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RATE AND PREDICTORS OF DECLINE IN DEMENTIA OF THE ALZHEIMER TYPE AS MEASURED BY THE HIERARCHIC DEMENTIA SCALE (HDS)

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A Thesis

in

the Department

of

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Abstract

Rate and Predictors of Decline in Dementia of the Alzheimer Type as Measured

by the Hierarchic Dementia Scale (HDS)

Dolly Dastoor, Ph.D.
Concordia University, 1998

Alzheimer's disease is characterized by progressive decline in several

domains of cognitive functions, which have variable rates of change in the

decline process. The overall objective of the study was to develop a model to

predict the rate of decline in individual patients as measured by the Hierarchic

Dementia Scale (HDS) based on the risk factors of age of symptom onset,

education, gender, and place of residence.

It was hypothesized that younger age of symptom onset would predict a

faster rate of decline on the total HDS score and in the seven cognitive domains

of orientation, language, memory, praxis, calculation, concentration, and

perception. A related question concerned the contribution of specific cognitive

functions of language and praxis in predicting rate of decline.

This study examined 60 patients with Alzheimer's disease assessed at 6-

month intervals over 18 months. At each assessment the HDS, an instrument,

based on Piagetian concepts and neuropsychological findings, was

administered to assess severity of impairment. Descriptive information were

obtained at entry into the study.

Using a repeated measures univariate and multivariate design format,

the results show significant age and time effects for the total HDS score and for

the seven cognitive domains. A model of decline in language and praxic functions was built using the Bayesian Information Selection Criterion (BIC). Of all the variables entered in the model (REML), age of onset, education level and place of residence were selected as predictors of decline.

Regression analysis revealed that, for every year of difference in age of symptom onset there was a significant difference of 1.60 points on the total HDS score, .72 points on the language score and .26 points on the praxic score. The covariates of education and place of residence predicted significant decline on total HDS and language scores, but not on the praxic score.

This study indicates that patients with Alzheimer's disease, who have earlier age of symptom onset, lesser education, and who live in an institution will decline faster on the total HDS and language function scores.

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I dedicate this thesis to the loving memory of my mother who suffered from dementia and to all the families and the people who have lived through this devastating disease.

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Theoretical Overview

Definition of Dementia

Dementia is the most serious psychiatric disorder of old age, occurring in about 5% of those over 65 years of age. Many definitions of dementia have been proposed. One that has the merit of brevity was proposed by Sir Martin Roth (1980), "the global deterioration of the individual's intellectual, emotional and cognitive faculties in a state of unimpaired consciousness". The American Psychiatric Association's (1987) Diagnostic and Statistical Manual of Mental Disorders (DSM III R), and The World Health Organization's (1989) International Classification of Diagnosis (ICD10) have both proposed operational definitions of this concept, with minor differences in emphasis. Both stress the decline in memory and other aspects of intellectual functioning, in the absence of clouded consciousness, sufficient to cause a restriction in normal activities. Both highlight decline, the difference being that the ICD10 specifies a duration of at least 6 months and the DSMIIIR does not set a duration. It is now generally understood that dementia is a syndrome characterized by cognitive, emotional, and psychomotor disturbances and belongs to a group of organic syndromes seen in the later part of life. This concept is limited to a clinical syndrome or a constellation of symptoms, independent of the etiology. Dementias are generally divided into four subgroups, idiopathic dementias (primary degenerative disorders), vascular dementias, secondary dementias, and others.

Alzheimer's Disease

The turn of the century marked a particularly intense period for research into the differentiation and classification of the dementias. In 1905, Klippel and L'Hermite described Senile Dementia, a disease with onset in the senium characterized by insidious progression of disorientation, as well as impairment of memory and of judgement.

In 1907, a German psychiatrist, Alois Alzheimer (Alzheimer, 1987) described a case of dementia in a 51- year- old woman, characterized by rapidly progressive disorientation and memory impairment associated with aphasia and apraxia. Kraepelin named this disorder "Alzheimer's Disease." By the 1960s, the results of clinical, pathological and genetic studies were sufficient to convince many European researchers that Senile Dementia and Alzheimer's Disease were in fact a single disease entity and until today the term Alzheimer's Disease (AD) refers to illness of both presenile and senile onset. It is the most common form of primary degenerative dementia, accounting for at least half of all cases of dementia.

In both the presenile and senile forms of this disease, neuropathological examination of the brain discloses characteristic abnormalities, which are the product of neural degeneration. The most studied pathological abnormalities are amyloid plaques and neurofibrillary tangles. Amyloid plaques are the result of abnormal processing of the amyloid precursor protein (APP) and the mutation of the gene for beta amyloid precursor protein. The overproduction or increased aggregation of this protein causes the formation of amyloid plaques.

Neurofibrillary tangles are the result of excessive phosphorylation of the protein tau leading to the formation of neurotoxic intracellular paired helical filaments. The filaments aggregate into tangles after they cause the death of the neurones. Although these abnormalities are far more abundant in the brains of those with Alzheimer's disease, they can be found in normal brains as well. These formations appear to predate the development of visible clinical symptoms of the disease.

Blessed, Tomlinson, and Roth (1968) were among the first to show that the density of neuritic plaques in the cortex of AD patients at autopsy correlates with the severity of their cognitive deficits. They reported a correlation of $+.77$, ($p <. 001$) between mean plaque counts and dementia score (high score = extreme incapacity) on the Blessed Test. Since the pioneering work of Blessed, substantial evidence has accrued, indicating excessive nerve cell loss in the brains of AD patients, especially in the frontal and temporal cortices (Braak, Duyckaets, Braak, & Piette, 1993). The cognitive deficits of AD have been attributed to abnormalities in the cerebral cortex and hippocampus (Martin, et al. 1986).

Findings from the Nun Study (Snowdon, 1997) indicate that neurofibrillary tangles in the neocortex have strong associations with poor performance on each of the eight cognitive function tests, measuring memory, concentration, language, visuospatial ability, and orientation to time and place, from the CERAD battery (Morris et al 1989) and the Object Naming derived from another source (Rosen, Mohs, & Davis, 1984), whereas neurofibrillary tangles

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in the hippocampus have moderately strong associations with poor performance on tests of memory. In the study, Sisters, with brain infarcts or with brain weights less than 1,000 grams, showed significantly lower performance on the cognitive tests than did Sisters without these conditions. The strength of association between neuritic plaques in the hippocampus and the neocortex with poor performance on cognitive tests is dramatically reduced after adjustment is made for the number of neurofibrillary tangles.

Neurochemical studies indicate that presynaptic cholinergic markers are significantly reduced in the cerebral cortex and in the hippocampus of people with AD. This cholinergic deficiency appears to be due to a loss of neurons in the basal forebrain cholinergic system which projects directly to the hippocampus and neocortex. Central cholinergic neurotransmitters play a role in the processing of recent memories, and abnormalities of this system underlie some of the symptomatic manifestations of AD (Hefti & Schneider, 1991).

A great deal of progress has been made in the understanding of the genetics of AD, and it has been suggested that amyloid accumulation plays a major role in AD. A recent finding that has major implications for the understanding of AD involves a specific lipoprotein, apolipoprotein E (ApoE). Each person inherits a copy of the ApoE gene from each parent and there are three alleles, E2, E3, and E4. Inheritance of two copies of E4 allele increases the risk of developing AD by 40% to 50% (Roses, 1995).

Clinical experience shows that although AD patients in the late stages of the disease manifest similar cognitive deficits, the array of cognitive deficits can

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be very different in the early and middle stages of the disease (Martin, 1990).
Martin et al. (1987), Neary et al. (1986), and Becker, Huff, Nebs, Holland and
Boller (1988) have shown that a large proportion of patients early in their
disease process had cognitive impairment and this cognitive impairment did not
affect all functions equally. Joanette, Poissant and Valdois (1989) using a
multiple single-subject paradigm have shown the existence of differential
patterns of cognitive decline in a group of 11 patients with AD. In 7 patients, the
impairment was different in each of the cognitive functions, e.g. language
functions were impaired in the presence of preserved perceptual abilities
orlanguage functions were preserved in the presence of impaired perceptual
abilities.

Incidence and Prevalence of Dementia

Jorm, Korten, and Henderson (1987), reviewing 47 studies published
between 1945 and 1985, reported that prevalence estimates for people aged
65 and over vary from 0.6% to 5.1%. All studies agree that rates increase
greatly with age so that approximately 22% of people over 80 and 30% of
people over 90 years of age are demented. In 22 of the 47 studies, Jorm and
colleagues, through the technique of quantitative meta-analysis, found a
consistent relationship between prevalence and age, with a doubling of
prevalence every 5.1 years of people over 65.

The Canadian Study of Health and Aging (CSHA, 1994) evaluated
elderly community and institutional residents living in five geographical regions
of Canada to estimate the prevalence of dementia in Canada. In each

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community, a randomly selected group of people aged 65 and over were interviewed and assessed on general health questions and a psychometric screening test for cognitive impairment. People screening positive for cognitive impairment were asked to undergo a clinical assessment to determine the presence of dementia and to provide a diagnosis. From those screening negative for cognitive impairment, a randomly selected sample was asked to undergo a clinical assessment as potential control subjects for a second phase caregiving and risk factors study. In the institutional sample, the high prevalence of dementia made screening redundant and all subjects underwent clinical assessment. The results of all clinical examinations were used to estimate the prevalence of subtypes of dementia. Of the combined community and institutional subjects, 64% of the cases were found to suffer from AD, yielding an overall prevalence proportion of 5.1% for Canadians aged 65 and over. The corresponding age specific estimates were 1% for 65-74 age group, 6.9% for 75-84 age group, and 26% for 85+ age group.

