimer's disease

Hospital in-patients (Erkinjuntti et al, 1986, Gagnon et al, 1988), out-patients (Broe et al, 1990, Shalat et al, 1987, Walsh et al, 1990), patients who attend specialist memory clinics (Philpot et al, 1989, Hier et al, 1989) and combinations of all these

sources (Hofman et al, 1989, Schoenberg et al, 1987, Traves et al, 1986) have been used as study samples in epidemiological research in Alzheimer's disease. The main advantages and disadvantages are shown in Table B.

Table B. Main advantages and disadvantages of study samples derived from hospital services.

ADVANTAGES	DISADVANTAGES
Retrospective data available	Selection bias; asymptomatic cases, mild cases and misdiagnosed cases missed.
Large numbers of sufferers can be identified quickly and cheaply	Demographic data not directly applicable
Useful in hospital service planning	Sample determined by availability of health services

Selection bias remains a cause for concern. Undiagnosed and misclassified people with Alzheimer's disease will be excluded from study. The number of such people may not be random, but reflect variations in local availability of health care.

(iii) Miscellaneous study samples in Alzheimer's disease.

A variety of other sampling sources have been used in epidemiological research in Alzheimer's disease. For examples, radiological (Martyn et al, 1988) and neuropathological records (Whalley and Holloway, 1985) have identified subjects for study. Both these sources have been widely criticised because of concerns about selection bias. The availability of CT scanners varies widely in and between geographical areas and people who have this investigation cannot be

considered representative of sufferers with Alzheimer's disease (Ebrahim, 1989, Schupf et al, 1989). The main use of post-mortem based studies in epidemiological research is to assess the validity of clinical criteria in the ante-mortem diagnosis of Alzheimer's disease (Boller et al, 1989, Risse et al, 1990).

Regional diagnostic registries of patients with Alzheimer's disease have also been used (Still et al, 1990). Problems arise in relation to the completeness and availability of these diagnostic registries and their validity remains to be established (Hughes et al, 1989).

(b) General limits imposed in studies in Alzheimer's disease.

General limitations are imposed on populations to find most efficiently those people with Alzheimer's disease. The limits are dictated by the study hypothesis, the time available to complete the study, ethical considerations and by available resources.

(i) Arbitrary age limits are a common and effective way of increasing the efficiency of study sampling. For example, all people aged more than 58 years (Rocca et al, 1990), 59 years (Philpot et al, 1989) and 64 years (Walsh et al, 1990) have constituted study populations. Similarly, age ranges have been imposed (Brayne and Calloway, 1989).

(ii) Time limits have been set. For example, patients with Alzheimer's disease between 1960 to 1964 (Schoenberg et al, 1987) and between 1980 to 1988 (Hofman et al, 1989) have been studied in defined communities. Time limits should allow ascertainment of sufficient numbers of people with Alzheimer's disease to test the study hypothesis and permit the application of demographic data accumulated through census or social studies.

(iii) Residential limits are rarely imposed, although the effects of migration within a population may be profound. Some studies have attempted to monitor the

residential stability of the population. For example, people have needed to be resident in study areas for at least one year (Schoenberg et al,1987) or ten years (Whalley and Holloway, 1985) to be accepted for analysis.

(iv) Other limitations are rarely imposed but have included gender (Shalat et al, 1987) and racial limits (Treves et al, 1986).

(c) Specific limits imposed in studies in Alzheimer's disease.

Specific limitations are imposed by the investigator to define Alzheimer's disease in the population. The limits are dictated by the natural history of the disease and reflect the difficulty in establishing the diagnosis and the time of symptom onset in individuals with the disease. The importance of clinical diagnostic criteria has already been discussed (Chapter - Definition of Alzheimer's disease).

Onset of symptoms and date of presentation to medical care are different in Alzheimer's disease (Hier et al, 1989, McGonigal et al, 1992). In prevalence studies the presence of symptoms of Alzheimer's disease at a fixed time point is sufficient (Zhang et al, 1990, Rocca et al, 1990). In other epidemiological studies, specific limits are imposed to define disease onset and age patients so that general limits can be applied.

Date of first presentation to medical care with symptoms of dementia has been used to age Alzheimer patients (Hofman et al, 1989). This date is discrete, objective and readily available from hospital records. However, the date is dependent on referral patterns of patient to primary care physician and of primary care physician to hospital, which could cause non-random selection bias. Also, a large proportion of the coarse of the disease is from time of symptoms to presentation and will be excluded from study (Walsh et al, 1990, McGonigal et al, 1992).

Date of onset of symptoms of Alzheimer's disease has been used to age patients (Schoenberg et al, 1987, Ferini-Strambi et al, 1990). This date is less dependent on referral patterns and assesses the entire clinical course of the illness. Disadvantages relate to the insidious onset of Alzheimer's disease. This date is not discrete, is subject to recall error and may not be known. Criteria to define the date can have a critical influence on patient ascertainment (Breitner and Magruder-Habib, 1989).

Summary.

The population chosen for epidemiological research in Alzheimer's disease is dependent on the study hypothesis, financial and ethical concerns. Many sources have been used to generate study samples. No population sample is ideal when compared to studying an entire population, but this is rarely practical. Investigators must appreciate the limitations of population sampling and reasonably exclude sampling bias as an explanation of findings. What is considered 'reasonable' must be decided by colleagues and will be, in part, dependent on the gravity of the study's conclusions. For example, I suggest that for environmental exposure to aluminium to be accepted as a risk factor for Alzheimer's disease will require convincing evidence because of the economic and social impact of such a conclusion.

EPIDEMIOLOGY OF ALZHEIMER'S DIESASE

Alzheimer's disease presents a considerable challenge to society and the National Health Service in terms of caring for sufferers and relatives and in the cost of providing such care. Its importance in public health terms has substantially increased this century for a variety of reasons. Improved life expectancy coupled with demographic changes in the age structure of the population mean that more people are living to old age and developing dementing illnesses. Similarly, new treatments are improving the prognosis for previously chronic fatal illnesses, (e.g chronic renal failure), such that more sufferers reach old age with the inherent risk of dementia ("the failures of success").

Epidemiology is the study of the occurence and causes of disease (and health) in populations and aims to explain and monitor the distribution of disease in communities. It is the science of public health physicians and health service planners, providing a rational basis for preventative health policies, future health service planning needs, auditing current health care practice, ete.

This chapter reviews measures of disease frequency (incidence, prevalence and survival duration) and examines the effect of gender in Alzheimer's disease. Other epidemiological aspects of this illness are detailed elsewhere (associations, risk factors, "normal ageing", ete).

(a) Incidence of Alzheimer's disease.

Incident cases of a disease are those which *first* occur in a defined time period. There is a paucity of good quality, consistent population-based incidence data derived from defined communities detailed in the Alzheimer's disease literature (Molsa et al, 1982, Treves et al, 1986, Schoenberg et al, 1987). This deficiency is

important. Incidence rates are of value in defining individual risk of disease, in formulating and testing aetiological hypotheses and in planning diagnostic Health Service requirements (Morris, 1964). The reasons for this lack of information have already been alluded to in the preceeding chapters.

These methodological considerations also explain the wide range of reported incidence rates for Alzheimer's disease and undifferented dementia and make direct comparisons between different studies hazardous, though not without reward (Table C). There are some important, consistent findings reported in these studies.

The incidence rate of Alzheimer's disease and that of undifferentiated dementia increases as a function of age in all studies but data at extremes of the disease distribution is rare. Information on early onset disease is scarce because dementia is rare in this age group (Treves et al, 1986). This deficiency is important in testing aetiological hypotheses because early onset cases may have a greater exposure to a causative agent and may be more easily identified from routinely collected health service returns. Additionally, major advances in understanding the genetic nature of early onset Alzheimer's disease cannot be extrapolated to the general population unless the basic epidemiology of this aspect of the disease is understood.

Data on the incidence rate of disease in the eighth and subsequent decades of life is limited by finite human-life span and the size of populations studied. There has been a suggestion that age-specific incidence rates of Alzheimer's disease may decline in later life. If true then those who survive to old age would represent a survival elite (Gruenberg, 1977, Jarvik et al, 1980). Current evidence does not support this hypothesis with studies reporting a steep rise in incidence rates of Alzheimer's and undifferentiated dementia with age (Akesson, 1969, Molsa et al, 1982, Nilsson, 1984, Hagnell et al, 1983, Rorsman et al, 1986); though the accuracy

of rates in the older age groups are diminished by small denominators and must be interpreted with caution (Molsa et al, 1982, Rorsman et al, 1986).

The inexonerable rise in the incidence of Alzheimer's disease with age would suggest that early-onset and late-onset Alzheimer's disease are not uniquely distinct pathologies but a continuum of the same disease process (Treves et al, 1986). However, I could locate only one national survey on the incidence of early onset Alzheimer's disease and further data on early onset disease is required (Treves et al, 1986).

Incidence studies have consistently concluded that increased age is a definite risk factor in Alzheimer's disease. Before the full interaction between age and this illness can be understood more information is needed at the extremes of the disease distribution. On current evidence it is likely that the incidence of Alzheimer's disease rises inexonerably with age and that there is a disease continuum between early and late onset disease.

Table C. Selected incidence rates of undifferentiated dementia and Alzheimer's disease.

STUDY	AGE GROUP (Years)	DISEASE	INCIDENCE / 100 000 pop
Schoenberg 1987	> 29	Dementia	187.5
Molsa 1982	>40	Dementia	58
	>65		447
Nilsson 1984	70-75	Dementia (men)	17.7
	75-79		32.3
Schoenberg 1987	>29	Alzheimer's disease	123.3
Treves 1986	<60	Alzheimer's disease	2.4

(b) Prevalence of Alzheimer's disease.

Point prevalence is the number of cases of disease in a population at one point in time, taken as a proportion of the total population at the same point in time. Prevalence is frequently used to plan the allocation of health service resources and is a good indicator of the total disease burden in the community (Morris, 1964). Prevalence studies are, therefore, of obvious importance in Alzheimer's disease.

Reported prevalence ratios vary considerably and any generalizations about the prevalence of dementia are, like incidence studies, hazardous (Henderson and

Kay, 1984). Consistent findings remain important and evidence of any change in prevalence of disease would be of interest.

The prevalence Alzheimer's disease and undifferentiated dementia increases with age (Table D). Meta-analysis of 22 pooled prevalence studies indicate that the prevalence of undifferentiated dementia doubles approximately every five years while that of Alzheimer's disease doubles every four and a half years, though actual prevalence rates varied considerably (Jorm et al, 1987).

Prevalence rates per 100 000 of population at risk have been calculated for presenile Alzheimer's disease, but small denominators make interpretation of these difficult. Rates range from 31.8 (C.I. 0-67.9) based on three people with the illness (Kokmen et al, 1989) to 54.7 (0-116.5) based, again, on three people (Schoenberg et al, 1985).

Disease prevalence is approximately equal to the product of disease incidence and mean duration of survival. Any variation in the prevalence of Alzheimer's disease would, therefore, indirectly signify a change in the natural history of the illness. Temporal variation in the prevalence of Alzheimer's disease has been studied by repeating studies in populations using identical methods to those used previously to allow direct comparisons. No significant change in the prevalence of Alzheimer's disease was demonstrated between rates in Rochester, USA in 1975 and 1980 (Beard et al, 1991) and between 1947 and 1972 in Lundby, Sweden (Rorsmanet al, 1986). This suggests there has been no major change in the incidence or mortality associated with the illness over time in these two locations.

Table D. Selected prevalence rates for Alzheimer's disease and undifferentiated dementia.

STUDY	AGE GROUP (Years)	DISEASE	PREVALENCE (% pop at risk)
Zhang, 1990	>55	Alzheimer's disease	1.5
	>60		2.0
	>65		2.9
Pfeffer et al, 1987	>65	Alzheimer's disease	15.3
	>80		35.8
Rocca et al, 1990	>59	Alzheimer's disease	2.6
Evans et al, 1989	65-74	Alzheimer's disease	3.0
	75-84		18.7
	85+		47.2
Erkinjuntti et al, 1986	>54	Dementia	9.1
	55-64		0.8
	85+		41.4
Rocca et al, 1990	>59	Dementia	6.2
Zhang, 1990	>55	Dementia	2.6
	>60		3.5
	>65		4.6

(c) Survival in Alzheimer's disease

Epidemiological data on duration of survival in Alzheimer's disease is needed for a variety of reasons. A basic understanding of the prognosis of the disease is needed by all those caring for sufferers and relatives (councilling implications). Any change in duration of survival will significantly alter the prevalence of the illness (health care planning implications). A frequently used outcome measure in therapeutic trials is length of survival. A baseline measurement is required to assess efficacy of treatment (therapeutic implications).

Studies that attempt to define duration of survival in Alzheimer's disease have additional methodological difficulties. Alzheimer's disease is an insidious disorder and time of symptom onset may be subject to considerable information bias. Time of presentation to hospital care is usually more definitively obtained but excludes a large proportion of the natural history of the illness and is dependent on local health care provision and practice (McGonigal et al, 1992). In addition, it is likely that Alzheimer's disease has a prolonged asymptomatic "latent" period which may vary considerably between individuals and be dependent on a variety of ill - defined factors, for examples, stereotyped attitudes towards failing memory and individual acceptance of degrees of memory failure.

Most studies that have assessed survival time in Alzheimer's disease have been concerned with late onset disease (Go et al, 1978, Walsh et al, 1990). The illness does shorten life expectancy.(Go et al, 1978, Kay, 1962) but the effect of an early onset of disease on duration of survival is uncertain. Studies of survival duration in presenile Alzheimer's disease are rare and have produced conflicting results: a significantly shorter duration of survival has been reported for early onset Alzheimer's disease in some studies (Barclay et al, 1985, Heyman et al, 1987), while others have found no such association (McGonigal et al, 1992, Hier et al, 1989).

Estimates of mean duration of survival have been variously obtained for Alzheimer's disease: 7.1 years (Sjorgen et al, 1952) in a group of early onset disease, 5.7 years (Molsa et al, 1986) and 9.7 years (Hier et al, 1989) in groups of late onset disease. I have reported mean survival in presenile Alzheimer's disease to be 7.4 years, with sufferers taking an average of 3.2 years to present to hospital care (McGonigal et al, 1992).