Diagnosis and Assessment of Alzheimer's Disease

The clinical diagnosis of AD always carries an element of uncertainty as it is based on the exclusion of other potential etiologies. The most commonly used guidelines in the diagnostic process are those of the revised third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM IIIR) (1987) for primary degenerative dementia of the Alzheimer type. These criteria, require demonstrable evidence of impairment in short, and long- term memory, together with a deficit in at least one of the following: impairment of abstract thinking,

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judgement, disturbances of higher cortical functions of aphasia, apraxia, agnosia, constructional ability, or personality change. These impairments must also significantly interfere with work and social activities.

The most commonly developed guidelines for possible, probable, and definite AD are those developed in 1984 by a working group created by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) (Mc Khann et al. 1984). The differences between possible, probable, and definite AD reflect the available information (clinical and pathological, as opposed to clinical only) and how closely the patient's syndrome resembles classic AD.

Possible AD is diagnosed when there is a dementia syndrome with no apparent cause, but with variations in the onset, presentation, or clinical course compared with typical AD. There may also be another systemic illness or brain disorder sufficient to produce dementia, but not considered to be the cause of the dementia. In addition, there could also be a single gradually progressive deficit in the absence of any identifiable cause.

Criteria for probable AD require the presence of dementia to be established by a questionaire and confirmed by neuropsychological testing. For probable AD there need to be deficits in two or more areas of cognition, together with progressive worsening of memory, with no disturbance of consciousness, onset between ages 40 and 90, and an absence of systematic disorders or brain diseases that could account for the memory and cognitive

deficits. According to these criteria, dementia is defined by decline in memory and other cognitive functions, in comparison with previous levels of functioning.

Criteria for definite AD require that the patient has met clinical criteria for probable AD while alive and has histopathological evidence of AD obtained by autopsy. The diagnostic accuracy of these criteria have been assessed in a number of studies. Lopez et al.(1990), Baldereschi et al.(1994), and Kukull et al.(1990) reported that the inter-rater reliability of the NINCDS/ADRDA criteria ranged from 0.36 to 0.65 and estimates of validity of these criteria ranged from 60% to 100% (Kukull et al., 1990; Tierney et al., 1988; Morris, McKeel, Fulling, Torack, & Berg, 1988). These results indicate that pre-mortem, as many as one third of patients with a clinical diagnosis of AD may not in fact have the disease. Post-mortem, the diagnoses can be confirmed with an accuracy rate of 80 % to 85%.

The question often arises as to which cognitive and ADL functioning tests or scales should be used to assess deficits in AD. Clinical research in AD and other dementias has been characterized by a abundance of rating scales and psychomotor tests that measure two main types of decline: the first assesses the effects of the disease on activities of daily living, while the second assesses cognition directly through neuropsychological tests.

In developing an assessment tool for dementia, it is essential to take account of a wide range of information available and to rate patients along a number of dimensions. Assessments for dementia can be made for diagnosing subjects, for developing a management plan, or for measuring functional

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change prospectively. Measures appropriate for one purpose, however, may be inappropriate for another. When the aim is to measure change in the various cognitive functions prospectively, the most appropriate measures are quantitative ones which yield a wide range of scores that are sensitive to change over time respecting the heterogeneity in the clinical course of the disease.

Clinical Manifestations

Clinically, AD is characterized by a global, progressive, and as yet, irreversible decline in mental functions, such as failing memory, intellectual deterioration, and behavioural disturbance. This decline results almost invariably in a steadily diminishing capacity for self care and a shortened life expectancy (Burns & Levy, 1992; Hasegawa, 1991; Neary et al., 1986). Based on observations of people in various stages of AD, the clinical features can be grouped into several areas: amnestic/cognitive, affective, psychomotor and neuropsychological. In the course of the disease, these deficits may evolve synchronously, or one of them may dominate the clinical picture depending on how the brain lesions develop.

As the onset of the disease is insidious and initial changes often subtle and imperceptible, the precise time of onset is generally difficult to determine. As the disease evolves, diverse signs and symptoms emerge, some persisting or progressing as the disease advances, while others regress. Wide variability exists among AD patients during the illness, with different features and symptoms emerging as the disease progresses. The rate of disease

progression is also variable with some individuals deteriorating rapidly, while others experience little or no decline for years. The median survival time following onset is estimated to be between 5 and 9 years, with a range of 1 to 18 years (Walsh, Welch, & Larson, 1990).

Clinical Features

Amnestic Functions. In the initial stages of AD, memory impairment is characterized by failure to acquire new information in the course of everyday activity (American Psychiatric Association Practice Guidelines, 1997; Reisberg, Ferris, Franssen, Kluger, & Borenstein, 1986). Later, short-term memory, which includes recall of recent events, paired associate learning, or remembering a series of objects or digits after a several minute interval, becomes impaired. This progressive impairment in short-term memory is then accompanied by an impairment in remote memory (Hasegawa, 1991). As there is difficulty in recalling events from different life periods, these gaps may be filled by recalling events from earlier stages of their life or by confabulations or false recognitions. At this stage, few cortical signs exists, that is, few impairments occur in higher cortical functions like abstraction and calculation. The clinical picture is much like that of Korsakoff's psychosis. As the disease progresses and extends outside the hippocampus to the cortical areas, encoding (intimately related to attention and concentration) becomes markedly impaired, with the affected individual being unable to remember information for even 10 to 20 seconds (Albert, Moss, & Milberg, 1989; Butters, Delis, & Lucas, 1995). The sequence of impairments, recent, remote and registration, is important clinically for

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differential diagnosis for sub-types of dementias, which have management and treatment implications (Bouchard & Rossor, 1996).

Affective Functions. In the initial stages of the disease, there may be significant affective changes: marked anxiety and restlessness associated with delusions and hallucinations (Rosen & Zubenko, 1991) and mild to moderate depression (Fitz & Teri, 1994). With the progression of the disease, a progressive loss of affective functions appears paralleling the loss of memory functions. Delusions, depression, apathy, agitation, and sleep disturbances are among the most frequently observed symptoms. Emotional life becomes progressively more flat and shallow with very little reaction to situations that would have previously elicited an emotional response. The results of studies showing early damage to the outflow tracts of the raphe nuclei or the locus ceruleus or to other structures involved in emotion provide a physiological bases for these observations (Zubenko & Moossy, 1988).

Psychomotor Functions. As the disease progresses to the frontal lobes and/or basal ganglia, psychomotor aspects of the disease appear. There are three different types of disorders of movement: changes in muscle tone, stereotypies, and the appearance of the primitive release phenomenon (McKhann et al., 1984; Reisberg, Ferris, Torossian, Kluger, & Monteiro, 1992).

Changes in muscle tone are reflected in progressive loss of spontaneity (i.e ability to initiate activity voluntarily), movement trunk flexion, slow small-step gait with loss of rhythm, loss of associated movements, difficulty starting, turning and stopping movements, and an inexpressive face. This may develop into

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catalepsy, immobility and face muscle contractures (Stern et al, 1994; Chui, 1994). Stereotypies are purposeless, repetitive movements, which occur later in the disease, progressing from simple stereotypies such as folding or pleating of clothes, rubbing of hands on thighs, to massaging gums and taking all objects to the mouth to be sucked. Release phenomena refer to series of reflexes present in the infant, such as grasping and sucking. These reflexes usually disappear with maturation of the brain, but reappear as AD progresses. Reappearance of the grasp reflex (tendency to cling on to any object brought close) is followed by reappearance of oro-visual reflex (tendency to open mouth to suck any object brought close to the mouth), and in the most severe stage, the oral-tactile reflex (tendency to turn face towards the stimulation) reappears with sucking or attempting to suck (Burns, Jacoby, & Levy, 1991; Huff & Growden ,1986; Tweedy et al., 1982; Stern et al., 1994).

Neuropsychological Functions

The higher cortical neuropsychological functions that deteriorate in AD are praxic, language, and gnostic functions.

Praxis. Praxic functions are of three types: constructive, ideomotor, and ideational. Constructive praxic function involves the ability to draw by copying or command, or the ability to construct a three-dimensional design from a model or a two-dimensional picture. Decline in this constructive ability is hierarchical in nature, with difficulties in three-dimensional perspective followed by the production of a cube in one dimension, and finally the production of only one face of the cube (Bouchard & Rossor, 1996). Ideomotor praxic function involves

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the orienting and use of one's body movement meaningfully. Impairments progress from difficulty in imitating complex gestures of the hands to difficulty imitating gross body movements (Bouchard & Rossor, 1996). Ideational praxis, the ability to use objects meaningfully, is relatively resistant to deficits caused by the disease process. While dyspraxias with imagined objects appears at the intermediate stage of the disease, only in the moderate to severe stages do difficulties using actual objects appear (Bouchard and Rossor, 1996).

Language. A similar hierarchical decline occurs with respect to language functions, nominal aphasia (inability to name objects), followed by paraphasia of usage (description of object by its use), then semantic paraphasia (naming objects from the same conceptual field), phonemic paraphasias (naming objects from the same sound field), and finally the appearance of deformed words (words that do not have any meaning). Reading, writing, comprehension, and abstraction all follow similar hierarchical pattern (Bouchard & Rossor, 1996)

Gnostic. The decline in gnostic functions (failure to recognize or identify visual stimuli despite intact sensory functions) are felt to be the result of disease in the occipital parietal areas. In the early stages of the disease, visual selection and discrimination are impaired together with an inconstant autotopognosia (inability to identify exact location of touch). At later stages, the digital autotopognosia becomes constant, with impairment of right and left discrimination, a bilateral stereognosia, and finally a corporal autotopognosia and pain asymbolism (inability to react to pain). In a typical case of AD, the

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progression is hierarchical, uniform, and sequential in all the clinical functions (Bouchard & Rossor, 1996).

Heterogeneity of Clinical Findings and Rate of Progression

Considerable individual variation occurs in AD patients, not only in terms of disease duration and the emergence of specific disease features, but also when symptoms appear in the course of the disease. Although memory loss is the most common feature of the disease, approximately 10% of patients experience an atypical onset characterized by deficits of language problems, difficulty in performing tasks, and disorientation or personality disturbance (Katzman, 1986; Stern et al., 1993). The rate of disease progression is also variable with some individuals deteriorating rapidly while others experience little or no decline for years (Mielke, Herholz, Grond, Kessler, & Hess, 1994; Green, Mohs, Schmeidler, Aryan, & Davis, 1993; Katzman, et al., 1988). This heterogeneity among AD patients is seen especially in the early and middle stages of the disease (Joanette, Ska, Poissant, & Beland, 1992; Valdois, Joanette, Poissant, Ska, & Dehaut, 1990) and has led to speculation and debate regarding the possibility of the existence of AD subtypes (Joanette et al., 1992; Martin, 1990; Becker, Huff, & Nebes, 1988; Jorm, 1985; Ritchie & Touchon, 1992).

A variety of factors have been found to be associated with the rate of deterioration. The chief ones are discussed below.

Age and Age at Onset

Until recently, AD was divided into a presenile and senile form based on

biochemical differences (Etienne, Robitaille, Wood, Gauthier, Nair, & Quirion, 1986). Supported by several studies which showed no effects of age on the course of AD, the disease is now considered to encompass both forms (Berg , Miller, & Storandt, 1988; Burns, Jacoby, & Levy, 1991; Drackman, O'Donnell, Lew, & Swearer, 1990; Katzman, et al., 1988, Mayeux, Stern, & Spanton,1985).

A 9-year multi-centre Italian longitudinal study by Bracco et al. (1994) showed that patients with disease onset before or after 65 showed no differences in relative survival or time to reach pre-determined functional and cognitive end-points. Other longitudinal studies also failed to show any association between age at onset of symptom and progression (Burns & Levy, 1992; Katzman et al., 1988; Ortof & Crystal, 1989, Thal,. Grundman & Klauber, 1988). However, there is still disagreement on this question. Early onset (under 65 years) of the disease has been found to be associated with a more rapid rate of progression (Dastoor & Cole, 1988; Heston, Mastri, Anderson & White, 1981; Jacobs et al., 1994; Seltzer & Sherwin, 1983). Haxby, Rafaele, Gillette, Schapiro and Rapoport (1992) observed a faster rate of decline for subjects who were younger than 65 at the onset of the disease, however, when the two subjects in the study with disease onset at age less than 50 and with a faster rate of decline were excluded, the correlation between the age of onset and rate of decline was no longer significant. The discrepancies in results may be due to different sample size, differences in statistical analysis, the use of co-variates like baseline severity, and the use of age at onset as a continuous or dichotomous variable.

The age of onset is generally estimated from information provided by a family member or a caregiver as the patient may no longer be able to accurately recall this information. Hence age of onset may be misclassified due to differences in recall of events by the caregiver, and family variables such as knowledge of the disease and prevalence of age stereotypes which may bias recall. The predictive value of age of onset needs further investigation.

Gender and Duration of Symptoms

Gender has been found neither to influence rate of decline (Katzman et al., 1988; Reisberg, Ferris, & Leon, 1989; Drackman, et al., 1990), nor the length of the disease course (Huff, Growdon, & Corkin, 1987). The only exception is the study by Galasko, Hansen and Katzman (1994) where men had a shorter survival time from symptom onset to death.

Education

The role of education as a predictor for rate of decline has been controversial, and many studies have found education to be a poor predictor of rate of decline (Drachman et al., 1990; Huff, Growdon, & Corkin, 1987; Filley & Brownell, 1985). Bracco et al., (1994) did not find differences in disease progression to be a function of education. Stern, Alexander, Prohovnik and Mayeux (1992) found an inverse relationship between education and parietotemporal perfusion deficit in AD. Katzman (1993) has proposed that higher levels of education enable an individual to develop a cognitive reserve of skill and knowledge that delays the onset of visible clinical symptoms in AD by 4 to 5 years. Highly educated subjects perform well on cognitive screening

tests by developing strategies to cope with memory deficits, which allow them to escape early detection and delay recognition of overt dysfunction until later in the disease process. Studies in Shanghai (Zhang, Katzman, Jin, & Salmon, 1990), Netherlands (Friedland, 1993), and in Canada (CSHA Risk Factors, 1994) support the argument that higher levels of education may be protective against AD. In an incidence study of 593 non-demented individuals aged 60 years and older, listed in a registry of individuals at risk for dementia and followed for 1 to 4 years, Stern et al.(1994) reported that of the 106 individuals who became demented, the findings were consistent with the hypothesis that higher lifetime educational and occupational attainment can influence the incidence of AD, either by reducing ease of detection or by providing a reserve against the early manifestation of AD.

Language

Language is one of the main cognitive processes affected in AD, (McKhann et al., 1984), beginning with loss of verbal fluency and word finding difficulties (Chobor & Brown, 1990). With progression of the disease, the breakdown of language skills, both receptive and expressive, eventually precludes cognitive testing (Lee, 1991). The inability to name correctly early in the disease process predicts a faster rate of decline (Seltzer & Sherwin 1983, Berg & Smith, 1987; Huff , Growdon, & Corkin, 1987; Burns, Jacoby, & Levy, 1991). Even though the validity of evaluating language impairment as a predictor of decline is suspect because of the dependence of cognitive performance on language, the prognostic value of this function is supported by

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many studies. Snowdon et al.(1996) investigated the relationship of linguistic ability in early life to cognitive function with neuropathologically confirmed AD in late life, in a subset of the Nun Study population who had handwritten autobiographies from early life. Findings support a strong negative relationship between cognitive ability in early life, as indicated by linguistic ability and AD in late life.

Psychiatric Symptoms and Extra-Pyramidal Signs (EPS)

Psychiatric symptoms such as depression, hallucinations, delusions, and paranoia appear in about 20 to 40 % of subjects with mild AD (Rubin, 1990). Initial studies had reported that psychiatric symptoms, when present, predicted faster decline (Lopez & Boller, 1990; Stern, Hesdorffer, Sano, & Maueux, 1990), but in these studies the levels of impairment for the psychotic and non-psychotic patients had not been matched. When levels of dementia have been controlled for severity, these results have not been replicated (Drackman et al.1990; Huff, Growdon, & Corkin, 1987). The only exception to the general absence of predictive value for psychiatric symptoms appears to be the findings of Chui, Lyness, Sobel, and Schneider (1994) who found the presence of hallucinations and agitation to be predictive of faster cognitive decline in subjects with mild dementia. Depression does not appear to affect the rate of decline as measured by the Mini-Mental State Exam (MMSE) scores (Lopez & Boller, 1990).

Extra-pyramidal signs (EPS) which include rigidity, motor stiffness, bradykinesia, and resting tremor are more prevalent in the later stages of the

disease (Burns, Jacoby, & Levy, 1991), with 50% being affected by six years post-onset (Chen, Stern, Sano, & Mayeux, 1991). Several studies (Chui, Lyness, Sobel, & Schneider, 1994; Mayeux, Stern, & Spanton 1985; Stern, Albert et al., 1994) show that EPS is one of the most solid prognostic factors for faster decline. Although EPS is observed more frequently in advanced stages of the dementia, it appears to be independent of dementia severity or duration as a predictor of poor prognosis (Chui, Lyness, Sobel, & Schneider 1994, Stern, Albert, & Brandt, 1994). Mayeux, Stern and Spanton (1985) report that EPS early in the dementia predicts faster decline.

Electrophysiological and Radiological Changes

Attempts have also been made to predict clinical decline through radiographic and electrophysiological tests. Studies of the effects of aging on the measurement of brain electroencephalographic activity (EEG) have made it possible to study the changes in cortical electrical activity occurring early in the course of AD. In AD, EEG activity is characterized by a slowing down of the dominant occipital rhythm and more accentuation of theta and delta activity. As the disease progresses, AD patients show increasing activity in the low frequencies (theta, then delta) and less activity in the high frequencies (Muller, Engelsman, Nair, & Robitaille, 1997). In a 4-year longitudinal study of 139 AD patients, no clear link was found between changes on repeated tracings in conventional EEG and disease progression (Rae-Grant & Blume, 1987). The use of evoked potentials is a technique that involves the summation and computer averaging of EEG responses to a simple repetitive stimulus, which is

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either visual, auditory, or somatosensory. P300 (P3) is the late component of evoked potentials and its latency is a sensitive and robust measure of information processing time and subsequent cognitive functioning. Some studies (Goodin & Aminoff, 1986; Pfefferbaum, Wenegrat, & Ford, 1984; St. Clair & Blackburn, 1988) have shown that a delayed latency of a P 300 (P3) wave in patients can discriminate between dementia and control subjects. Ball, Marsh, Schubarth, Brown, and Strandburg (1989) in a 3-year longitudinal study of 18 AD patients and 15 normal controls showed that the rate of increase in P3 latency was significantly greater for the patient group than for the controls. In studies using computerized tomographic (CT) findings to predict cognitive deterioration of AD, baseline ventricular size was not helpful in predicting cognitive status one year following entry into the study (Berg & Smith, 1987; de Leon, George, & Reisberg, 1989). However, Burn and Levy (1992), in their study of 138 subjects with AD, and with repeat CT scans available for 63 subjects showed that both change in ventricular size and increase in cortical atrophy was a statistically significant predictor of cognitive decline over a 12-month period.