The suggestion that survival duration in Alzheimer's disease has improved in recent times remains unproven due to methodological limitations (Blessed and Wilson, 1982, Christie, 1982). These studies used hospital based populations from a variety of institutions and their conclusions may reflect changes in admission policy over time rather than improved survival. Another study has found no change in survival in patients with Alzheimer's disease admitted to a single Toronto hospital over a ten year period (Thompson and Eastwood, 1981). The fact that prevalence has not altered significantly indicates that long-term survival has not altered in Alzheimer's disease.

(d) Gender and Alzheimer's disease.

Female gender is a recognised independent risk factor for Alzheimer's disease (Whalley, 1991). Incidence and prevalence studies have consistently found significantly higher rates in women compared to men (Zhang et al, 1990, Akesson et al, 1969, Molsa et al, 1982, Hagnell et al, 1983). Indeed, more than 13 population surveys and the meta-analysis by Jorm have supported the association (Jorm et al, 1987). Whether the incidence of early onset Alzheimer's disease is higher in females remains debatable. Several studies have reported similar incidence rates in males and females in this age group, but small numbers make interpretation of these results difficult (Treves et al, 1986, Molsa et al, 1982, Sulkava et al, 1983). If incidence rates of Alzheimer's disease in males and females are differentially

influenced by age of disease onset, then this would be of considerable aetiological importance.

Alternative explanations for the relationship between gender and Alzheimer's disease are possible. It may reflect differences in the pattern of health care provision between the sexes (Pfeffer et al, 1987). Also, diagnostic bias may play a part. Rocca found that women had a higher prevalence of clinical Alzheimer's disease but that men had a higher prevalence of clinical multi-infarct dementia (Rocca et al, 1990). However a high proportion of people with multi-infarct dementia clinically have neuropathological evidence of Alzheimer's disease (Buhl and Bojsen-Moller, 1988). Thus clinical limitations in the diagnosis of true disease could support erroneous relationships.

GENETICS OF ALZHEIMER'S DISEASE

The role of genetic factors in the aetiology of Alzheimer's disease continues to be extensively researched and is relevant to clinical practice. The past decade has seen important advances in understanding the molecular genetics of familial Alzheimer's disease and related disorders. This chapter summarises these and their clinical relevance is discussed.

(a) Twin studies.

Twin studies have provided an informative starting point in the assessment of genetic risk in Alzheimer's disease. Estimation of concordance between monozygotic (with identical DNA genotype) and dizygotic (with different DNA genotype) pairs allows the likely importance of genetic factors to be quantified. Concordance for Alzheimer's disease between monozygotic pairs is approximately 43% but in dizygotic pairs it is 8% (Kallman et al, 1951). The age at onset of Alzheimer's disease can, however, vary within monozygotic and dizygotic twin pairs and discordant pairs may subsequently become concordant (Cook et al, 1981). An approximate concordance of 40% is suggested for both monozygotic and dizygotic twins (Nee et al, 1987).

Discordance and variability of age at onset of Alzheimer's disease in monozygotic twin pairs is unlikely to result from genetic heterogeneity (though recently the effects of maternal mitochondrial genes has been hypothesized) and provides evidence against a simple genetic cause of the disorder. Twin studies provide support for genetic factors in Alzheimer's disease yet indicate that factors other than genetic may modify genetic expression in some instances of the disorder.

(b) Pedigree studies.

Many examples of families in which Alzheimer's disease seems to follow autosomal dominant inheritance are reported (Nee et al, 1983, Landy et al, 1970). Although there is one single report of a family in whom only women developed the disorder, this is so unusual as to effectively discount the likelihood of X-linked transmission (Posteraro et al, 1988). Most studies suggest that familial Alzheimer's disease is transmitted as an autosomal dominant trait in a proportion of early onset families. In others, however, most pedigrees provide too few data to be confident about the mode of transmission, a feature that is largely related to the late onset at age of disorder and the fact that many informative first-degree relatives have yet to complete most of the period of risk for Alzheimer's disease. In addition, few pedigrees have more than one autopsy-validated diagnosis of Alzheimer's disease. In summary, the majority of sufferers of Alzheimer's disease have a late onset disorder and it is by no means clear that the unusual early onset pedigrees with autosomal dominant inheritance can provide data that are relevant to the majority of patients with Alzheimer's disease.

(c) Proband studies.

Population proband studies have been used to clarify inheritance of Alzheimer's disease. Sjorgen (Sjorgen et al, 1952) has suggested that multifactorial inheritance provided the most likely explanation of the patterns of inheritance he observed in his sample of Alzheimer's early onset cases in Sweden. His study did not include late onset patients. Larson (Larson et al, 1963) has suggested autosomal dominance is the likeliest explanation of his observations, again in Sweden, and his conclusions appear robust almost 30 years later (Mohs et al, 1987). Other studies suggest an estimated cumulative lifetime risk in first degree relatives of probands with Alzheimer's disease of approximately 50%, in keeping with a presumed

autosomal dominant mode of inheritance (Mohs et al,1987, Martin et al, 1988, Farrer et al, 1990). Further studies have shown that cumulative lifetime risk of Alzheimer's disease in the relatives of early onset probands is approximately 50% but that the relatives of late onset probands appear to be at much lower risk (Heston et al, 1981, van Duijn et al, 1991). In addition, the relative risk in Alzheimer's disease is known to increase substantially with increases in the number of first degree relatives affected by dementia.

These observations have prompted the suggestion that there may be several genetically distinct sub-types of Alzheimer's disease and that these include a non-inherited sub-type (Fitch et al,1988, Chandra and Schoenberg, 1989). The hypothesis of genetic heterogeneity is supported by evidence of intra-familial correlations in age at onset. The relatives of early onset probands who develop Alzheimer's disease have a significantly lower age of onset than affected relatives of late onset probands (Breitner et al, 1988, Powel and Folstein, 1984).

Proband studies do not prove conclusively that Alzheimer's disease is transmitted as a autosomal dominant trait but do support the twin and pedigree studies that suggest a strong genetic component in the risk of development of the disorder. Alzheimer's disease is highly prevalent in old people and some instances of dementia in the relatives of probands with the disorder may be coincidental, an inference that would be supported by the small sample size of many studies. Shared environmental factors may also be important.

(d) Genetic linkage studies.

Amyloid protein precipitates in the brains of patients with Alzheimer's disease especially in senile plaques and vessels (Glenne and Wong, 1984). The protein (amyloid b protein) is quite specific and is found in Down's syndrome and Alzheimer's disease (Glenne and Wong, 1984, Musters et al, 1985).

Characterization of the structure of amyloid b protein has been a major step in genetic linkage studies as it has allowed complementary DNA (cDNA) clones of amyloid b protein to be analysed (Goldgarber et al, 1987). Sequence analysis revealed amyloid b protein to be part of a large precursor protein (amyloid precursor protein, APP) that is highly conserved in vertebrate evolution and may function at the cell membrane (Kang et al, 1987). Amyloid b protein is found in senile plaques, the walls of cerebral vessels and within surviving neurones in Alzheimer's disease. It is also found in the brains of many old people not affected by dementia.

Molecular genetic studies have sustained two separate approaches to the genetics of Alzheimer's disease. Firstly, the APP gene was mapped to chromosome 21, as predicted by the Down's syndrome model of Alzheimer's disease (Goldgarber et al, 1987, Goate et al, 1989). Secondly, linkage studies identified a locus on chromosome 21 that segregated with Alzheimer's disease in affected families at a site close to, but not identical with, the APP gene (St George Hyslop et al, 1987, Hardy et al, 1989). Although an early study claimed detection of a gene dosage effect of excess APP expression in Down's syndrome and Alzheimer's disease, it soon became clear that this was unlikely and, more importantly, that Alzheimer's disease, as revealed by molecular genetic studies was a genetically heterogeneous group of disorders. Patients with late onset disease and many early onset cases did not show linkage to a chromosome 21 locus (Tanzi et al, 1987, Podlisny et al, 1987). The extent and precise quantification of genetic heterogeneity in Alzheimer's disease could be potentially resolved by molecular genetic techniques. So far, an uncertain proportion of early onset Alzheimer patients have been shown to carry a defect in the APP gene, although its precise nature varies between families. Three different point mutations on the APP gene have been identified in eight families (Goate et al, 1991, Murrell et al, 1991, Chartier-Harlin et al, 1991). Although it is premature to argue for a molecular biological classification of the dementias, such an approach

might become mandatory if the technique leads to the ready identification of mutations elsewhere in the APP gene and their frequencies in affected and non-affected populations.

(e) Platelet membrane fluidity.

"Membrane fluidity" decreases with age from 40 to 90 years. Platelet membrane fluidity is increased in Alzheimer's disease and a genetic basis for this abnormality has been proposed (Zubenko et al, 1987(b)). When the 90th centile for elderly patients is used to classify Alzheimer's disease patients (Zubenko et al 1987(a), Cohen and Zubenko, 1985) two subgroups can be identified. In one there is increased platelet membrane fluidity with an earlier onset and more rapid course of dementia. In this group there is often a family history of dementia. These findings may be relevant to the abnormal ageing hypothesis of Alzheimer's disease and to premature senescence..

Summary.

There is a substantial genetic contribution to the risk to develop Alzheimer's disease. The existence of a first degree relative with Alzheimer's disease increases the risk by about two-fold and in some instances of early onset Alzheimer's disease the gene responsible is probably on chromosome 21 and in a minority of cases, the abnormality can be precisely located to the APP gene. However, differences between monozygotic twin pairs in Alzheimer's disease suggest that non-genetic factors may also be important. Most genetic hypotheses make reference to possible mutations that lead to the formation of brain proteins that are difficult to degrade and to exclude from the nerve cells. Several metabolic pathways have been carefully examined in Alzheimer's disease and a great deal is now known about the molecular biology of brain amyloid. Unfortunately, little is known about the molecular

biology of the neurofibrillary tangle only about 10% of which has been structurally characterized.

NEURONAL AGEING, DEMENTIA AND ALZHEIMER'S DISEASE

"In fact to draw a distinction between disease and normal ageing is to attempt to separate the undefined from the indefinable"

The previous chapter on genetics highlights one major risk factor for the developement of Alzheimer's disease, this chapter explores another - Age. To appreciate the interrelationship between physiological ageing processes and Alzheimer's disease it is necessary to examine the boundaries between 'normal' neuronal ageing, dementia and Alzheimer's disease.

Normal Neuronal Ageing

This starts in utero. From the earliest period of development large number of cells die as a result of 'programmed cell death' (Schwartz LM, 1991). This process is vital in sculpting body form, removing vestigial tissues, maturation and ,ultimately, senescence. A cells 'decision' to die is a differentiative event under specific genetic control which has, presumably, been open to evolutionary influences (Charlesworth, 1980). In man, a species with extensive genetic heterogeneity, thousands of genes may be involved in modifying and controlling this process and, therefore, senescence phenotype.

Two common hypotheses of ageing are the 'wear and tear' (neuronal fallout model) and the 'use it or lose it' (plasticity model) theories. The former commonly uses the analogy of a large boulder being worn down to rubble by the tides of time (Hanley, 1974). As cells are stimulated and used, they are more likely to die. This progressive process relentlessly reduces the functional reserve of the brain until cognitive changes appear. The rate of decline is individually determined by

genotype and environmental influences. Modification of this process would either require genetic manipulation of 'programmed cell death' or, alternatively, an understanding of the interaction between environment and genotype. Both these solutions are not obtainable at present.

The 'use it or lose it' theory argues that the physiological activation of cells may maintain them (Curzio et al, 1982). Some neurones can grow and alter function in response to unexpected challenges; neurones that do not die may take over the function of those that do. This could explain the recovery of various neuronal systems during ageing after the restoration of missing stimuli. Environmental therapies could, in theory, produce successful ageing and be applicable now. However, neuronal ageing is a complex, heterogeneous physiological process not easily fitted to any model.

The differentiation of disease from normal ageing is a dilemma which confronts clinicians daily. Nowhere is this more true than in the care of patients with dementia. Memory loss is considered a cardinal feature of senescence, and yet is a hallmark of dementing illnesses (Finch and Landfield, 1985, Martin, 1978, Murphy,1978). Not surprisingly, the boundaries between pathological state and physiological cognitive decline are not well defined. Indeed, no categorical boundary exists, but the change from 'normal cognitive function' to dementia is a threshold phenomenon controlled by a variety of divergent processes (Meier-Rage et al, 1991). Clinicians, through greater awareness about the importance of accurate diagnosis of dementing illnesses, have a crucial role to play in defining this boundary.

Cognitive Ageing and Dementia.

Physiological cognitive ageing is an ill-defined entity which is confounded by functional, sociological and pathological considerations (O'Connor et al, 1991).

Old people expect their memory to faulter and are more likely to complain about memory loss, which is not necessarily congruent with actual memory functioning (Jarvik and Falek, 1963, Kahn et al, 1975). These negative sterotypes of age have been questioned and well-designed longitudinal studies have associated memory deterioration with increased mortality (Schaie KW, 1974). In addition, level of education and co-existent physical and psychiatric illness all influence what should be considered 'physiological' cognitive functioning for *an individual* (O'Connor et al, 1991). Lack of substantial population-based normative data make this a difficult clinical decision (Gangali et al, 1991).

The diagnosis of dementia is warranted only if there is demonstrable evidence of memory impairment, that along with other features of dementia, is of sufficient severity to interfere with social or occupational functioning (ICD - 10, DSM-III-R). Dementia is not synonymous with ageing, but must take into account the cognitive performance of an individual over time. It has a threshold set between health and sickness dependent on social function. Sociodemographic factors (e.g, age, sex, social class, education, race, ete) are important determinants of this threshold in an individual. This is not dissimilar to many medical conditions where an individual's ability to adapt to their environment is the principal determinant of disease state.

The putative differentiation between ageing and dementia based on clinical assessment of cognitive function is problematical. The threshold hypothesis necessarily incorporates a social dimension which favours a continuum between age and dementia rather than discrete categorisation. Since cognitive impairment implies a decline from a healthy level of cognition for an individual, a reference range for normal cognitive function is needed which accounts for confounding sociodemographic factors. A baseline in which the influences age and education have been evaluated can be provided by the National Adult Reading Test (NART),

which estimates pre-morbid Intelligence Quotient (IQ) and is stable in dementia. Old people with the greatest discrepancy between observed cognitive function and that expected when age and NART-predicted IQ are taken into account will lie towards the disease end of the age-dementia continuum, and may merit further investigation (Starr et al, 1992). This enables quantification of what doctors have known for a long time that, at the same level of current mental ability, they should be more concerned about a patient who was once a professor than one who had been a labourer.

Dementia is not a discrete diagnosis but a sympom complex with over 100 different causes (McGonigal et al, 1992). In addition to differenting symptoms of dementia from those of normal cognitive ageing, another difficulty arises in the diagnosis of the specific pathology. In many instances this can be straightforward (for example, dementia pugilistica and dialysis dementia), but the differentiation between Alzheimer's disease, the commonest cause of dementia, and normal cognitive ageing is much more difficult.

Alzheimer's disease and 'normal' cognitive ageing.

Increased age is an unequivocal risk factor in Alzheimer's disease and it may affect upwards of 50% of people in their ninth decade (Jorm et al, 1987). In one sense, then, it is 'normal'for the very old to have Alzheimer's disease, which could be viewed as a model of accelerated ageing. This simplistic model of Alzheimer's disease is unacceptable without further clarification as indicated by an example from tropical medicine. Onchocerciasis is a filarial infection which is responsible for up to 35% of middle aged and elderly people being blind in regions of Africa. There is a considerable delay between the initial infection and blindness. Visual impairment is also a principal feature of old age, but no-one would consider onchocerciasis a model of accelerated ageing because there is a definitive

aetiological agent, associated eye pathology is distinct from that seen in the elderly, and other body organs are unaffected.

Just as the clinical paradigm is a continuum between disease and age, so too are the neuropathological findings (Table E). There is no pathognomonic feature of Alzheimer's disease that cannot be found in the brains of 'normal' non-demented old people. The difference between physiological cognitive ageing and Alzheimer's disease is based on symptoms of dementia and the degree of organic change, not uncommonly decided with the benefit of hindsight!

Table E. Features of "normal" ageing and Alzheimer's disease.

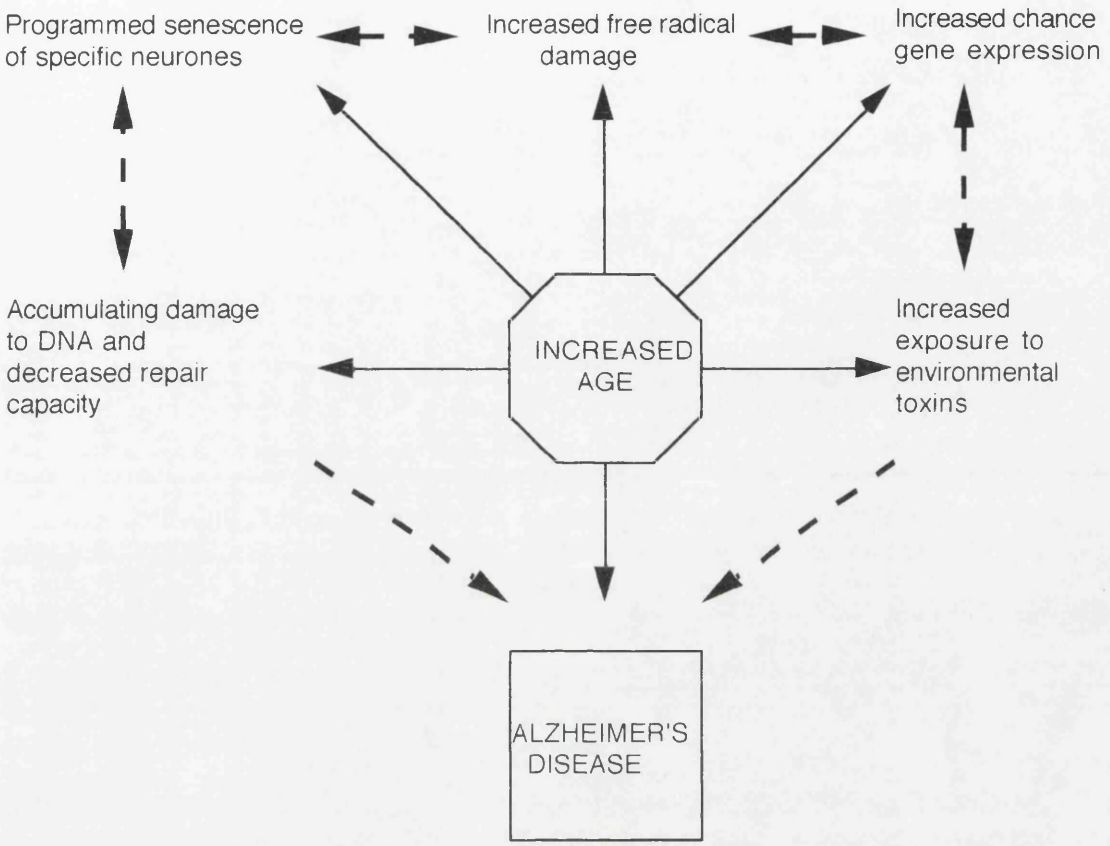
FEATURE	AGEING	ALZHEIMER'S
CLINICAL		
Cognitive Impairment	? / +	+++
NEUROHISTOLOGICAL		
Neuritic Plaques	+ / ++	+++
Neurofibrillary Tangles	+ / -	+++
Cortical Neuronal Loss	+	+++
NEUROCHEMICAL		
Cortical Choline Acetyltransferase decrease	+	+++
Somatostatin reduction	+	++
RADIOLOGICAL		
Cerebral atrophy	+ / ++	++ / +++

Unsurprisingly, biological and clinical markers for Alzheimer's disease have remained elusive, since they would need to exhibit a strong association to be detectable. One promising area is that of neuroimaging, where functional data collected by single photon emision or positron emission tomography can be combined with the structural data from the more standard techniques of computerised tomography and magnetic resonance imaging. Yet even if their promise is fulfilled, such investigations are unlikely to be available to most elderly people with unexplained memory loss.

Interaction between age and Alzheimer's disease

A clear distinction between cognitive impairment associated with 'normal' ageing and that secondary to Alzheimer's disease cannot be easily made on clinical or pathological grounds. The relationship between disease (Alzheimer's disease) and non-disease (normal ageing) can be considered in five interactions proposed by Ottman, synthesised in the figure A (Ottman, 1990).

Figure A. Interactions between Ageing and Alzheimer's disease.



(1) Genotype does not cause a disease directly but acts by increasing the level of expression of a risk factor. If the risk factor for Alzheimer's disease is age, individual genotype may modify its expression.

(2) Risk factor has a direct effect on the disease (and may cause it directly), but genotype influence this effect (though genotype has no effect on its own). Alzheimer's disease could be an inevitable consequence of ageing; its effects being modified by individual genotype so that some patients develope the disease early, while in others the potential expression of the disease is limited by human life-span.

(3) Genotype has a direct effect on the disease (and may cause it directly) but risk factors influence this effect (though the risk factor has no effect on its own). Alzheimer's disease may be caused entirely by genetic factors, their expression being influenced by age and other environmental influences.

(4) Both genotype and risk factor can influence the disease by themselves, but the risk increases when both are present. The combination of genetic susceptibility and age may interact either additively or multiplicatory to increase the risk of Alzheimer's disease.

(5) Genotype and risk factor can influence disease risk independently. Genetic linkage linkage studies have proven that a minority of patients with Alzheimer's disease have a direct genetic cause, whether age can cause Alzheimer's disease independently remains open to debate (the ageing hypothesis of Alzheimer's disease).

The aetiological case for a dichotomy between Alzheimer's disease and ageing depends on genetic studies. Down's syndrome has proved a useful model. Trisomy of chromosome 21 is associated with an Alzheimer's type dementia which is neurohistologically indistinguishable from senile Alzheimer's disease (Musters et al, 1985). Other features of premature ageing found in Down's syndrome are a greater incidence of age-related neoplasia, premature hair greying and loss, amyloid and lipofuscin pigment deposition, diabetes mellitus, hypogonadism, degenerative vascular disease and cataracts. This model favours Ottman's paradigm (1) with increased free radical damage and impaired DNA repair as the probable molecular biological mechanisms responsible (Boerrigier ME et al, 1991). On the other hand,

mutations detected in pedigree studies suggest underlying abnormalities of amyloid processing consistent with paradigm (5)(Murrell et al, 1991). The other interactions fall between these two extremes.

Summary

The overlap between normal cognitive ageing and Alzheimer's disease is great and presents a diagnostic dilemma to physicians. Reaching a diagnosis has practical importance in councilling patients and relatives and, on a wider stage, planning health service requirements. Although cognitive impairment is present in both 'normal' ageing and Alzheimer's disease, the rate of progression is typically greater in the disease state. Diagnosis is further hampered by negative stereotypes of memory loss and remains predominantly one of clinical judgement. The danger of diagnosis in such a difficult situation is that it may deceive doctors into the belief that they know more than they do. Labelling a patient as demented without further quantification as to specific disease and to the degree of cognitive impairment is relatively uninformative about prognosis

The boundaries between normal cognitive decline, dementia and Alzheimer's disease remain blurred. The interaction between age and Alzheimer's disease is complex and not understood. Clinicians have a vital role to play in defining these boundaries. Accurate diagnosis of the specific causes of dementia, based on sound clinical practice *and* re-evaluation of patients over time, will improve the quality of data available on such patients. The epidemiology of the causes of dementia and of ageing could then be described, aetiological associations discovered, public health programmes instituited and councelling services improved.

ALUMINIUM AND ALZHEIMER'S DISEASE

Aluminium is the third commonest element on the earth's surface and the commonest metallic substance. Exposure to environmental aluminium may be associated with the development of Alzheimer's disease (Martyn et al, 1989, Michel et al, 1990). In this review the basic chemistry, human physiology and evidence that links aluminium to Alzheimer's disease is examined.

Environmental Aluminium Exposure

Aluminium sulphate, the common naturally occuring form of aluminium, has a simple ionic structure at acidic pH, but at neutral pH it becomes highly complexed and water insoluble. A European Community overview found the concentration of naturally occuring aluminium in groundwater at neutral pH to be very low (<0.05mg/l), but accepted that it may be higher in areas subject to acid rain (Simpson et al, 1988). Most aluminium is removed from the public water supply in the purification process, however geographical variation in the concentration of aluminium in the water supply exists (Martyn et al, 1989). Man is also exposed to aluminium in the household. It is commonly found in cookware, in food additives and in a number of non-prescription drugs (Lione 1985, Tennakone and Wickramanayake, 1987).

Human Physiology

Most absorption of aluminium occurs in the gut (Alfrey, 1980) but small amounts are absorbed along olfactory pathways (Rifat et al, 1991, Perl and Good, 1987). An estimated average daily intake of aluminium is 20mg orally (range 1-100) and 3-15ug via inhalation. The plasma level of aluminium is between 1.5-

15ug/l and total body aluminium is estimated at 30-45mg/l (Jones and Bennet, 1985, Perl and Good, 1987). This contrasts with its natural abundance and reflects the insolubility of naturally occuring aluminium, the gastro-intestinal barrier to absorption and the efficiency of renal excretion (Ganrot, 1986).

Aluminium follows the iron transport pathway in the extracellular environment and is bound to transferrin and lactoferrin (Trapp, 1983). This aluminium-transferrin complex is stable enough to suppress any interaction of aluminium with all other ligands in plasma (Martin, 1986). Much is unknown about the intracellular actions of aluminium. It may coexist with iron in the cytosolic labile iron pool (May and Williams, 1980) and affect a number of molecular biological responses. For example, aluminium may inhibit the incorporation of inositol into phospholipids at the cellular level (Johnson and Jope, 1986).

Neurotoxicity of aluminium.

In 1962 a single case report linked pulmonary fibrosis and encephalopathy to the inhalation of aluminium dust (McLaughlin et al, 1962). However, no further case reports linking aluminium dust inhalation and encephalopathy have been described. Animal studies provided some evidence for the neurotoxic effects of aluminium but definitive proof occured with the discovery that the encephalopathy experienced by renal patients on dialysis was caused by a high concentration of aluminium in the dialysate (Wills and Savoy, 1983, McClure and Smith, 1984, O'Hara and Marnaghan, 1982). Furthermore, this encephalopathy responded to aluminium chelation therapy with desferrioxamine and so was, in part, treatable (Sprague et al, 1986). The encephalopathy is, however, clinically and neuropathologically distinct from Alzheimer's disease (Walton, 1991).

Aluminium and Alzheimer's disease

(a) Animal evidence - a historical perspective

Animal studies provided the first indication that there could be an association between aluminium and Alzheimer's disease. In 1965 the injection of aluminium chloride into the central nervous system of rabbits lead to the development of neurofibrillary tangles, a neuropathological feature of Alzheimer's disease (Klazo et al, 1965, Terry and Pena, 1965). It was hoped that this discovery could result in a reliable animal model to facilitate research into Alzheimer's disease, however the tangles were histologically distinct to those found in human disease (Terry and Pena, 1965, Troncoso et al,1986). In addition, there is wide interspecies susceptibility to the neurotoxic effects of aluminium which makes the validity of any animal model doubtful (Wisniewski et al, 1980).

Animal studies have described some in vivo actions of aluminium that may be important in man and in Alzheimer's disease. For example, aluminium increases the permeability of the blood-brain barrier (Banks and Kastin, 1983) and alters cyclic AMP and cyclic GMP levels in the rat (Johnston and Jope, 1987). Despite the problems with the validity of animal studies in relation to man they could facilitate a greater understanding of the molecular biological actions of aluminium in normal and disease states.