The pattern of regional cerebral blood flow (rCBF) in AD is more heterogenous than previously thought and single photon emission computed tomography (SPECT) data are of limited use in modeling disease severity (Greene, Miles, & Hodges, 1996). Though SPECT and positive emission tomography (PET) (Jagust, 1994) greatly increase the specificity of diagnosis of AD and other dementing syndromes, none of these measures at baseline have

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consistent predictive value for future rates of decline in AD. These tests may be useful for following patients in geriatric clinical pharmacology, but do not as yet augment information which is obtainable from sensitive rating scales.

Severity of Dementia

Studies examining rates of progression as a function of initial dementia severity in probable AD have yielded conflicting results, depending on the stage of the disease examined, and on differences in severity when the AD was diagnosed. Subjects in the earlier stages of the disease, as well as in the later stages of the disease, appear to decline more slowly (Brooks, Kraemer, Tanke, and Yesavage, 1993).

Summary

While several authors have described the clinical evolution (Sjogren, Sjogren, & Lindgren, 1952; Sim & Sussman, 1962; Rosen & Mohs, 1982), mortality trends (Heston, Mastri, Anderson, & White, 1981) and the clinical features of proposed sub-categories of AD (Seltzer & Sherwin, 1983), none have provided a detailed psychometric profile of decline of mental functions in AD over time. The relationship between the variability among the clinical features and the rate of cognitive decline in AD has not been established.

Theoretical Model of Cognitive Decline in AD

Hierarchy of Cognitive Development. Piaget (1952, 1960, 1973) developed a conceptual hierarchy of cognitive development: a sensory motor stage, the most primitive stage of development, followed by a preoperative stage that is followed by a stage of concrete operations and finally the stage of

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formal operations. The child's cognitive abilities mature from ego-centered thought where out of sight is out of mind, to sophisticated abstract thought. This model of human development is based on the assumption that all stages of cognitive development are prerequisites for the subsequent stages.

Subsequently, de Ajuriaguerra and colleagues have noted analogies between the losses in AD and reciprocals in normal human development. As dementia progresses, there is a fairly consistent hierarchical decline in mental function (de Ajuriaguerra, Rey, Bellet-Muller, & Tissot, 1964; Cole & Dastoor, 1980; Constantinides & Richard, 1978; Leeds,1960; Matteson, Linton, Barnes, Cleary, & Lichtenstein, 1996; Nolen,1988; Reisberg, Ferris et al., 1985, 1986, 1989; Bickel, 1996). They have demonstrated that functional decline in people with dementia approximates Piaget's developmental stages in reverse: there is a reverse progression on test performance characteristic of each developmental stage. There is some evidence that decline in neuropsychological functions in dements also follows similar hierarchical patterns (Constantinidis & Richard, 1978; Nolen, 1988; Auer, Sclan, Yaffee, & Reisberg, 1994; Sclan, Foster, Reisberg, Franssen & Welkowitz, 1990; Reisberg et al., 1996; Zandi, 1994; Bouchard & Rossor, 1996). For example in the decline of language functions, nominal aphasia usually precedes the appearance of paraphasias, and paraphasia usually precedes the appearance of deformed words (de Ajuriaguerra & Tissot, 1975). The ability to draw a three-dimensional cube is impaired earlier than the ability to draw a square which is impaired before difficulty in drawing a circle. Reisberg (1986) and Reisberg et al (1996), using

the Functional Assessment Staging (FAST) in AD, have demonstrated quite dramatically that the progressive deficits in AD proceed in a relatively consistent pattern across various clinical modalities. Borenstein and Reisberg (1987) in a cross-sectional study found 50 of the 56 patients with AD followed the FAST functional deterioration course precisely, i.e. developmental stages in reverse.

Based on clinical observations, a neurological/neuropsychological model of hierarchical decline of mental functions in AD (Table 1) has been developed by the Geneva School (de Ajuriaguerra, Rey, Bellet-Muller, & Tissot, 1964; Bouchard & Rossnor, 1996). Based on this model, it appears as if AD is a disease that involves, first and most severely, the hippocampal areas of the brain, spreads progressively into the prefrontal and the occipital areas, and then into the parietal areas with sequential and progressive impairment of function.

Longitudinal Studies

Research in the dementia of AD has entered a new phase in which longitudinal studies are given high priority, as there is a growing realization that the progression of dementia cannot be studied through static cross-sectional observations only. Although cross-sectional studies provide valuable information on AD, they do not permit distinctions between patients who manifest different patterns of decline of different abilities and between patients at different stages of the disease. Longitudinal designs are more appropriate for the study of AD because of patient-to-patient variation in the symptomatology of AD and the progressive nature of the disease.

Methodological Problems. There are several methodological problems

Table 1

Examples of Hierarchical Decline of Mental Functions in Alzheimer Disease**

Operative Level (Piaget)	Ideomotor Praxic Functions	Gnostic Functions	Release Phenomemon (Prefrontal Signs)*	Languages	Memory
Formal Operations (Dissociation of Weight, Volume)	Complex hand gestures on imitation	Digitial gnosia	Tactile prehension	Nominal aphasia	Impairment of recent memory
Concrete Operations	Conventional gestures on order	Right/Left discrimination	Proprioceptive prehension	Paraphasia of usage	Impairment of remote memory
Pre-Operative	Conventional gestures on imitation	Bilateral stereognosis	Oro-visual reflex	Semantic or phonemic paraphasia	Impairment of registration
Sensory-motor	Imitation of body postures		Oro-tactile reflex	Deformed words	

* = Reversed hierarchy

** = No relationship between hierarchies

Cole, M.G. (1980). Clinical aspects of Alzheimer's Disease. St. Mary's Hospital Medical Bulletin, 291-297.

(LaRue, 1987) in doing longitudinal studies. The appropriate choice of precise measures is the most important. Tools are needed that will permit the evaluation of the disease's progression throughout the entire span, i.e. tests sensitive enough to detect decline at all stages of the disease. Floor effects in tests can have dramatic consequences by underestimating the rate of decline. Psychomotor tests may be limited by insensitivity of instruments on floor effects, e.g. a patient may score 0 (maximum impairment) on the MMSE and hence be no longer "testable," yet continue to progress in dementia severity. By addressing patient performance in many domains over a specified time period, global clinical scales can incorporate day-to-day fluctuation which can impair single test performance. They are less subject to floor and ceiling restrictions by tracing disease progression.

Attrition through death is a serious problem in longitudinal studies of the demented elderly. However, as the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) report (Morris et al., 1993) mentions periods less than a year are of limited value to study disease progression and optimum reliability can be inferred for change in cognitive status only when the observation period is greater than 1 year.

Annual Rate of Change (ARC). Progressive cognitive decline is a hallmark of AD and precise information is needed to quantify the decline over time. This can be obtained by administering global measures of cognitive or functional disease severity at regular intervals over the course of the disease to arrive at the annual rate of change (ARC) in scores for that particular measure.

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Several methods have been used for estimating the annual rate of change (ARC) in test scores for individual subjects, namely the difference between the first and last available score on a cognitive measure, divided by the number of years between the two assessments (Yesavage, Poulson, & Sheikh 1988; Katzman et al., 1988; Salmon, Thal, & Butters, 1990). This unrestricted 2-point estimate is quite simple, and it assumes a linear change over time, does not utilize all data points, and may be affected by ceiling and floor effects. The least-squares regression method is used to estimate the annual rate change by calculating the slope of the linear regression of the cognitive measure on years from the baseline assessment for each subject. This method uses all intermediate data points and assumes linearity as well (Stern, Mohs et al., 1992). Not all AD patients show exactly the same pattern of deficits, nor do they all decline at the same rate. The two methods described above assume that decline is linear throughout the disease, however Galasko, Corey-Bloom, and Thal (1991) suggest that decline is not uniformly linear. Haxby, Rafffaele, Gillette, Schapiro and Rapoport (1992) propose a bilinear regression model of decline assuming an initial plateau phase followed by a decline phase. The trilinear regression model of decline (Brooks, Kramer, Tanke & Yesavage, 1993) accounts for two plateaux, one at the onset of the disease where no perceptible decline occurs followed by a period when decline occurs at varying rates for different patients, and the second plateau in the final stages of the disease where no perceptible decline occurs. Teri, McCurry, Edland, Kukull and Larson (1995) have pointed out that the longitudinal

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modeling of disease progression is more difficult for diseases in which time of onset is uncertain. A realistic model to measure the ARC should take into account òbetween subjectó variability, plateaux during the course of the illness, uncertainty in age of onset, and age as a continuous variable (Belisle, Joseph et al., 1996).

Decline in the cognitive functions in AD can be predicted by looking at the Annual Rate of Change (ARC). There are, however, important differences in the mean ARC values observed in different studies using the same scale, which may reflect the variations in the study samples and/or methods. Longitudinal data exists for (LaRue, 1987; Katzman et al., 1988), the Blessed Information Memory Concentration Test (BIMC), (Blessed, Tomlinson & Roth, 1988), Mini-Mental State Exam (MMSE), (Folstein, Folstein, & McHugh 1975), and Alzheimer Disease Assessment Scale (ADAS) (Rosen, Mohs, & Davies, 1984), Hierarchic Dementia Scale (HDS) (Cole and Dastoor, 1983).