(b) Human evidence

Aluminium is present in the central nervous system of man at a concentration of approximately two parts per million (Crapper McLachlan, 1986). Several studies have suggested that the concentration of aluminium in the brains of patients with Alzheimer's disease is increased compared to controls (Crapper et al, 1973 and1980, Edwardson and Candy, 1989). Other studies have not found this association and the evidence remains inconclusive (Markesburg et al, 1981, Trapp et

al, 1978). Aluminosilicates are present in the senile plaque core, a neuropathological feature of Alzheimer's disease (Candy et al, 1986) and in neurofibrillary tangle bearing neurones (Perl and Brody, 1980). However, whether this accumulation is caused or effected by Alzheimer's disease is unknown.

Epidemiology has provided some evidence that aluminium may be associated with Alzheimer's disease. On a general level there is evidence that the encephalopathy experienced by residents of Guam is caused by an environmental toxin and is not due to mutational events in the genetic pool (Garruto et al, 1985, Reed and Brody, 1975). The water on Guam contains a high concentration of aluminium (and a low concentration of calcium and magnesium) and there is evidence of aluminium accumulation in the neurones of patients with this encephalopathy (Perl et al, 1982). This illness provides an epidemiological model of a chronic dementing disease which may be caused by environmental toxins of which aluminium is clearly implicated.

In Alzheimer's disease there is inconclusive evidence that a raised concentration of aluminium in the public water supply may be associated with Alzheimer's disease (Martyn et al, 1988, Flatten, 1986, Michel et al, 1990, Neri and Hewitt, 1991). Primarily problems with study design, population migration and disease diagnosis have resulted in caution in the interpretation of these studies but they all support a possible association between environmental aluminium exposure and the development of Alzheimer's disease. Definite causation or even association has not been established and one study has failed to find any association (Wettstein et al, 1991).

A therapeutic study has assessed the response of patients with Alzheimer's disease to treatment with desferioxamine (CrapperMcLachlan et al, 1991). The study was a two year single blind study and there was some evidence that treatment slowed the rate of decline in daily living skills in patients with Alzheimer's disease.

Desferioxamine chelates aluminium along with a large number of other metals and reduces iron-mediated free radical formation. Further evaluation is required before its mode of action in Alzheimer's disease is quantified and understood.

Summary

Aluminium is a common naturally occuring element and exposure to it in the environment is almost inevitable. Ironically this means that epidemiological proof of a direct causal association between aluminium and Alzheimer's disease will be difficult to prove. Aluminium is mainly absorbed via the gut and is present in the central nervous system in small concentrations in normal people. The encephalopathy associated with renal dialysis showed that aluminium is neurotoxic to humans, however its role in the aetiology of Alzheimer's disease remains speculative and controversial. The distinction between aetiology and pathogenesis remains unproven though animal, epidemiological, neuropathological and therapeutic studies suggest an association may exist.

OTHER RISK FACTORS AND ALZHEIMER'S DISEASE

Previous chapters have discussed estabished risk factors for Alzheimer's disease and one factor which remains controversial, the role of aluminium in the disease. A variety of other risk factors have been implicated in the aetiology of Alzheimer's disease. The suggested association between head trauma and the disease has been most extensively investigated and is considered in some detail. Other associations are listed but none have been definitively proven and remain speculative.

Head Trauma and Alzheimer's disease.

The development of dementia after recurrent head trauma, for example in boxing, is well established - dementia pugilistica or 'the punch-drunk syndrome' (Corsellis, 1978, Wisniewski et al, 1976). Neurofibrillary tangles, indistinguishable from those that are hallmarks of Alzheimer's disease, occur in abundance in the cortex of such patients (Corsellis, 1978, Roberts, 1988). More recently, neuronal plaques have also been described (Roberts et al, 1990). This has led to the hypothesis that dementia pugilistica and Alzheimer's disease may share a common pathogenesis.

Several case-control studies have found a significantly increased frequency of head trauma in patients with Alzheimer's disease compared to age-sex matched controls (Heyman et al, 1984, Mortimer et al, 1985). Others have found an excess of head trauma in patients which did not reach statistical significance (Shalat et al, 1986, Amaducci et al, 1986) or have found no association (Chandra et al, 1987, Bharucha et al, 1983). A small study has even demonstrated a reverse association

with a history of head trauma more common in controls compared to patients with Alzheimer's disease (Soininen and Heinonen, 1982).

All case-control studies performed to test the hypothesis that an association exists between a history of head trauma and the development of Alzheimer's disease have been too small to test the hypothesis adequately. Meta-analysis is a method that can increase statistical power. Seven pair-matched case-control studies have been pooled and re-analysed (Mortimer et al, 1991). The findings support a significant association between head trauma with loss of consciousness and Alzheimer's disease with an increased odds ratio of 1.82. However, caution is required in the interpretation of these results because there a number of possible sources of bias.

Selection bias is always a major concern in case-control studies. Data collection in the case-control studies combined for the meta-analysis was not standardised; different criteria were used to define Alzheimer's disease, head traumatized and community controls. Although the meta-analysis pooled studies with community controls only, case-control studies that used controls sampled from hospital populations reported higher odds ratios (Mortimer et al, 1985, Amaducci et al, 1986). Information or recall bias is another source of error. Patients and / or informants are more likely to remember a head injury if they are suffering from a neurological disease. The meta-analysis was restricted to case-control studies in which severe head trauma with loss of consciousness was used to define injury in the belief that this would be less subject to recall bias. Finally, it is possible that confounding factors may result in systematic error. For example, there is a suggestion that head injury may hasten the onset of Alzheimer's disease (Gedye et al, 1989). People who would have developed dementia in old age or in whom their finite human-life span would have prevented expression of the disease may develop

symptoms earlier because of head trauma. This could result in a spurious association being found between the illness and head trauma.

In summary, there is increasing evidence that severe head trauma and Alzheimer's disease are associated, but the association remains unproven. There is a need for a large sample prospective epidemiological survey set up specifically to address the issue.

Some other suggested associations

A plethora of other conditions have been linked to Alzheimer's disease with inconclusive results (Table F). Studies have been to small to adequately test the reported associations and biases further limit their conclusions. For example, a history of heavy alcohol consumption excludes a diagnosis of clinical Alzheimer's disease in many studies because it is a cause of cognitive impairment in its own right. Alcohol consumption is positively associated with head trauma, which could further confound results. Furthermore, many studies were not designed to assess one specific risk factor and the effects of data 'dredging' may be significant. Again, well designed prospective studies are needed to test each proposed association.

Table F. Selected conditions that have been linked to Alzheimer's disease.

PROPOSED ASSOCIATION	SIGNIFICANT ASSOCIATION	NO SIGNIFICANT ASSOCIATION
Hypothyroidism	Heyman et al, 1984	Lopez et al, 1989
Atopy	None	Amaducci et al, 1986
Alcohol	None	Graves et al, 1991
Smoking (protective)	Hofman et al, 1990	Barclay et al, 1989
Smoking (increase risk)	Shalat et al, 1987	

Section 2: The epidemiology of Alzheimer's presenile dementia in Scotland 1974-88

AIMS, DESIGN AND HYPOTHESIS

Aims

The following questions will be answered:-

(a) Can current clinical criteria used to diagnose Alzheimer's disease be improved and modified for specific use in epidemiological research?

(b) What is the incidence rate of presenile Alzheimer's disease in Scotland?

(c) Is gender a risk factor in presenile Alzheimer's disease?

(d) What is the natural history of presenile Alzheimer's disease?

Design

The literature review provides an introduction to this thesis. Alzheimer's disease is the commonest type of primary degenerative dementia and although presenile disease is much rarer it represents an important form of the illness. The study sample will be derived from retrospective scrutiny of hospital and public records identified from central and local data collection systems. The reference population is the Scottish population. This observational 'historical' design has a number of advantages:-

(1) A large number of people with presenile dementia can be ascertained within the financial constraints of the study.

(2) National Scottish data can be described.

(3) Sufficient people with presenile Alzheimer's disease who underwent neuropathological examination will be described and clinical diagnostic criteria used to define the illness can be critically evaluated.

Scotland is uniquely placed for this type of epidemiological research. There are well organised health services with, relative to the population size, reasonable neuropathological and neurological investigative facilities. The Information and Stastics Division (ISD) of the Scottish Home and Health Department maintains a computerised record of all admissions, discharges and deaths from all general and psychiatric hospitals. Within the constraints of normal ethical procedure, this information is readily available. In addition, a number of hospitals, neuropathology and neurology departments maintain independent local diagnostic registries of patients with presenile dementia.

The aims of this study can be achieved if a valid and reliable population of people with presenile Alzheimer's disease can be described. The study sample will comprise patients who were admitted, discharged or had died in psychiatric hospitals within Scotland between 1974 and 1988 and who were identified through ISD. The validity of this sampling method will be tested by reference to other independent data sources.

Two major assumptions have been made in this sampling frame. Firstly, that the identity of all patients with presenile Alzheimer's disease who have been admitted to psychiatric hospitals can be reliably obtained from ISD. This assumption will be tested in the pilot study. Secondly, that the majority of people with presenile Alzheimer's disease are admitted to psychiatric institutions at some stage in their illness. This will be tested by reference to general hospital data, death certificate data obtained from the Registrar General of Scotland and selected neurology diagnostic registries.

Important methodological concerns about the study design will be discussed: -

(i) Admission policies for patients with presenile Alzheimer's disease may vary between psychiatric hospitals.

(ii) Hospital record quality may show temporal and geographical variation across Scotland.

(iii) The availability of psychiatric health care may be different between geographical regions in Scotland.

(iv) The effects of population migration between small geographical areas in Scotland may be significant and limit the usefulness of reporting local incidence rates of Alzheimer's disease.

These considerations could have profound effects on completeness of patient ascertainment and be a source of systematic bias. Adequacy of case ascertainment will be discussed in detail in the discussion section of the thesis.

Hypothesis

The hypothesis that "Female gender is an independant risk factor for presenile Alzheimer's disease" will be examined in detail.

Female gender has become an established risk factor for senile Alzheimer's disease. However, the relationship between female gender and the risk of presenile disease is controversial. If the influence female gender has on the risk of Alzheimer's disease is age dependent then this will be of aetiological importance. It would suggest that either presenile and senile Alzheimer's disease are differentiative pathological processes or that changing female physiology with age alters disease risk.

PILOT STUDY

Summary

The Information and Statistics Division (ISD) of the Scottish Home and Health Department maintains a computerised record of patients who have been admitted to, discharged from or have died in Scottish psychiatric hospitals. This chapter assesses the quality of these data in relation to patients with verified presenile dementia who have been discharged from the Royal Edinburgh Hospital between 1974 and 1988. The accuracy and completeness of ISD data is evaluated by comparison with data available from the hospital's independent diagnostic register and information obtained after hospital record scrutiny.

17% of presenile patients were not identified and 23% of patients were wrongly classified on ISD data. More than 93% of patients with presenile Alzheimer's disease were identified, though often under a variety of other diagnostic codes. 1% of hospital records contained insufficient information to validate the diagnosis of presenile dementia.

The feasibility of using ISD data to define an unbiased national sample of people who have suffered from presenile Alzheimer's disease is discussed. Caution is needed in such an approach and other independent data sets would need to be explored to validate the population sample.

Background

The main body of work will rely on the identification of all patients with an onset of symptoms of Alzheimer's disease under age 65 years who were admitted to a psychiatric hospital in Scotland between 1974 to 1988. In theory, clinical and

demographic information is available for all patients admitted to psychiatric hospitals. A SMR-4 form is completed for each patient on admission , discharge or death from hospital and details sociodemographic information and diagnostic codes selected from the International Classification of Disease (ICD - 9, 1977). The data contained are checked for clerical errors at the hospitals and at the Information and Statistics Division (ISD) of the Scottish Home and Health Department before being stored on computer. However, the usefulness of the data is dependent upon its quality.

Dementia is a symptom complex and not a discrete diagnosis. A patient with dementia should receive two ICD diagnostic codes: a general code classifying dementia and a specific code to describe the presumed cause. Those who develop symptoms of dementia under the age 65 years are coded as presenile dementia, older patients as senile dementia. The accuracy of the diagnostic code documented on the SMR-4 form can be evaluated in patients with Alzheimer's disease by reference to standard clinical criteria.

Aims and Objectives

The pilot study has the following aims:-

(1) To define the nature of the data request to ISD to identify patients with presenile Alzheimer's disease who have been admitted to psychiatric hospitals in Scotland.

(2) To critically evaluate the accuracy and completeness of data available from ISD.

(3) To assess the feasibility of applying diagnostic criteria for Alzheimer's disease to psychiatric hospital records.

Method

The Royal Edinburgh Hospital is the largest psychiatric hospital in Scotland and medical record staff maintain an independent register of patients who have been admitted to, discharged from or have died in the hospital. The register was used to provide a list of patients aged less than 73 years who had in-patient treatment between 1974 and 1988 and who were given ICD diagnostic codes for Alzheimer's disease (331.0), presenile dementia (290.1), senile dementia (290.0), arteriosclerotic dementia (290.4), senile dementia with acute confusional state (290.3), senile dementia with paranoia or depression (290.2), dementia other (290.8) or dementia, unspecified (290.9). These codes were chosen to identify all patients *with dementia* who were admitted to the hospital.

The hospital records of these patients were located and scrutinised by a single observer (G.M). Age at disease onset under age 65 years was used to categorise patients as suffering from either presenile or senile dementia. Information was extracted from each hospital record and patients who fulfilled the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable Alzheimer's disease received this diagnosis.

The NINCDS-ADRDA criteria are not unambiguously defined in usable form. The interpretation of the criteria used are outlined (Table 1). They were strictly applied and any evidence of co-existent systemic or neurological disease excluded probable Alzheimer's disease.

An identical information request to that detailed was sent to ISD. A comparison was made between the diagnostic categories detailed on the Royal Edinburgh Hospital list, the ISD list and those derived after hospital record scrutiny.

(1) The diagnostic codes detailed on the ISD data of patients who fulfilled NINCDS-ADRDA criteria for probable Alzheimer's disease after hospital record

review were examined. This provided an indirect estimate of diagnostic coding errors in the ISD data.

(2) The Royal Edinburgh data list was compared to that from ISD. The two data lists should have contained identical information: any unexplained deficiencies in the ISD data would indicate incompleteness.

(3) The number of hospital records in which there was insufficient documented clinical information to apply the diagnostic criteria were ascertained.

Approval to scrutinise hospital records was obtained from the Privacy Committee at ISD and from the Ethical Committee of Lothian Health Board.

Results

The independent hospital register identified 588 hospital records within the limits of the data request. All the records were located and scrutinised. 196 of these hospital records documented patients with presenile dementia: the rest detailed patients with an onset of dementia after age 65 years.

(1) Accuracy of diagnosis.

The diagnostic codes detailed on the ISD data list for these 196 patients are detailed in Table 2. Forty-five patients (23%) were wrongly classified under diagnostic codes for senile dementia (290.0, 290.2 or 290.3).

Ninety-one of the 196 patients met NINCDS-ADRDA criteria for probable Alzheimer's disease. Such patients should receive two diagnostic codes, 290.1 to indicate presenile dementia and 331.0, the specific code for Alzheimer's disease. Their actual diagnostic codes on the ISD data are shown in Table 3. Fifty-seven patients with Alzheimer's disease (64.6%) were coded correctly.

(2) Completeness of ISD data

Thirty-four patients (17.3%) who had presenile dementia after hospital record scrutiny were absent from the ISD data list. Six of these had validated presenile Alzheimer's disease.

(3) Poor quality records

All hospital records were located. Two records (1.0%) contained insufficient information to validate the diagnosis of presenile dementia.

Discussion

The first aim of this pilot study was to define the nature of the data request to ISD. This aim cannot be divorced from the second to assess the accuracy and completeness of data available from ISD.

The study showed that data available from ISD was not accurate. Forty-five patients (23%) with verified presenile dementia on hospital record review were wrongly coded as having senile dementia. Thirty-four patients (37%) with presenile Alzheimer's disease were incorrectly coded on the ISD data list. The ISD data was not complete with 34 patients (17%) with presenile dementia and 6 patients (7%) with presenile Alzheimer's disease not listed.

Coding inaccuracies in general hospital in-patient data between 17% and 20% have been reported for the diagnostic accuracy of ulcerative colitis, Crohns disease and myocardial infarction at ISD (Murchiston et al, 1991, Patel et al, 1976). The 7% omission error and 23% diagnostic error found are consistent with these findings.

Inaccuracy of diagnosis is outwith the control of ISD and occurs in hospital. There were three main reasons for a patient with presenile dementia receiving a wrong diagnostic code in the study. Firstly, a patient who presented after age 65 years but clearly had symptoms of dementia prior to that age was commonly

diagnosed as senile dementia. Secondly, the diagnosis of senile dementia, if mentioned, seemed to "stick" to patients. Some patients with presenile dementia admitted to hospital for investigation had senile dementia mentioned and that diagnosis then became preferentially accepted. This probably reflects a greater general medical and public awareness of senile dementia. Finally, patients with presenile dementia admitted to hospital who had no ICD diagnosis clearly and unambiguously stated in their hospital record were frequently coded as senile dementia.

The diagnostic codes requested for the pilot study were decided upon after consultation with experienced psychiatrists, hospital records staff and staff at ISD. It is possible that patients with Alzheimer's disease may have received other erroneous codes other than those requested. However, it was not possible to scrutinise the hospital records of all patients admitted to the Royal Edinburgh Hospital between 1974 and 1988 for logistical reasons.

All patients with Alzheimer's disease were coded as either senile dementia, presenile dementia or arteriosclerotic dementia (Table 2). The other diagnostic codes failed to identify any patients with Alzheimer's disease (Table 1). Therefore, it is unlikely that requesting diagnostic codes outwith those selected would significantly improve case ascertainment.

The accuracy of diagnosis of Alzheimer's disease may vary within psychiatric hospitals in Scotland. The Royal Edinburgh Hospital is a teaching hospital and several academic staff have a particular interest in dementia. It is likely that standards in the diagnosis of presenile dementia in this hospital are at least equivalent to, and probably better than, other psychiatric hospitals in Scotland. All the diagnostic codes requested in the pilot study would be retained in the main data request to ISD to compensate for diagnostic inaccuracies in other psychiatric hospitals.

A further consideration was to define the upper age limit to the data request. A proportion of people who first have symptoms of dementia before age 65 years will not present to hospital until after that age. Clerical officers at ISD estimated that a list of approximately 6,000 hospital records would be generated in Scotland by an upper age limit of 73 years. Within the constraints of time and money, this would be the maximum number of hospital records that could be scrutinised.

Most people with Alzheimer's disease die within 8 years of symptom onset and present to medical attention several years before this event. The incidence of the illness rises exponentially with age. Any increase in the age limit would result in a dramatic rise in the number of hospital records that need scrutiny, the majority of which would represent people with senile and not presenile disease. Based on these considerations an upper age limit of 73 years was set on the data request to ISD.

The final aim of the pilot study, to assess the feasibility of applying diagnostic criteria for probable Alzheimer's disease from information obtained retrospectively from hospital record scrutiny, is self-evident from the previous discussion. Only two hospital records that detailed patients who suffered from presenile dementia contained insufficient clinical information to validate the diagnosis. Quality of hospital record recording may vary from hospital to hospital, however an unforeseen advantage in reviewing historical records was that, at some stage in their prolonged illness, the majority of patients with presenile dementia had a detailed history documented and physical examination performed. Reviewing the entire natural history of the illness in a large number of patients with presenile dementia optimised the ability to apply the diagnostic criteria comprehensively.

This study has highlighted limitations of data available from ISD. If appropriate diagnostic codes are requested over 90% of patients with Alzheimer's disease can be successfully identified. This study suggests that the same data request to that used would successfully identify the great majority of patients who

were admitted to psychiatric hospitals in Scotland between 1974 and 1988. The study *does not* validate the data from ISD on a national level.. Further evidence from alternative independent data sources would be required to validate the completeness of the final study sample. However, the pilot study does support the feasibility of defining a sample of people with presenile dementia from ISD.

METHOD

Population sample

The study data are obtained from retrospective hospital record scrutiny. A list of patients aged less than 73 years who were given ICD diagnostic codes for Alzheimer's disease (331.0), presenile dementia (290.1), senile dementia (290.0), arteriosclerotic dementia (290.4), senile dementia with acute confusional state (290.3), senile dementia with paranoia or depression (290.2), dementia other (290.8) or dementia, unspecified (290.9) was received from ISD for all psychiatric hospitals in Scotland for the period between 1974 to 1988 inclusive (Pilot Study). The psychiatric hospitals included Argyll and Bute, Dykebar, Ravenscraig, Ailsa, Dingleton, Crichton Royal, Stratheden, Bellsdyke, Royal Cornhill, Bilbohall, Kingseat, House of Daviot, Gartloch, Gartnavel Royal, Leverndale, Woodilee, Southern General Hospital (psychiatric unit), Craig Dunain, Hartwood, Bangour, Herdmanflat, Rosslynlee, Royal Edinburgh, Murray Royal, Royal Liff and Sunnyside Royal.

Medical Records Staff within each hospital attempted to locate the hospital records of patients listed. All available records were scrutinised by one of two experienced observers, G McGonigal (GM) and C McQuade (CM). A third observer, L.J.Whalley (LJW), blindly examined a randomly chosen sample of 100 records

Prior to the start of data entry GM and LJW agreed diagnostic information that would be extracted from the hospital records. A patient was accepted if there was a documented history of dementia with symptom onset between ages 40 and 64 years inclusive. The lower age limit was set by the NINCDS-ADRDA clinical criteria for probable Alzheimer's disease, the upper age limit by the arbitrary

division between presenile and senile disease . The NINCDS-ADRDA criteria (Table 1) and a Hachinski score (Table 4) were applied to each patient from information documented in their hospital records. All three observers met weekly throughout the coarse of the study to standardise interpretation of these criteria.

Patients were classified into three diagnostic groups: (a) 'Probable' Alzheimer's disease if they fulfilled the NINCDS-ADRDA criteria for this diagnosis and had a Hachinski score less than 5; (b) 'Broad' Alzheimer's disease defined after reclassification of all presenile patients using discriminant analysis, this group included all those diagnosed as 'probable' Alzheimer's disease (see below); and (c) Multi-infarct dementia if a patient had a definite history of at least one cerebrovascular accident and a Hachinski score greater than 6.

Completeness of Ascertainment

The study sample would be seriously biased if the assumption that 'the majority of patients with presenile Alzheimer's disease have been admitted to psychiatric hospital at some stage in their illness' was false. This could result in underascertainment of people with Alzheimer's disease and impair the validity of any conclusions. Adequacy of ascertainment was assessed by reference to several independent data sources:

(1) In Scotland, death certificates record primary, secondary and tertiary causes of death and place of death. This information is stored on computer and available from the Registrar General of Scotland. A list of all people aged between 40 and 64 years inclusive who had died in Scotland after 1974 with any mention of Alzheimer's disease or presenile dementia documented on their death certificates was provided. GM scrutinised all available hospital records of people who died in institutionalised care outwith psychiatric hospitals to ascertain whether a significant proportion were unknown to the psychiatric service. Because patients known to the

psychiatric service would be less likely to die in other forms of institutionalised care, this sample should overestimate the proportion of patients who were unknown to the psychiatric service.

(2) People with Alzheimer's disease are frequently investigated by neurologists. A proportion of these patients may never be cared for by psychiatrists. To estimate whether this was a significant source of underascertainment, two neurology departments in Scotland in which a registry of out-patients is maintained were visited (Western General Hospital, Edinburgh and Ninewells Hospital, Dundee). Hospital records of all patients aged less than 73 years for whom a diagnosis of dementia was recorded were scrutinised by GM.

(3) All Chief Administrative Medical Officers in Scotland were contacted and their advice sought concerning the nursing management of patients with presenile dementia. This matter was discussed in local family doctor committees throughout Scotland. Similar advice was requested from medical advisers to the Mental Welfare Commission for Scotland

(4) In Grampian, all in-patient and out-patient psychiatric patient events have been notified to the Grampian Psychiatric Case Register since 1963. This register was used to assess whether any patient with presenile Alzheimer's disease was investigated by a psychiatrist as an out-patient but was never admitted to hospital.

Statistical methods

(a) Can current clinical criteria used to diagnose Alzheimer's disease be improved and modified for specific use in epidemiological research?

All patients with presenile dementia who had undergone neuropathological examination were identified within the study population. Each patient record was assigned a clinical diagnosis of either 'probable' Alzheimer's disease, and classified as group 1, or 'other dementia type' and classified as group 2 (this group included

patients with multi-infarct dementia) on the basis of the NINCDS-ADRDA criteria alone and, also, by the combination of the NINCDS-ADRDA criteria with the Hachinski score before the results of neuropathological examination were known.

Neuropathological diagnosis was obtained from the discrete neuropathological record of each patient. A diagnosis of Alzheimer's disease was accepted if there was documented proof of senile plaques and neurofibrillary tangles present in the hippocampus (Ball, 1977, Ball et al, 1985) in the absence of any evidence of an ischaemic vascular lesion (Molsa et al, 1985). These criteria were applied to the detailed neuropathological records by GM, who was blind to the clinical diagnosis at the time of scrutiny. This neuropathological diagnosis was the 'gold-standard' to which diagnoses based on clinical criteria applied directly and after discriminant analyses were compared. The clinical criteria were the selected variables for discriminant analyses (Table 5).

Discriminant analyses derives a linear composite, the discriminant function, which maximally discriminates between groups. A discriminant score which maximises the F ratio of the between-group and within-group mean squares was provided for each patient. The discriminant function was derived by the direct method which simultaneously enters all variables that pass tolerance criteria (set at 0.001). The discrimination achieved by this analyses (Analyses A) was compared with the results of two further discriminant analyses, one with 11 randomly selected patients from group 1 removed (Analyses B), the other with 18 randomly selected patients from group 1 and 13 randomly selected patients from group 2 removed (Analyses C). These further analyses provided a test of 'spuriousness' of the results of the first analyses (Whalley et al.,1989).

Specificity, sensitivity and diagnostic accuracy of the clinical criteria before and after discriminant analyses were calculated (Fig 1).

Interobserver reliability in the application of the clinical criteria was assessed using Cohen's kappa statistic. This is a statistic that is relatively unaffected by the prevalence of disease. The two main observers, GM and CM, were compared to the third, LJW, who acted as a standard. No direct comparison was made between GM and CM. No neuropathological 'gold-standard' was involved in this analysis.

(b) What is the incidence rate of presenile Alzheimer's disease in Scotland? and

c) Is gender a risk factor in presenile Alzheimer's disease?

The incident date was that of first presentation to hospital services, either as an in-patient, out-patient or domiciliary consultation. Denominators for incidence calculations were taken from the 1981 census and used to estimate the 'at risk' population aged 40 to 64 years. 95% Confidence Intervals were calculated with exact error factors for Poisson mean for numbers less than 30 and with the asymptotic error factor approximation for larger numbers. Mantel-Haenszel weights were used for the summary risk ratios.

(d) What is the natural history of presenile Alzheimer's disease?

Age at first presentation to specialist care was used to age the sample. Date and place of death was ascertained from death certificates available from the Registrar General for Scotland. Duration of survival was calculated from these two dates.

(i) Censured data.

Probability of survival in patients with 'probable' Alzheimer's disease was calculated for the total sample by the life-table method (follow-up through to 1 July 1992). Additional life-tables were calculated for males and females, for those who presented before and after 1981 and for those who presented before and after age 52

years. Survival curves in each of these paired groups were compared by the log rank test.

(ii) Actual data.

In those patients who had died in the follow-up period, actual survival duration was compared in males and females, those with Alzheimer's disease who presented before and after age 52 years and those who presented before and after 1981. This analysis was performed to examine the consistency of the life-table analysis. In addition, survival duration in those who died in psychiatric hospital was compared to those who died at home and in general hospitals. The distribution of survival time was positively skewed in all groups. Logarithmic transformation normalised the distribution and group geometric means were tested using unpaired t tests.