BIMC or mBIMC. Lucca, Comelli, Tettamanti, Tiraboschi and Spagnoli (1993), Katzman et al., (1988), Thal et al., (1988), Ortof and Crystal (1989), Salmon, Thal and Butters (1990), and Stern, Mohs et al., (1992) have all looked at the annual rate of change in their prognostic studies, and have estimates ranging from 3.2 (9.6 %) to 5.5 (15.1 %) points of the actual score on the BIMC or mBIMC.

MMSE. Using the MMSE, a number of studies have reported rates of change in AD from 6% (Becker, Huff, Nebes, Holland, & Boller, 1988) to 15% of the actual score (Mortimer, Ebbitt, Jun, & Finch, 1992) over a 1-year period

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where the rate of change is affected by the severity of cognitive impairment. Subjects in the mild stage (high scores) of dementia showed the lowest ARC of 6% (Becker, Huff, Nebes, Holland, & Boller, 1988), subjects in the severe stage of dementia had the highest ARC ranging from 15% to 12% per year (Yesavage, Poulson, & Sheikh, 1988), and those with intermediate levels of dementia showed intermediate ARC of 8% per year (Uhlman & Larson, 1986; Salmon, Thal, & Butters, 1990; Teri, Hughes, & Larson, 1990).

Tinklenberg, Brooks and Tanke (1990), in examining the patterns of relations among the items of MMSE in both cross-sectional and longitudinal data, found the factor structure of the average rates of change of items to be quite different. Cross-sectional data yielded a 2-factor solution that accounted for 62 % of the variance: the first factor may relate to general functioning and the second to concentration ability. The longitudinal data yielded a 5-factor solution that accounted for 75% of the variance and is composed of factors pertaining to orientation, obeying commands, language repetition, language expression, and recall. Galasko, Corey-Bloom, and Thal (1991) mention that most studies using "global" measures such as the MMSE provide a rather coarse estimate of the overall rate of decline. The MMSE was designed to be a brief screening test, not a thorough neuropsychological test battery, and hence it is not suitable to determine ARC in longitudinal studies.

ADAS. In a study by Kramer-Ginsberg & Mohs (1988) using ADAS in a 1-year follow-up study of 60 patients, an ARC of 9.32 (13.3%) points on the scale was estimated and in another study an ARC of 8.28 (11.82%) points was

estimated on 30 patients (Yesavage, Poulson, & Sheikh, 1988). Even though the ARC for all different subscales of ADAS was fairly consistent, the SDs were large, roughly equal to the means, indicating substantial individual variability.

HDS. The Hierarchic Dementia Scale has been used by Dastoor and Cole (1986) to study the 48-month course of 13 patients with AD (6 males, 7 females, aged 47 to 88 years, mean age 66.2 years). Their intellectual deterioration had been obvious to their families for less than 3 years. At the time of initial contact, all the subjects were autonomous and living in the community with their families. There were no language or praxic impairments, but they all had mild deficits of memory and mild disorientation of time. The mean initial scores for this sample on all subscales was higher than the mean scores by validation sample for the HDS, which was a high functioning group. The 13 subjects were assessed initially on the HDS and every 12 months for a period of 48 months (Figure 1). For the purpose of comparing individual functioning profiles, total scores for each subject were plotted as a percentage of the initial (100%) score. As Figure 1 indicates, the total scale score declined consistently and progressively over time but with considerable inter-individual variations in patterns of decline. Three subjects demonstrated severe decline after 24 months and 5 subjects a mild decline after 48 months.

Because of reports (Heston, Mastri, Anderson, & White, 1981) suggesting that severity of the illness depends upon the age when the symptoms of AD become noticeable, that is before the age of 65 or after the age of 65, the 13 subjects were divided into two groups: an early onset group (n = 7) whose

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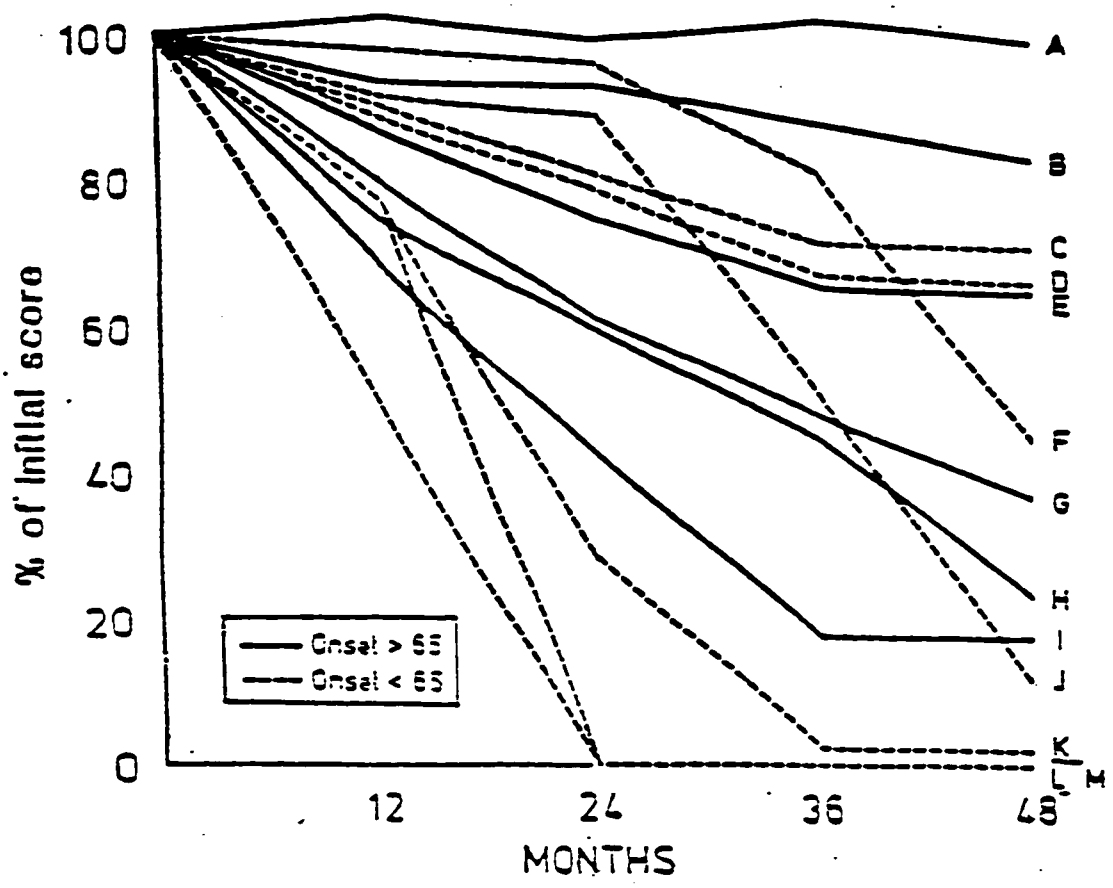
Figure 1. Course of Alzheimer's Disease on the HDS in a study of 13 subjects assessed over 48 months.

mean age at initial contact was 56.1 years (range 47-64) and a late onset group (n = 6) whose mean age at initial contact was 78.0 years (range 69-88 years).

The mean scores of each subscale are plotted in Appendes A-E. The pattern of decline between the age groups was dissimilar over time and the rate of decline in the younger age group was steeper with more severe dementia at 48 months. The early onset group at initial contact was globally functioning at a higher level, but their rate of decline at 48 months was steeper resulting in more severe dementia. Looking at individual clinical features in the pilot study, language functions do not appear to show differences in decline between the two age groups over the 48-month period except denomination where the early onset group declined more rapidly. For praxic functioning and for higher cognitive functioning, i.e. similarities and calculation, the early onset group appear to show steeper decline at 48 months. For memory functions over the 48-month period, the dramatic change was seen in the under 65 age group for remote memory but not for recent memory and registration (Dastoor & Cole, 1988).

Using this measure of assessment, a degree of heterogeneity in broad categories of degeneration of functions can be seen that seems to be related to the age of onset. More severe manifestations of functions appear with a rapid decline when dementia occurs in the under 65 age group, i.e. the dementing process is more pronounced in the early onset group. However, in both groups clinically noticeable change in function appears 24 months after the onset of dementia suggesting that this point is critical for the development of long-term

care plans for the AD patient.

Roth (1980) and Naguib and Levy (1982) claim that the appearance of focal parietal signs early in the disease, after 1 or 2 years of symptom onset, indicates rapid progression even in older patients. The results of praxic, gnostic, and language functions of naming and writing substantiated this finding in the pilot study. This is in contrast to amnestic functions where the rate and severity of decline in the two groups are parallel after 24 months. Patients not showing marked changes at this period are likely to continue on a slower and more gradual course irrespective of their age group.

The difficulty of developing annual rate of change (ARC) becomes clear, as the results of this study of 13 patients indicates that the slope of decline is different for the different age groups and for the different functions.

In another longitudinal study using the HDS as a measure of cognitive function, Gold, Dastoor and Zieren (1996) were able to show a significant decrease in the total HDS score and in all the 20 subscale scores over a 2 year period in 78 community- dwelling people with dementia. Initial scores on the HDS significantly predicted patient institutionalization or death.

The HDS was used in a random stratified sample of 507 community-dwelling patients of general practitioners in Mannheim, Germany, to assess the ability of the general practitioners (GP) to detect dementia in their over 65-year-old patients (Cooper, Bickel, & Schaufele, 1992). Based on the assessment of cognitive impairment of the HDS, the GPs achieved 92% sensitivity and 76% specificity identifying the mild and severe cases. The profiles of the 20 subscale

scores clearly differentiated the mildly demented from the clinically demented, with the clinically demented having a reduced level of performance on all subtests, whereas the mildly demented were impaired chiefly on recent memory and similarities.