Ethics

Ethical Approval to scrutinise hospital records was obtained from Ethics Committees of all Health Boards in Scotland and from the Privacy Committee of the Scottish Home and Health Department.

RESULTS

ISD identified 6581 patients. 5874 hospital records were located and scrutinised (707 records were lost or inadquate) of which 1679 were records that documented patients with verified presenile dementia. Of these 1217 patients were aged 40 to 64 years at presentation to hospital services.

(a) Can current clinical criteria used to diagnose Alzheimer's disease be improved and modified for specific use in epidemiological research?

(i) Validity of clinical diagnosis before and after discriminant analysis vs neuropathological 'gold standard'.

Sixty-one patients (3.6%) with presenile dementia underwent neuropathological examination. Thirty-six patients had neuropathological confirmation of pure Alzheimer's disease (true group 1); 16 patients had no evidence of this disease at post-mortem and 9 patients had mixed pathology (true group 2). Criteria confirming the presence of cognitive impairment failed the tolerance test: all other criteria passed. Standardised canonical discriminant function coefficients are given for each of the three initial analyses (Table 5). The classification of patients comparing the clinical diagnosis to that derived from analysis A are shown (Table 6). Analysis B correctly classified 22 patients with pure Alzheimer's disease (88%) and analysis C 17 patients (94.4%).

The specificity, sensitivity and diagnostic accuracy of clinical and discriminant classifications are shown (Table 7). The discriminant classification was more accurate than clinical classification using solely NINCDS-ADRDA criteria and also by clinical classification by these criteria used with the Hachinski Score.

(ii) Reliability of clinical criteria used to diagnose Alzheimer's disease.

One hundred hospital records were scrutinised by LJW. Sixty of these records had previously been reviewed by GM. Kappa values of 0.72 and 0.61 were obtained when comparing GM and CM to LJW.

(b) What is the incidence rate of presenile Alzheimer's disease in Scotland?

and (c) Is gender a risk factor in presenile Alzheimer's disease?

Scrutiny of 1217 hospital records identified 569 broad cases of Alzheimer's disease (of which 317 were probable cases) and 267 cases of multi-infarct dementia. If each psychiatric hospital had the same proportion of missing or inadequate records (317 / 5784 = 5.4%) then about 38 cases of probable Alzheimer's disease (5.4% of 707) were omitted because of lost or inadequate records.

Tables 8 and 9 give the age-sex specific incidences and female to male risk ratios for probable and broad Alzheimer's disease. Increasing age and female gender were associated with an increased incidence of Alzheimer's disease. The summary sex risk ratios for probable and broad Alzheimer's disease were similar. Crude division of overall incidence by 15 (number of years studied) gave annual rates of 1.5 / 100 000 and 2.7 / 100 000 for probable and broad Alzheimer's disease respectively. These compare with the actual rates of 1.6 (95% C.I. 1.0 to 2.6) and 3.5 (2.6 to 4.7) per 100 000 for probable and broad Alzheimer's disease for the 1981 census year. Females had significantly less risk of multi-infarct dementia compared to males (Table 10).

(d) What is the natural history of presenile Alzheimer's disease?

Of the 317 people who fulfilled criteria for 'probable' Alzheimer's disease, 244 (77.0%) had died before the end of the follow-up period: 193 (79.1%) in

psychiatric hospitals, 31 (12.7%) in general hospitals, 16 (6.6%) at home and 4 (1.6%) in nursing homes.

(i) Censured survival data.

Overall five year survival was 51.2%, decreasing to 17.3% at ten years (Figure 2). Descriptive data on males and females are shown together with curves that describe and contrast survival (Table 11, Figure 3). Males had a significantly shorter duration of survival compared to females ($p < 0.025$). The ratio of death rates in males to those in females was 1.4 (Table 11).

No significant difference in survival duration was found in those who presented before and after age 52 years and in those who presented before and after 1981.

(ii) Actual survival data

The findings detailed were consistent in the group of patients who had died before the end of follow-up (Table 12). Females survived 1.3 times longer than males (C.I. 1.04 - 1.61; $p < 0.02$). Place of death, age at presentation and year of presentation did not significantly affect survival duration.

Completeness of Ascertainment

(1) Data from the Registrar General of Scotland identified 199 patients who had died in instituitions other than psychiatric hospitals and who were not ascertained in the study sample. These patients hospital records were requested, 89 (44.7%) were located. Nine of the records scrutinised documented patients with 'probable' Alzheimer's disease, 3 of whom had not been previously admitted the psychiatric hospital (the other 6 patients presented to psychiatric hospital prior to 1974).

(2) One hundred and twenty nine neurology outpatient records were reviewed. Twenty-four patients suffered from 'probable' Alzheimer's disease, 20

of whom were already known to the psychiatric service. The remaining 4 presented to neurology outpatients after 1983.

(3) Anecdotal assurance was received from all Chief Administrative Medical Officers and from medical advisers to the Mental Welfare Commission for Scotland that the vast majority of patients with presenile dementia were cared for in the psychiatric health services.

(4) The Grampian Psychiatric Case Register had no record of any patient with presenile dementia in North-East Scotland who may have had presenile Alzheimer's disease but was never admitted to psychiatric hospital.

TABLES AND FIGURES

Table 1. The interpretation of the NINCDS-ADRDA criteria for probable Alzheimer's disease used in the study.

CRITERIA	INTERPRETATION
History of progressive memory loss.	As a dominant initial feature
Confirmed loss of at least 2 areas of cognitive function	Documented from patient or hospital record
Insidious onset	Symptoms over a period of at least 3 months
Mentally alert	Alert at time of symptom onset and presentation.
No co-existent systemic disease	Absence of alcoholism, ischaemic vascular disease, diabetes etc
No co-existent brain disease	Absence of head injury, neoplasm, cerebro-vascular events etc
Investigations performed to exclude other causes of dementia	Thyroid function tests, normal MCV and syphilis serology.

Table 2. ICD diagnostic codes documented in 196 hospital records of patients with presenile dementia.

ICD CODE AND DEFINITION	NUMBER (%)
290.1 Presenile dementia	81 (41.3)
290.0 Senile dementia	37 (18.9)
290.4 Arteriosclerotic dementia	28 (14.3)
290.8 Dementia-other	22 (11.2)
290.9 Dementia-unspecified	20 (10.2
290.3 Senile dementia, acute confusion	5 (2.6)
290.2 Senile dementia, depressed / paranoid	3 (1.5)

Table 3. ICD diagnostic codes documented in 91 hospital records of patients with presenile Alzheimer's disease.

ICD CODE AND DEFINITION	NUMBER (%)
331.0 (and 290.1) Alzheimer's disease	57 (62.6)
290.0 Senile dementia	18 (19.8)
290.1 (not 331.0) Presenile dementia	13 (14.3)
290.4 Arteriosclerotic dementia	3 (3.3)

Table 4. The Hachinski score. A score less than five suggests Alzheimer's disease, greater than six, multi-infarct dementia.

Criteria	Score
Abrupt onset of symptoms	0 if no; 2 if yes
Stepwise deterioration	0 if no; 1 if yes
Fluctuating coarse	0 if no; 2 if yes
Nocturnal confusion	0 if no; 1 if yes
Preservation of personality	0 if no; 1 if yes
Depression	0 if no; 1 if yes
Somatic complaints	0 if no; 1 if yes
Emotional incontinence	0 if no; 1 if yes
History of hypertension	0 if no; 1 if yes
History of stroke	0 if no; 2 if yes
Evidence of arteriosclerosis	0 if no;1 if yes
Focal symptoms	0 if no; 2 if yes
Focal signs	0 if no; 2 if yes

Table 5. Standardised discriminant function coefficients of clinical criteria used to diagnose pure Alzheimer's disease.

CRITERIA (VARIABLE)	ANALYSIS A (n=61; 36 vs 25)	ANALYSIS B (n=50; 25 vs 25)	ANALYSIS C (n=30; 18 vs 12)
HACHINSKI SCORE	0.55	0.48	0.55
CO-EXISTENT BRAIN DISEASE	0.54	0.61	0.68
CO-EXISTENT SYSTEMIC DISEASE	0.49	0.44	0.00
HISTORY OF EPILEPSY	-0.26	-0.38	-0.17
RESULTS OF INVESTIGATIONS	-0.13	-0.11	0.11
MENTALLY ALERT AT PRESENTATION	0.07	0.05	-0.10
INSIDIOUS ONSET	0.06	0.13	0.00
HISTORY OF MEMORY LOSS	-0.03	-0.04	-0.09

Table 6. Classification of 61 patients with dementia according to clinical diagnosis and discriminant classification.

		Predicted diagnostic group: No. (% correctly classified)	
Neuropathological Diagnosis	n	Clinical Classification	Discriminant Classification
Alzheimer's Disease (Group1)	36	22 (61.1%)	32 (88.9%)
Other type of Dementia (Group 2)	25	22 (88.0%)	19 (76.0%)

Table 7. Specificity, sensitivity and diagnostic accuracy of clinical and discriminant classification of patients with presenile dementia who had neuropathological examination.

	CLINICAL CLASSIFICATION			DISCRIMINANT CLASSIFICATION		
Criteria	Specificity (%)	Sensitivity (%)	Accuracy (%)	Specificity (%)	Sensitivity (%)	Accuracy (%)
NINCDS-ADRDA AND HACHINSKI	61.1	88.0	72.1	76.0	88.9	83.6
NINCDS-ADRDA ALONE	88.0	61.0	72.1	80.0	75.0	77.1

Table 8. Incidence (95% confidence intervals) per 100 000 at risk population of cases of probable Alzheimer's disease presenting in Scotland 1974-1988.

Age / years	Males	Females	All	Female to male risk ratio
40-44	0.7	2.0	1.4	2.9
45-49	7.2(3.4-13.2)	8.9(4.7-15.2)	8.1	1.2
50-54	20.1(13.9-29.1)	34.7(26.5-45.4)	27.6	1.7
55-59	29.6(21.8-40.3)	48.9(39.0-61.4)	39.7	1.7
60-64	27.1(19.1-31.5)	46.8(36.5-59.9)	37.8	1.7
Total	16.5(13.8-19.8)	28.2(24.5-32.4)	22.6(20.2-25.2)	1.7*

* Mantel-Haenszel summary estimate

Table 9. Incidence (95% confidence intervals) per 100 000 at risk population of cases of broad Alzheimer's disease presenting in Scotland 1974-1988.

Age / years	Males	Females	All	Female to male risk ratio
40-44	0.7	5.5	3.1	7.7
45-49	10.1(5.5-16.9)	13.7(8.1-21.1)	11.9	1.4
50-54	29.4(21.7-39.9)	55.3(44.6-68.6)	42.8	1.9
55-59	44.8(35.0-57.5)	91.2(83.7-99.3)	69.1	2.0
60-64	62.0(55.1-80.2)	95.8(87.8-104.)	80.4	1.5
Total	28.1(26.1-30.2)	52.0(49.4-54.7)	40.5(38.9-42.3)	1.8*

* Mantel-Haenszel summary estimate

Table 10. Incidence (95% confidence intervals) per 100 000 at risk population of cases of multi-infarct dementia identified from psychiatric hospital records in Scotland 1974-1988.

Age / Years	Males	Females
40-44	5.0	2.0
45-49	7.2	3.4
50-54	17.2	8.7
55-59	34.0	20.5
60-64	70.8	33.6
Total	25.1(23.3-27.1)	13.4(12.1-14.8)

Table 11. Characteristics of the total study sample who had 'probable' Alzheimer's disease.

Gender	**Number**	**Median age in years (Q_1-Q_3)**	**Five year survival**	**Relative death rate**
Male	111	59 (55-63)	43.3%	1.23
Female	206	59 (56-63)	56.2%	0.89

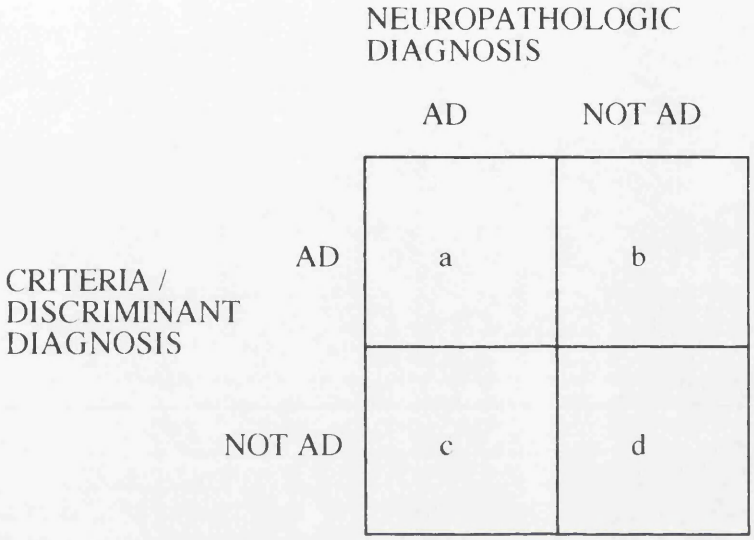
Table 12. Characteristics of those people with 'probable' Alzheimer's disease who died in the follow-up period.

Gender	**Number**	**Median age in years (Q_1-Q_3)**	**Median survival in years (Q_1-Q_3)**
Males	93	60 (56-63)	3.8 (2.2-5.9)
Females	151	60 (57-63)	4.7 (2.8-6.7)

Table 13 Guidlines for interpreting kappa values (Landis and Koch, 1977).

Kappa Range	Level of agreement
0.00 - 0.20	slight
0.21 - 0.40	fair
0.41 - 0.60	moderate
0.61 - 0.80	substantive
> 0.81	almost perfect

Figure 1. Definition of terms. AD signifies Alzheimer's disease.



SPECIFICITY = d/b+d

SENSITIVITY = a/a+c

DIAGNOSTIC ACCURACY = a+d/a+b+c+d

Figure 2. Survival of 317 people with 'probable' Alzheimer's disease.