In a 2-year prospective study, using the HDS to detect an early dementing process and its progression, Cooper, Bickel and Schaufele (1996) were able to demonstrate that after a mean interval of 27 months, a repeat assessment of the HDS on 507 community-dwelling elderly people, revealed that all the new cases of clinical dementia had arisen in persons with mild cognitive deficits at initial assessment. Furthermore a highly significant interaction between severity and time occured. In other words, the greater the degree of impairment at first assessment, the larger the subsequent drop in the total HDS score.

In a predictive study (Hamel et al.1990) to examine caregiver reaction to aggressive behaviour and the association between aggression and cognitive functioning in 213 community-based demented elderly, the level of cognitive deterioration as measured by the HDS did not predict aggression.

Variability Over Time. Salmon, Thal, and Butters (1990) in a 2 year study of 55 community dwelling patients with AD investigating the ARC on the scores on BIMC, and MMSE found a change of 3.24 (9.81 %) points on the BIMC, 2.8 points (9.33 %) for MMSE. The degree of decline in the second year was greater on both the scales than in the first year but this finding was not statistically significant. The ARC for the first year did not predict decline for the

second year, implying that decline over time is not uniform.

This variability can be explained by three hypotheses: (a) AD does not progress uniformly between subjects and within subjects, (b) some subjects may "plateau" early or cognitive functioning does not show a linear pattern of decline, or (c) test-retest variability adds uncertainty to the ARC calculations.

Researchers have generally adopted a linear model to describe the progression of AD, although some (Galasko, Corey-Bloom, & Thal, 1991) suggest decline across time is not uniformly linear. Patients in a longitudinal study are not all at the same stage of the disease. The linear model is incapable of distinguishing between lack of decline due to a less impaired stage of the disease or lack of decline due to a very impaired stage. As well, some tests are insensitive to decline at extremes (i.e. at high or low levels) and do not reflect differences in the rate of progression of the disease itself.

Purpose of the Study and Hypothesis

Understanding the natural history of AD and the factors influencing its progression is essential to provide patients and their families with an accurate prediction of the disease course, to respond to demands for medical and social services and to design studies for the evaluation of potential treatments to slow the progression of the disease.

Because of the progressive nature of the disease, deficits in cognitive functioning increase over time, but with considerable variability in the decline process. The patient, the family and the physician need to know the expected change per year in the patient's overall cognitive functioning and the risk factors

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that can affect the rate of decline every year, in order to plan for the future, to anticipate financial demands, and to provide increasing levels of care.

The wide variability and heterogeneity among individuals in the rate of progression of the disease has prompted researchers to try to identify factors that may be useful in better allowing the prediction of the disease course in individual patients or a group of patients. Although numerous demographic and clinical features have been investigated, the prognostic importance of most remains controversial (Galasko, Corey-Bloom, & Thal, 1991; Drachman et al., 1990; Mortimer et al., 1992). Lack of agreement in the research literature may be, in part, due to methodological diversity, limitations of prognostic studies, and insensitivity of measuring instruments across the range of impairment.

The overall objective of this research is to develop a model of decline in dementia using the Hierarchic Dementia Scale.

Hypothesis #1

Early age of symptom onset will predict faster rate of decline on the total HDS score.

Based on pilot data, it is hypothesized that the cognitive functions as measured by the total HDS score of patients with AD will decline faster per each six-month period in people whose onset of symptoms is below the age of 65, than in those whose onset of symptoms is above the age of 65.

Hypothesis #2

The rates of decline will vary across the seven cognitive domains as measured by the HDS, with age of symptom onset affecting the decline

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specially in language and praxic functions.

Based on the findings of heterogeneity of decline in cognitive functions, it is hypothesized that the rate of cognitive decline, per each six-month period, will differ on the seven domains of HDS: language, praxic, memory, concentration, calculation, perception, and orientation, and those whose symptom onset is under the age of 65 will decline faster than those whose symptom onset is over age 65.

Hypothesis #3

Scores in the domains of language and praxic functions will predict the rate of decline.

Empirical findings report (Burns, Jacoby, & Levy, 1991; Yesavage, Brooks, Taylor & Tinklenberg, 1993) that once clinical dementia has been reached, performance on language and praxic functions are of great value in charting the disease's progression. Due to the clinical relevance of these functions in the daily life of the patient and the caregiver, it is hypothesized that low composite scores on language function subscales of denomination, comprehension, reading, writing, and abstraction as well as low composite scores on praxic function subscales of ideomotor praxic, ideational praxic, constructional praxic, and graphic praxic functions will predict a faster annual rate of decline on total HDS scores.

Hypothesis #4

A model of cognitive decline based on risk factors will predict the annual rate of change in AD.

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As low levels of education (Stern, Gurland, Tatemichi et al., 1994; Canadian Study of Health and Aging, 1994), younger age at disease onset (Jacobs, Sano, Marder et al. 1994), gender (Van Duijin, 1996) and place of residence have been identified as risk factors, it is hypothesized that a model of decline based on the risk factors associated with AD will predict the annual rate of decline in cognitive functions as measured by the total HDS score and by the composite scores of the subscales of the HDS in the domain of language and praxic functions.

Methods and Procedures

Subjects

The subjects were recruited from the Memory Clinic of the Douglas Hospital with one subject being recruited from St. Mary's Hospital. These centres receive ongoing referrals from community resources, viz: GPs in the community, and local community centers (CLSCs) provide diagnostic assessments of cognitive and memory impairment of elderly people. The subjects undergo a comprehensive psychogeriatric assessment, comprising neurological and physical examinations, laboratory investigations, including routine blood work, urine analysis, electrocardiogram, neuropsychological, and psychiatric evaluations. In addition, all subjects have electroencephalographic (EEG) recordings and computerized tomodensitographic (CT) tracings. The subjects as well as their family members are interviewed by multiple health care professionals who then meet as a group to discuss the problem and arrive at a diagnosis.

Between February 1992 and June 1994, 103 subjects were referred. After assessment, 84 subjects who met the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Associations (ADRDA) criteria (Appendix F) and who scored 14 or less on the Geriatric Depression Scale were enrolled in the study. Nine subjects scoring above 14 were excluded. DSM III R criteria for primary degenerative dementia (290.0-290.4 on Axis I) was also applied (Appendixes G and H). Subjects with physical illnesses, generally associated

with increasing age, were not excluded from the study. Cardiovascular problems requiring cardiovascular medications were one of the more frequent complaints. None of the subjects were enrolled in cognition enhancing drug trials at Douglas Hospital.

There were 29 men and 55 women between the ages of 52 to 92 years in the study sample. The mean age of symptom onset was estimated by subtracting the duration of symptoms, provided by the family at initial contact, from the present chronological age. Both Anglophone and Francophone subjects participated in the study.

From Time 1 to Time 4, 84, 83, 76, and 60 subjects were available for assessment. Of the 84 subjects enrolled in the study, 4 died, 8 refused to continue, 7 moved and contact was lost, and 5 became too physically ill to continue. There was a drop-out rate of 28.5% (n = 24).

Chi-square analyses between the subset which completed the four assessments (n = 60) and those who did not complete the four assessments (n = 24) showed no significant differences of gender, marital status, type of primary caregiver, place of residence, except for significant differences in the cardiovascular status ($x2$ = 5.38, df 1, p <.05) with more cardiovascular problems in those who dropped out of the study.

T-tests for independent samples on the demographic and clinical variables between the two subsets showed no significant differences in age of symptom onset, duration of the illness, education, level of depression or level of severity of dementia. The initial level of severity of dementia on the total HDS

and on the MMSE was mild. An analysis of variance yielded no significant effects of age and gender on the level of severity. Table 2 shows means and standard deviations of the demographic variables for the total sample, as well as for the subset of 60 subjects who completed the four assessments and for the subset of the 24 subjects who did not complete the study.

As age of symptom onset is an important variable in the study, the demographic and clinical variables of the total sample (n = 84) are divided into two groups, those with onset of illness under 65 years of age and those with onset over 65 years of age (Table 3 for means and standard deviations). A chi-square analysis between the two groups showed a significant gender difference ($x2$ = 6.34, df 1, p <.01) with more females in the above 65 age group, and a significant difference in marital status ($x2$ = 11.69, df 3, p < .001) with a higher percentage of people married in the under 65 age group. A significant difference existed in the type of primary caregiver ($x2$ =12.89, df 4, p < .01) with more spouses as the primary care-giver in the under 65 age group. The over 65 age group consumed significantly more cardiovascular medications ($x2$ = 3.88, df 1, p < .05). No significant difference occurred between the groups in the place of residence.

A two-tailed t-test showed no significant differences between the two age groups for education and the clinical variables of severity of symptoms. At baseline, the early onset group was cognitively more impaired than the late onset group as measured by the HDS, but the difference was not significant on the total and subscale scores. As expected, early onset subjects were

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Table 2

Distribution of Patients' Characteristics of Total Sample (N = 84), Sample with 4 Assessments (N = 60), and Sample Which Did Not Complete 4 Assessments (N = 24)

	N = 84	N = 60	N = 24
DEMOGRAPHIC & SOCIAL CHARACTERISTICS			
Age (Mean ± SD) range 52-92	73.99 ± 8.97	74.02 ± 9.50	73.92 ± 7.65
Male	34.5% (N = 29) 69.90 ± 8.37	33.3% (N = 20) 70.60 ± 9.28	37.5% (N = 9) 68.33 ± 6.04
Female	65.5% (N = 55) 76.15 ± 8.58	66.7% (N = 40) 75.73 ± 9.26	62.5% (N= 15) 77.27 ± 6.57
Education			
(in years ± SD)	8.00 ± 3.80	7.72 ± 3.62	8.54 ± 4.23
Marital Status			
Married	45.2% (N = 38)	48.3% (N = 29)	37.5% (N = 9)
Widowed	39.3% (N = 33)	36.7% (N = 22)	45.8% (N = 11)
Single	11.9% (N = 10)	10.0% (N = 6)	16.7% (N = 4)
Other	3.6% (N = 3)	5.0% (N = 3)	
Place of Residence			
Home	81%	76.6%	91.7%
Institution	19%	23.3%	8.4%
Primary Care-Giver			
Spouse	39.3%	41.7%	33.3%
Daughter	22.6%	20.0%	29.2%
Son	8.3%	8.3%	8.3%
Other	28.6%	30.0%	25.0%
None	1.2%		4.2%

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Table 2 continued ....

CLINICAL FEATURES

Duration of Illness (months ±SD)	29.33 ± 20.01	27.76 ± 20.20	33.17 ± 19.40
Age at Onset (years ±)	71.37 ± 9.12	71.49 ± 9.67	71.08 ± 7.78
Physical Illness			
Cardiovascular	59.5%	51.7%	79.2%*
Metabolic	32.1%	30.0%	37.5%
Skeletal Illness	27.4%	28.3%	25.0%
Medication			
Cardiovascular	36.9%	33.3%	45.8%
Anti-depressants	20.2%	21.7%	16.7%
Dx on Axis I (DSM IIIR) (290.0 - 2904)	87.9%	86.3%	87.5%
Hierarchic Dementia Scale	170.00 ± 26.31	171.29 ± 21.29	165.71 ± 30.56
MMSE	21.26 ± 4.74	21.46 ± 4.72	20.74 ± 4.73
Geriatric Depression Scale	10.33 ± 6.16	10.15 ± 6.33	10.80 ± 5.83

Note: X^2 p < .05

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Table 3

Distribution of Patients' Characteristics of the Total Sample (N = 84) Divided into Early Onset (N = 21) and Late Onset (N = 63)

	Early Onset < 65 (N = 21)	Late Onset > 65 (N = 63)
DEMOGRAPHIC & SOCIAL CHARACTERISTICS		
Age (Mean + SD)	62.00 ± 6.94	77.98 ± 5.22**
Male	57.1% (N = 12), 61.58 ± 4.46	27.0% (N = 17), 75.76 ± 4.52
Female	42.9% (N = 9), 62.56 ± 9.61	73.0% (N = 46), 78.80 ± 5.26**
Education (in years + SD)	8.38 ± 4.61	7.81 ± 3.52
Marital Status		
Married	80.8%	38.1%**
Widowed	14.3%	47.6%
Single	4.8%	14.3%
Place of Residence		
Home	90.5%	77.8%
Institution	9.5%	22.2%
Primary Caregiver		
Spouse	71.4%	28.6%*
Daughter	14.3%	25.4%
Son		11.1%
Other	14.3%	33.3%

continued ....

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Table 3 continued.....

Duration of Illness (month ± SD)	30.05 ± 22.72	29.10 ± 19.26
Age at Onset (years ± SD)	58.15 ± 4.39	75.57 ± 5.46
Physical Illness		
Cardiovascular	46.7%	63.5%
Metabolic	33.3%	31.7%
Skeletal	19.0%	30.2%
Medication		
Cardiovascular	19.0%	42.9%*
Antidepressants	19.0%	20.6%
Dx on Axis (DSM IIIR)		
290.0 - 290.4	95.2%	85.3%
Time I Baseline		
HDS Total	164.85 ± 34.48	171.71 ± 19.89
MMSE	20.85 ± 5.70	21.39 ± 4.63
Geriatric Depression Scale	11.17 ± 5.82	10.05 ± 6.30

* X^2 p < .01   ** X^2 p < .001

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significantly younger than the late onset subjects at baseline (t = -11.16, p < .001) as well as age at first symptom onset.(t = -12.98, p < .001) .

When the subset that completed the four assessments (n = 60) was divided into 2 age groups, those with onset of illness under and over 65 years of age, no chi square differences existed in gender, marital status, and primary caregiver (Table 4). The older age group exhibited significantly more problems in cardiovascular status ($x2$ = 5.00 df 1, p < .05) and the consumption of cardiovascular medication ($x2$ = 6.4, df 1, p<.05). The t-test showed no significant differences in education, duration of illness, and level of severity of dementia, except for a significant difference in the two age groups for the age of symptom onset (t = -12.93, df 57, p < .001).

Measures

Two measures were used to assess Cognitive Functions and Depression.

The Hierarchic Dementia Scale (HDS) (Cole & Dastoor, 1983). The measurement of cognitive impairment (Constantinides & Richard, 1978; Nolen, 1988; Reisberg et al., 1985; Matteson et al., 1996) in dementia, which reflects a hierarchical organization and decline of mental functions, has resulted in the development of the Hierarchic Dementia Scale (Cole & Dastoor, 1980, 1983). The HDS has 20 subscales measuring nine categories of cognitive functions including orientation, memory, praxic, language, cognition, motor, gnostic, looking, and concentration abilities. The first step in the development of the HDS was the compilation of a list of mental functions in which hierarchies might

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Table 4

Distribution of Patients' Characteristics of the Total Sample (N = 60) Who Completed All Four Assessments Divided Into

Early-Onset (N = 15) and Late Onset (N = 45) Groups

	Early Onset < 65 (N = 15)	Late Onset > 65 (N = 45)
DEMOGRAPHIC & SOCIAL CHARACTERISTICS		
Age (Mean + SD)	61.07 ± 7.89	78.33 ± 5.01**
Male	46.6% (n=7), 59.57 ± 4.19	28.9% (n=13), 76.53 ± 4.29
Female	53.4% (n=8), 62.38 ± 10.25	71.1% (n=32), 79.06 ± 5.16
Education (in years + SD)	8.13 ± 4.19	7.58 ± 3.45
Marital Status		
Married	73.3% (n=11)	40.0%** (n=18)
Widowed	13.3% (n=12)	44.4% (n=20)
Single	6.7% (n=1)	11.1% (n=5)
Place of Residence		
Home	86.7% (n=13)	73.3% (n=33)
Institution	13.3% (n=2)	20.0% (n=9)
Primary Caregiver		
Spouse	66.7% (n=10)	33.3% (n=15)
Daughter	13.3% (n=2)	22.2% (n=10)

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Table 4 continued.....

Son	-	11.1% (n=5)
Other	20.0% (n=3)	33.3% (n=15)
Duration of Illness (month ± SD)	30.05 ± 24.64	26.91 ± 18.85
Age at Onset (years ± SD)	56.64 ± 4.33	76.11 ± 5.08**
Physical Illness		
Cardiovascular	26.7% (n=4)	60.0%* (n=27)
Metabolic	33.3% (n=5)	28.9% (n=13)
Skeletal	20.0% (n=3)	31.1% (n=14)
Medication		
Cardiovascular	6.7% (n=1)	42.2%* (n=19)
Antidepressants	20.0% (n=3)	22.2% (n=10)
Dx on Axis (DSM IIIR)		
290.0 - 290.4	93.3%	84.1%
Time I Baseline		
HDS Total	161.92 ± 36.26	174.20 ± 13.15
MMSE	21.43 ± 5.26	21.47 ± 4.67
Geriatric Depression Scale	11.31 ± 6.14	9.78 ± 6.42

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* X² p < .01   ** X² p < .001

be constructed. From an initial list of 45 commonly observed functions, 25 were excluded because they contributed little information or were functions for which it seemed impossible to construct hierarchies. The final list includes 20 functions: orienting, prefrontal, ideomotor, looking, ideational, denomination, comprehension, (verbal and written) registration, gnosis, reading, orientation, construction, concentration, calculation, drawing, motor, remote memory, writing, similarities, and recent memory.

Based on clinical experience, a list of 5 or 10 items was prepared and ranked in order of decreasing difficulty for each of the 20 functions. These tentative hierarchic subscales were then administered to 30 patients with differing levels of cognitive decline, ranging from minimally demented to those with severe dementia. Correct responses to each item in each hierarchy were recorded and a frequency distribution of correct responses to the items within each hierarchy was determined. An item analysis for each hierarchy was performed to determine the rank order of item difficulty. Each item carries a score of 1 or 2 points, depending on the number of items in the hierarchy. The maximum score for each subscale is 10 and the maximum score for the entire scale is 200 indicating no impairment. By utilizing a subscale for each function, the HDS uses a "staging" scheme.

The examiner starts the test at an item estimated to be appropriate to the functional level of the patient. This procedure rapidly determines the patient's highest level of performance for each cognitive function. Examiners are instructed to attempt to maximize patient performance by repeating instructions,

demonstrating what is required and praising correct responses. To determine the reliability and concurrent validity of the HDS (Cole & Dastoor, 1980), 50 consecutively admitted patients with senile dementia, Alzheimer type (N = 35) or multi-infarct dementia (N = 15) were examined. The group included 18 males and 32 females ranging in age from 65-97 years. Each patient was assessed independently by two trained examiners using the HDS and two other established dementia scales: The Blessed Dementia Scale (Blessed, Tomlinson, & Roth, 1968) and the Crichton Geriatric Behavioural Scale (Robinson, 1961).

Fifteen days following the initial assessment each patient was reassessed independently with the HDS by the same two examiners. The inter-rater reliability between first and second assessment was reported to be .89 for the total HDS scale and between 0.54 - 0.87 for the subscales. The test-retest reliability was reported as .84. Coefficient alpha, a measure of the internal consistency of the scale, was reported to be .97. Correlation of the ratings on the HDS with ratings on the Blessed and Crichton scales permitted an estimate of the concurrent validity of the scale. A concurrent validity correlation of .72 ($\underline{p}$ <.001) is reported for the Blessed Scale and .74 ($\underline{p}$ <.001) for the Crichton Scale (Cole & Dastoor, 1983).