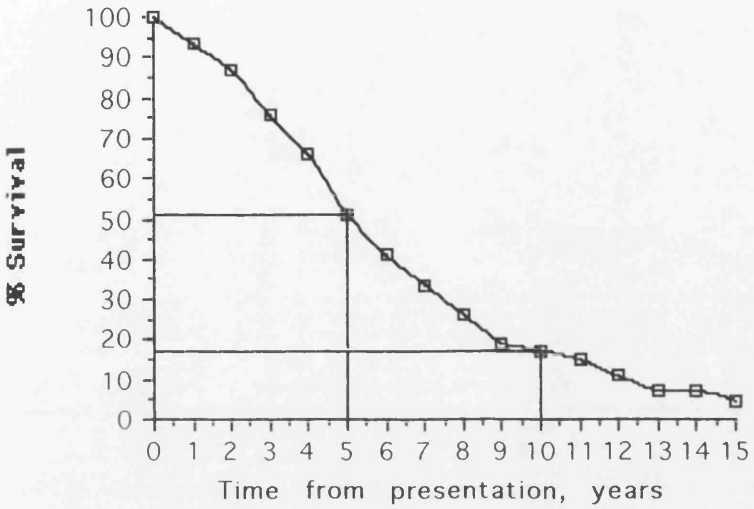


Figure 3. Survival by gender in 317 people with 'probable'Alzheimer's disease.

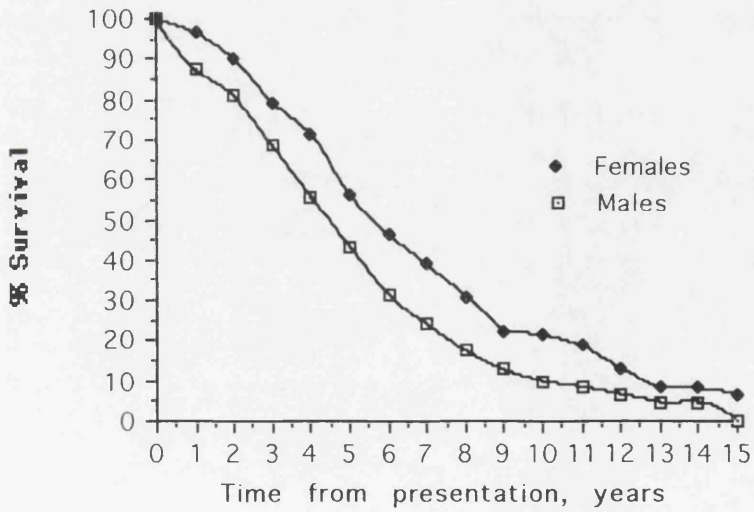


Figure 4. Possible patterns of health care provision to patients with Alzheimer's disease.

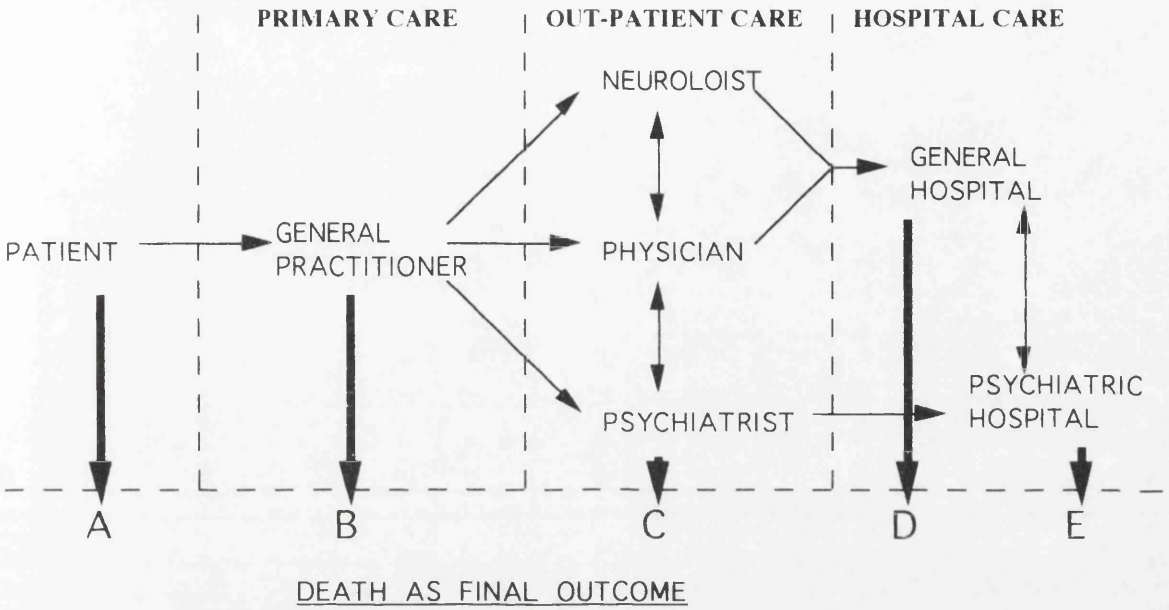
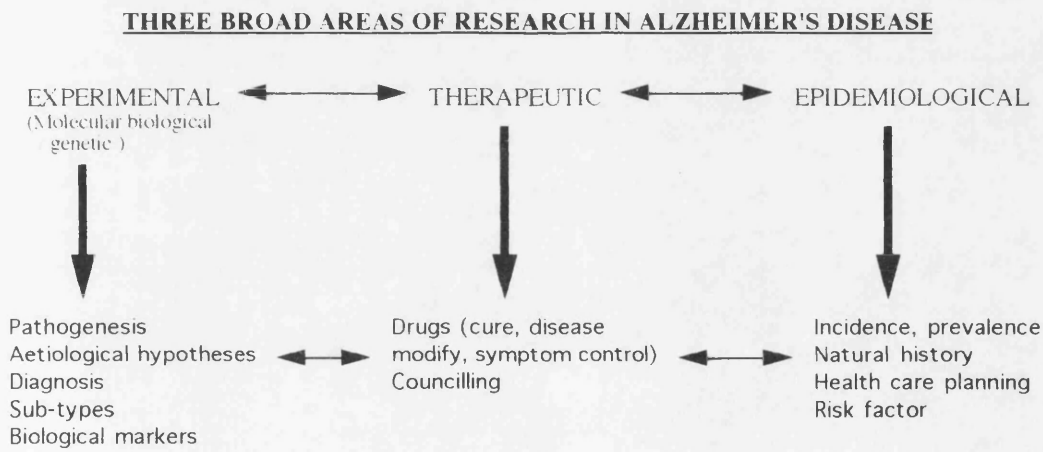


Figure 5. Three areas of research in Alzheimer's disease with some main outcome measures.



DISCUSSION

(a) Can current clinical criteria used to diagnose Alzheimer's disease be improved and modified for specific use in epidemiological research?

Discriminant analysis based on the Hachinski Score and the NINCDS-ADRDA criteria correctly classified 51 patients (83.6%) with presenile dementia (Tables 6 and 7). This compares to 44 patients (72.1%) correctly classified who received diagnoses directly from both clinical criteria. Analysis that used only the NINCDS-ADRDA criteria classified 47 patients (77.1%) correctly compared to 44 patients (72.1%) diagnosed clinically (Table 7). The variables of highest discriminating value were the Hachinski Score, the presence of co-existent neurological disease and the presence of co-existent systemic disease (Table 5).

Discriminant analysis is a statistical method for testing a classificatory system (Kendell, 1975, Moran, 1966). The validity of any distinction found between groups rests upon the analysis meeting four criteria. Firstly, the co-variance matrices for each of the diagnostic groups must be equal to avoid spurious results (Kendell and Post, 1973). Secondly, the number of subjects in the analysis needs to be more than the product of the number of variables and the number of groups. Thirdly, the two diagnostic categories must have a bimodal distribution with a 'point of rarity' between groups. This was demonstrated between the 'gold-standard' Alzheimer's disease group 1 and group 2: 11.1% misclassified after analysis A, 12% after analysis B, 5.6% after analysis C. Fourthly, the results should be replicated on an independent data set. The first three criteria were met but the latter was not possible in the present study.

The ability of clinical and discriminant analysis to correctly classify patients was evaluated by reference to the 'gold standard' of neuropathological diagnosis.

However, the diagnostic accuracy of clinical criteria is influenced by the neuropathological criteria used to define Alzheimer's disease (Chapter - Definition of Alzheimer's disease). Neuropathological examination is not routinely performed as part of a post-mortem examination in Scotland. When conducted detailed results are documented by the pathologist. This study used accepted neuropathological criteria that could be directly and easily applied to the information contained in neuropathological records. The criteria used were selected on this principal; other neuropathological criteria may have produced different results. Standard neuropathological criteria are needed to avoid this source of bias in the future. The unsatisfactory situation at present is that all studies which directly validate clinical criteria to diagnose Alzheimer's disease can be criticised on the 'gold-standard' criteria used. However, this methodological limitation should not exclude attempts to improve clinical and research practice.

In classifying patients with mixed dementia into group 2 there were no patients in which the diagnosis reached after neuropathology record scrutiny by GM. differed from that of the pathologist, even though GM was blind to the reported diagnosis. It is unlikely, therefore, that neuropathological diagnostic error has biased the results.

The exclusion of patients with both histological features of Alzheimer's disease and multi-infarct dementia (i.e.mixed dementia) from the Alzheimer's disease group limit the conclusions of the study to the differentiation of uncomplicated disease from all other types of dementia. This is problematical. Patients who have mixed dementia have a 'degree' of Alzheimer's disease but are excluded from that diagnostic group. This limitation is appreciated but this study was not able to define all patients with uncomplicated presenile Alzheimer's disease by strict application of inclusive and exclusive clinical criteria. The diagnostic

accuracy of the criteria would have been further reduced if patients with mixed dementia had been included in group 1.

This study used a large retrospective epidemiological survey to define patients in which neuropathological information was available. These 61 patients were a selected group and represent 3.6% of the total sample of people with presenile dementia who were ascertained. Major determinants of whether a patient had a post-mortem performed were: place of death, local availability of neuropathological services, individual practice of psychiatric consultants, degree of certainty in diagnosis ete.

The discriminant analysis described does not differentiate between all categories of Alzheimer's disease and all other forms of dementia. This is clearly true if people with mixed dementia are not included in the Alzheimer's disease group. Also, it is unlikely that the 'gold-standard' sample of patients with uncomplicated Alzheimer's disease represent a random, homogeneous sample of the population with presenile Alzheimer's disease. The low post-mortem rate in the presenile population would make this a difficult argument to sustain. The discrimination is between a sub-sample of patients with Alzheimer's disease and all other forms of dementia, which may include other people with various 'degrees' of Alzheimer's disease. As clinical criteria to diagnosis Alzheimer's disease do not define all patients with the illness, but rather sub-samples of people with various degrees of certainty in the diagnosis, the use of discriminant analysis on this selected group remains valid. The usefulness of this statistical technique would be greater if the post-mortem rate were improved.

Diagnostic limitations imposed on investigators in epidemiological research in Alzheimer's disease have been highlighted. No clinical criteria can accurately define all patients with this illness in the community. Discriminant analysis may be a method by which diagnostic accuracy can be improved. The technique is limited

by the low post-mortem rate in people with presenile dementia and the lack of consensus as to what constitutes definite Alzheimer's disease. The results reported are encouraging, but must be *validated on an independent data* set before the use of the technique can be recommended. It is possible that the results reported are due to chance alone and the consistency of the method needs to be tested.

Reliability of clinical criteria is an important consideration in improving the quality of epidemiological research in Alzheimer's disease. Poor reliability suggests poor validity, however it is possible to have a high degree of agreement amongst observers but for them all to be wrong. Subjective guide-lines for interpreting kappa values have been proposed (Table 12 - Landis and Koch, 1977).

Most clinical judgements vary between clinicians. Kappa values for interpreting electrocardiograms (normal or abnormal) have been reported at 0.70, reporting on intravenous pyelograms (presence or absence of pyelonephritis) at 0.27 and in deciding, after clinical examination, whether a heart valve lesion was present at 0.60 (Koran, a and b, 1975). Kappa values between 0.53 and 0.74 have been reported for the diagnosis of possible and probable Alzheimer's disease using the NINCDS-ADRDA diagnostic criteria (Kukull, a, 1990).

This study reports kappa values of 0.72 and 0.61 using the interpretation of the NINCDS-ADRDA criteria described (Table 1). These are consistent with those previously reported. GM is a physician trained in general and geriatric medicine, CM is a trained Registered General Nurse and Psychology Graduate and LJW is a psychiatrist with a particular interest in dementia. The higher kappa value between physician and psychiatrist may reflect greater experience in diagnostic decision making. The level of agreement between nurse and psychiatrist show that the proposed criteria can be successfully applied by people less experienced in the diagnosis of dementia, and that further improvements in interobserver variation could be made with increased training and standardisation.

(b) What is the incidence rate of presenile Alzheimer's disease in Scotland? and

c) Is gender a risk factor in presenile Alzheimer's disease?

The reported rates for probable and broad Alzheimer's disease are minimum estimates of the true incidence. The data request may have omitted 6.5% of cases (Pilot Study), and a further 5.4% may have been lost because of inadequate hospital records. These errors are small compared with the effects of changes in diagnostic criteria: rates in the broad classification are appproximately double those in the probable category. Although the method used to define broad cases is novel and needs to be validated, the main findings are consisent in both categories of Alzheimer's disease. Female gender was significantly associated with the risk of Alzheimer's disease, though small numbers in the under 55 year age group make interpretation of a gender effect inappropriate.

Date of first presentation to specialist hospital care was chosen as the incident date. It is determined by referral practices of patient to General Practitioner and of General Practitioner to hospital. These practices will vary according to individual patients, doctors and the local availability of health care. Patients aged 64 years with mild memory failure may accept the deficit more readily than those aged 40 years. Referral thresholds of General Practitioner will vary according to previous experienced in investigating those with dementia and be determined by the degree of illness and patient's age. Hospital waiting times will also influence the time between symptom onset and presentation to hospital services.

The main advantage in using the date of presentation to hospital care as the incident date is that it is easily and reliably obtained from hospital record scrutiny. It is also directly relevant to those who plan diagnostic services for people with presenile Alzheimer's disease. The alternative incident date would be date of

symptom onset. This date was not precisely documented in psychiatric hospital records, is subject to recall bias and, in a substantial number of cases, was unknown.

Female gender has become a recognised risk factor for the development of Alzheimer's disease after age 65 years. To my knowledge, a significant association between gender and Alzheimer's disease with an onset before age 65 years has not been described. Several studies have found a small excess of female patients with early onset Alzheimer's disease in population studies, but the difference did not reach statistical significance (Treves et al, 1986, Molsa et al, 1982, Sulkava et al, 1983). This apparent inconsistency between female gender as a risk factor for Alzheimer's disease with an onset after age 65 years and that with an onset earlier was unexplained, but suggested an interaction between gender and the ageing process.

This study supports the association between female gender and an increased risk of presenile Alzheimer's disease. However, two other explanations for the association are possible. Firstly, variation in the utilisation of health services between the sexes could lead to an erroneous association. Doctors and other health care professionals may be more likely to refer females with memory impairment for specialist advice and/or male carers may not maintain their female relatives with dementia in the community for as long as female carers. If these assumptions are true, a similar excess of female sufferers with other forms of dementia would be expected. This was not the situation in those patients admitted to psychiatric hospital with multi-infarct dementia (Table10).

Patients categorised as multi-infarct represent a distinct clinical sub-group within the study sample, but it is debatable whether they accurately represent all patients with this illness in the population. The point of health service contact for patients with cerebrovascular disease and dementia is very variable and dependent on a number of factors not evaluated in this study (eg, which pathology appeared

initially, the relative dominance of symptoms, ete). The inverse association between female gender and the reported incidence rate of multi-infarct dementia, in the sub-sample of patients who entered the psychiatric hospital service, would suggest that variation in the use of health care services does not explain the association between female gender and Alzheimer's disease.

Secondly, diagnostic error may explain the association. This study has described an association between male gender and the clinical diagnosis of multi-infarct dementia in a sub-sample of patients admitted to psychiatric hospital. This study does not conclude that a generalisable association exists because the study was designed to ascertain people with Alzheimer's disease and not this specific type of dementia. However, a high proportion of people with multi-infarct dementia have co-existent neuropathological features of Alzheimer's disease. This will result in systematic underascertainment of men with Alzheimer's disease which may be of sufficient magnitude to cause a spurious association between female gender and Alzheimer's disease.

This study supports an association between female gender and clinical Alzheimer's disease. Deficiencies in clinical diagnostic techniques prevent conclusive evidence from being obtained; male patients with Alzheimer's disease may be differentially misclassified as other forms of dementia. If the association can be confirmed then the answers to two related questions will herald a major breakthrough in understanding the pathogenesis of Alzheimer's disease: what is it about being female that increases the risk of this disease?, or alternatively, what is it about being male that protects against the development of the illness?

(d) What is the natural history of presenile Alzheimer's disease?

Five year survival in the sample of people with probable Alzheimer's disease was 51.2% and females with the illness lived approximately 1.4 times longer than

males. Age at presentation to specialist care and place of death did not significantly alter survival duration. There was no evidence that survival duration had altered over the period of study. The consensus between censured and actual survival data indicated that those people with presenile Alzheimer's disease ascertained in the study but who were still alive at the end of follow-up did not represent a distinctive sub-group of individuals with the disease.

Age at presentation to specialist care was chosen to estimate survival duration because it provides prognostic information that is relevant to specialists who council relatives and patients with Alzheimer's disease. Also, this date was consistently and reliably obtained from hospital record scrutiny. However, the date is not an unbiased surrogate for time of disease onset and its use excludes a variable proportion of the natural history of the illness. The difference in the survival characteristics between males and females reported could be explained by variations in the referral practice of primary care physicians. They may refer or even detect the illness earlier in females compared to males.

In developed countries, death rates are consistently higher in males compared to females in all age groups because of the influence of a number of common diseases which have higher incidence rates in males. The diagnostic criteria used to define people with 'probable' Alzheimer's disease excluded those with other co-existent diseases which included those illnesses most responsible for the excess of mortality in males (ischaemic heart disease, peripheral vascular disease, lung carcinoma, cerebro-vascular disease ete). The excess mortality reported in males with presenile Alzheimer's disease is not explained by increased incidence rates of other diseases in this gender. The study sample was 'corrected' for this potential bias by the clinical diagnostic criteria; adjusting the figures for expected mortality in males and females in Scotland is, therefore, inappropriate.

It is unlikely that the natural history of Alzheimer's disease is altered by not being admitted to psychiatric hospital. Certainly, terminal care provision in an institution other than a psychiatric hospital did not influence survival duration. It is a reasonable assumption that the reported findings give an accurate and a generalisable description of the natural history of presenile Alzheimer's disease that are relevant to all professionals who council those with the disease.

Comparisons between the findings of this study and other studies are difficult due different methodology and age ranges. The observation that age at presentation did not alter survival duration is consistent with several other studies (Drachman et al 1990, Huff et al, 1987). Male gender has been associated with a shorter duration of survival in Alzheimer's disease (Barclay et al, 1985, Berg et al, 1988), however this has not been a consistent finding (Drachman et al 1990, Diesfeldt et al, 1986). The finding that females live longer after they have presented to specialist care is of obvious importance to those who plan health care services for dementia sufferers.

The natural history of presenile Alzheimer's disease has been described. The detailed information should help professionals who care for those people whose lives are affected by Alzheimer's disease. The findings are also recommended to health service planners who should note the increased survival duration in females with this disease. The differential effects of gender on survival duration in presenile Alzheimer's disease needs further study.

Completeness of Ascertainment

The central assumption in the sampling method is that the majority of patients with Alzheimer's disease with symptom onset aged less than 65 years are admitted to psychiatric hospital and are, therefore, listed in centrally available psychiatric health service returns (Pilot Study). This assumption needs to be

considered in some detail. There are several theoretical pathways of health care provision that could result in serious underascertainment of people with this illness (Figure 4).

People with Alzheimer's disease may never present to medical attention, but die in the community either undiagnosed or cared for by relatives who have never sought support (Pathway A, Figure 4). The number of such patients will be small because of the insidious course, the behavioural disturbances and the distress associated with the illness. In addition, people with symptoms of memory impairment in early life are more likely to present to medical care than accept negative stereotypes of memory failure and 'normal' ageing. However, some people with mild symptoms and a slowly progressive disease may remain independent until death. This situation is analogous to many other medical illnesses which do not produce sufficient distress for people to seek medical help, eg silent ischaemia in atheromatous heart disease, asymptomatic large bowel cancer ete. Such individuals are at one extreme of the disease distribution and, although important in their own right, will not significantly alter the reported incidence rates of Alzheimer's disease.

People with Alzheimer's disease may present to their General Practitioner (GP), but not be refered further along the health care pathway (Pathway B, Figure 4). As shown, GP's have a crucial, central role in deciding the pattern of future health care delivery to patients with Alzheimer's disease. They were not included in the sampling frame for a number of reasons. Firstly, local family doctor committees throughout Scotland discussed how they managed patients with presenile Alzheimer's disease and reported that the great majority of such patients were referred to psychiatrists or neurologists. Secondly, colleagues in Newcastle, whose aim was to estimate the prevalence of presenile dementia in a defined geographical area, found that approaches directly to GP's did not detect any patients with

presenile dementia who were not already known to the hospital services. Finally, the quality of GP record keeping is variable and most records are destroyed after a patient dies. The retrospective design of the study would require GP's to remember patients with presenile Alzheimer's disease because few maintained a diagnostic index for the time period between 1974 to 1988. Such an approach is unscientific and would be justifiably criticised.

Patients with Alzheimer's disease could be referred for out-patient specialist investigation, but never be admitted to hospital (Pathway C, Figure 4). Two independent data sources were used to examine whether significant numbers of patients followed this course. Only 3% (4 / 129) of patients with dementia who attended two neurology out-patient departments had not been admitted to psychiatric hospital. These patients presented after 1983 and had not developed major social and behavioural problems at the time of hospital record scrutiny. It is reasonable to postulate that these patients will be referred and admitted to psychiatric hospital as their illness deteriorates. In Grampian, no patient who attended psychiatric out-patient and received a diagnosis of presenile Alzheimer's disease was not admitted to psychiatric hospital. Although the evidence presented may reflect local practice by neurologists in Dundee and Edinburgh and psychiatrists in the North-East of Scotland it was consistent with advice received from Chief Administrative Medical Officers, medical advisers to the Mental Welfare Commission and experienced general psychiatrists in Scotland.

Patients with Alzheimer's disease could be admitted to general hospitals and never be detailed on psychiatric hospital returns (Pathway D, Figure 4). One-hundred and ninety nine non-psychiatric hospital records were requested, these included 169 records from district general or teaching hospitals and 34 from cottage or private hospitals. Over half of these records had been destroyed after the patient had died and could not be scrutinised. Of the 89 records scrutinised, three patients

(3.4%) had verified 'probable' Alzheimer's disease but had not been admitted to psychiatric hospital. Most patients who die in general institutions have been admitted to psychiatric hospitals at some stage of their illness. The sampling method used to validate psychiatric hospital data could not be expanded to general hospital returns because of the policy of general hospital record destruction.

This thesis assumes that the majority of patients with Alzheimer's disease are detailed on psychiatric hospital returns (Pathway E, Figure 4). Incidence rates of two classifications of Alzheimer's disease calculated using this study sample are consistent with results reported by other investigators who used different case ascertainment methods. As indicated, there are a small number of people with Alzheimer's disease who remain unknown to the psychiatric in-patient services. The evidence from several independent data sources indicate that such patients are rare and that the ascertainment method used was systematically unbiased in respect of the study's findings (i.e. the method did not differentially ascertain older people or females with Alzheimer's disease). I argue that limitations in epidemiological diagnostic criteria for Alzheimer's disease are a greater potential source of error in the reported incidence rates rather than errors introduced by incomplete sampling. The incidence rate of the 'broad' classification of Alzheimer's disease is more than double that of 'probable' disease. In addition, diagnostic criteria may differentially misclassify males and females with the illness. It is unlikely that a similar magnitude of people with Alzheimer's disease have been underascertained.

FUTURE RESEARCH

Progress in understanding the basic epidemiology of Alzheimer's disease has been slow. To date, family history and age are the only conclusive risk factors that have been discovered in an illness that is older than human literature and affects over one quarter of people in their 80th decade. This thesis highlights the problem of accurate diagnosis in dementia research. Although the importance of using standard diagnostic criteria has been accepted, several have been proposed and all remain in popular use! This prohibits a standard approach to the diagnosis of Alzheimer's disease.

There is an error in the clinical diagnosis of Alzheimer's disease which will remain until a unique pathognomonic feature or biological marker can be discovered. This source of bias confronts all epidemiological research in Alzheimer's disease. Attempts to improve the diagnostic accuracy of clinical criteria are useful in reducing this source of bias but will never eliminate it. Diagnostic errors must always be considered as explanations of risk factor and disease association. To overcome criticisms of disease diagnosis, future research must recognise its importance and actively seek neuropathological verification of clinical diagnoses.

Fundamental facts about the epidemiology of Alzheimer's disease are unknown and describing these should be major objectives of future research. Evaluation of geographical and temporal variation in health care provision and the effects of migration of people with Alzheimer's disease must be studied. Comprehensive data on environmental toxins linked to this illness must be collected in defined geographical areas over a prolonged time period.

Neither geographical nor temporal variation of incidence of any sub-type of dementia has been reliably demonstrated, even for categories (eg, alcoholic dementia) in which the environmental factor is beyond dispute. In the United Kingdom, there is a lack of information about the quality of the public water supply that can be used to assess exposure to environmental toxins within small geographical regions. Information on current concentrations of toxins in the environment is unsatisfactory since temporal changes over the prolonged asymptomatic period of the illness have probably taken place (eg, the effects of acid rain increasing aluminium leaching) (Pearce F, 1985). In addition,.the effects of population migration within this period cannot be ignored. People with dementia constitute a mobile population: the area in which they are living is not necessarily where the illness began.

There are many methodological issues in studying the epidemiology of Alzheimer's disease. Some sources of bias cannot be overcome but can be quantified (the first part of this thesis is devoted to that of diagnostic error). Investigators have attempted to find modifiable environmental associations of Alzheimer's disease without first addressing the limitations of their study and have succeeded in causing controversy by raising more questions than answers. Public fears have been aroused without sufficient epidemiological evidence.

Alzheimer's disease is an insidious disorder and definitive proof of environmental toxin causation will require a prospective epidemiological study in which the issues discussed have been addressed. This will be costly but there is no reason why risk factors for Alzheimer's disease should be easier to discover than those of cerebro-vascular disease, ischaemic heart disease, colonic cancer, ete.

Epidemiological research cannot be separated from therapeutic and experimental research in Alzheimer's disease (Figure 5). Councilling services must be planned with data on disease prevalence and natural history, hypotheses

postulated by finding neurochemical deficits in demented people's brains can be tested in therapeutic studies, genetic-epidemiological studies are needed to assess the population effect of isolating genes that cause Alzheimer's disease in single family pedigrees, ete. Future research must appreciate the interdependence of these areas and a co-ordinated approach to research in Alzheimer's disease is needed. Geneticists, molecular biologists, pharmacologists, epidemiologists and clinicians must work together. Does each not want to achieve the same goal?

What now?

In Scotland, ISD is a valuable data resource for further epidemiological research in Alzheimer's disease. There is an opportunity to update the data base used in this thesis to provide a comprehensive national register of people with Alzheimer's disease. This thesis has given original and important insights into the epidemiology of Alzheimer's disease in Scotland. No cause or cure for Alzheimer's disease has been described nor sought. The work needs to continue methodically. The population sample should be described from 1988 to present and geographical and temporal changes in disease incidence assessed. Neuropathological verification of disease diagnosis must be a priority. Data on environmental toxins must be collected and the study sample followed prospectively to test aetiological hypothesis in an unbiased manner. There now exists in Scotland a unique opportunity to comprehensively study the epidemiology of Alzheimer's disease.

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