Bickel (1996), Demonet and colleagues (1990), Ronnberg and Ericsson (1994), and Gold, Dastoor, and Zieren (1996) replicated the reliability and validity of the scale and obtained results similar to the standardization sample. Bickell (1996) reported correlations of .94 with the MMSE, and Ronnberg and

Ericsson (1994) reported correlations of -.71 with the CDR (Clinical Dementia Rating). Gold , Dastoor, and Zieren (1996) reported a correlation of 0.86 with MMSE. A factor analysis of the HDS (Gold, Dastoor, & Zieren 1996) indicated that 72 % of the variance was explained by two factors. The first factor which accounted for 64.2 % of the variance in HDS scores, loads highly on the looking, ideomotor, orienting, motor, reading, prefrontal, gnosis, denomination, comprehension, writing, drawing, and ideational subscales. The second factor, which accounted for 7.8 % of the variance, loads highly on the similarities, concentration, calculation, registration, orientation, remote memory, recent memory, and construction subscales.

The HDS is useful in measuring cognitive impairment in both mild and severe stages of dementia. The hierarchical structure and items of a wide range of difficulty controls for both floor and ceiling effects (Bickel, 1996). In a study using the HDS to assess the ability of general practitioners, to detect dementia and cognitive impairment in the elderly, Cooper, Bickel, and Schaufele (1992) reported that clinically and mildly demented groups are clearly differentiated both from one another and from the remainder of the sample. Bickel (1996) reported that the pattern of HDS scores clearly distinguished mild dementia from minimal or no dementia, and the severely demented from moderately demented. Ronnberg and Ericsson (1994) in a study on 50 subjects reported that scores of 23 to 55 on the HDS could be obtained even for those subjects who scored 0 on the MMSE, thus permitting a differentiation of their ability.

<u>Geriatric Depression Scale (Yesavage & Brink, 1983)</u>. Since depression can impair cognitive functioning and since there is a high prevalence of depressive symptoms in AD patients, a diagnosis of depression must be excluded in making a clinical diagnosis of AD. To eliminate the possibility of depression as a potential confounding factor, the geriatric depression scale was administered at initial assessment.

This 30-item simple- to-administer scale was designed (Yesavage & Brink 1983) to measure the intensity of depression in elderly subjects. One hundred questions believed to have potential for distinguishing elderly depressives from people with no depression were selected. They covered a wide variety of topics including somatic and cognitive complaints, motivation, future/past orientation, self-image, losses, agitation, obsessive traits, and mood. A yes/no format was used for easy administration. Thirty items that correlated best with the total score were chosen for inclusion in the Geriatric Depression Scale. Of the 30 items included in the final scale, 20 indicate the presence of depression when answered positively and 10 others indicated depression when answered negatively. A cut-off score of 14 yields a rate of 80% sensitivity and 100% specificity. The scale is a reliable and valid instrument (alpha coefficient of 0.94 for internal consistency, a correlation of 0.85 for test-retest reliability).

<u>Procedure</u>

A two-step diagnosis of dementia was made (a) according to the criteria developed by NINCDS/ADRDA for possible, probable or definite AD and (b)

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according to the criteria developed for the revised third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM IIIR) for primary degenerative disease (1987). The two sets of criteria are generally compatible, however, since the NINCDS/ADRDA criteria were specially developed for research, they are followed in this study. To eliminate the possibility of depression as a potential confounding factor at initial cognitive assessment, the Geriatric Depression Scale (Yesavage & Brinks, 1983) was administered by the examiner (Appendixes I & J). Subjects (8.9%) scoring 14 and above on the Geriatric Depression Scale were excluded.

Before enrolling in the study, informed consent (Appendixes K& L) was obtained from the subject or from the mandator by methods approved by the hospital ethics board. Subjects were assessed four times over an 18 month period at 6 month intervals. On repeat assessments, subjects were tested at the same place as at the base-line assessment, except in cases where the subject had been placed in a residence in the intervening period (n = 30 at Time 3, and n = 48 at Time 4). The scores at baseline assessment were entered as Time 1, and subsequent assessments were Time 2 (6 months), Time 3 (12 months), and Time 4 (18 months) after the initial assessment. The number of subjects available for assessment at Time 1 to Time 4 were 84, 83, 76, and 60 respectively.

Each session lasted 1 to 2 hours depending upon the level of impairment of the subject. In the beginning of the session, the subject and the caregiver were interviewed together to obtain general background information and history

of the illness. As attrition due to mortality is a major problem for any longitudinal study in dementia, the duration of the study was limited to 18 months.

Initial Assessment

Baseline personal data collected included: age, gender, reason and source of referral, symptoms (including psychiatric and behavioural complaints), age at symptom onset, duration of illness, medical history, concurrent illnesses, and family history of dementia. Additional demographic variables for which data were collected were: education, primary occupation, marital status, living arrangements, financial status, and caregiver data.

Base-line neuropsychological and functional assessments were carried out at the place of residence of the subject. The subject was alone with the examiner for cognitive assessments. All subjects were administered the HDS (Appendixes M & N) together with a battery of cognitive neuropsychological measures, which were not used for this study and will not be discussed.

Longitudinal Assessment

At each of the follow-up visits conducted at six month intervals, brief medical and pharmacological status were noted and the HDS was re-administered.

Results

<u>Plan of Analysis</u>

The analysis of results is based on the 60 subjects (20 men and 40 women) who completed the four assessments. The outcome measures on the HDS are represented by:

Total HDS score	(maximum score 200)
Language domain represented by the subscales of reading, writing, comprehension, denomination, and abstraction	(maximum score 50)
Praxic domain represented by the subscales of drawing, construction, ideomotor, and ideational task performance	(maximum score 40)
Memory domain represented by the subscales of registration, recent memory, and remote memory	(maximum score 30)
Perception (gnosis)	(maximum score 10)
Calculation	(maximum score 10)
Concentration	(maximum score 10)
Orientation	(maximum score 10)

A variety of techniques were used in analyzing the data:

(1)   Pearson product moment correlations to establish strength of associations between the dependent variables of total and subscale scores of HDS, and the indicator variables, i.e. the co-variates of age, gender, education, and place of residence at each of the four time periods.

(2)   A repeated measures analysis of variance (ANOVA) on two age groups to compare their scores on total HDS for four time periods.

(3)   A repeated measures multivariate analysis of variance (MANOVA) to compare the scores of the two age groups on seven outcome measures at four time periods.

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(4)   A model of decline in Alzheimer's disease using the Bayesian

Information Criterion (BIC) for model selection, built to predict rate of

decline, as measured by the HDS through (a) three repeated measures

ANOVA on language functions, praxic functions, and total HDS scores

predicting coefficient (rate) of decline, while controlling for age of

symptom onset, education, gender, and residence (b) a repeated

measures ANOVA used as a regression model to assess longitudinal

changes and develop the annual rate of change, while adjusting for time

of onset of the disease.

Preliminary Analysis

Raw data inspection began with a check for univariate outliers in the

sample for each of the four time periods. Data entry accuracy and the

distribution of all variables were investigated using the SPSS list wise

frequency analysis for valid observations. The minimum and maximum value for

each of the 20 subscales of the HDS and all the other demographic variables

were inspected for plausibility. No cases were rejected for out-of-range factor

values.

Descriptive statistics for ungrouped data using means, standard

deviations and frequency distribution for study variables were computed.

Percentages were calculated for dichotomous data and means were calculated

for continuous data. Chi-squares were calculated for dichotomous data and t-

tests for continuous data. Correlations among the variables were also

inspected and were found to be of moderate ranges, so as not to suggest

singularity or multicollinearity among the study variables.

Assumptions of General Linear Model Regression

Regression analyses requires a case to variable ratio of at least 4:1 (Tabachnick & Fidell, 1989). In the regressions presented in this study, the ratio is 15:1 (60 respondents to 4 IVs, i.e. age of onset, gender, education, and place of residence) well above the minimum requirements for regression. Tests for significance of regression coefficients were computed with 95% confidence intervals. Several regression models were tested for predicting decline in total HDS score, as well as decline in language and praxic domains. Using the BIC selection criteria, the restricted maximum likelihood model (REML) was chosen as the best predicting model.

Assumptions of MANOVA

Cochrane's C and Bartlett-Box F were found to be non-significant for univariate homogeneity of variance. Inspection of the Mahalanobis distance measure for the MANOVA failed to reveal multivariate outliers. Box's M test for all dependent variables was found to be non-significant, indicating homogeneity of the variance-covariance matrices.

Correlations Among Study Variables

In order to assess the stability over time of the seven dependent variables, a series of bivariate correlations were computed to assess the degree of relationship at each of the four time periods among the orientation, language functions, memory functions, praxic functions, concentration, perception, calculation, the total HDS score and the covariatess of age, gender, education,

and place of residence (Tables 5, 6, 7, 8).

All subscale scores showed a general pattern of significant intercorrelations at all four time periods. Correlation coefficients between the subscales ranged from .20 to .87 at Time 1 to .59 to .90 at Time 4. The scores on the language and praxic subscales were significantly correlated for all time periods. Correlation coefficients between the subscales and the total HDS score were significantly high for all time periods with the language score being most highly correlated with the total HDS score ranging from .87 at Time 1 to .94 at Time 4.

The correlation coefficients between the covariates of age of symptom onset, gender, education, place of residence, and the HDS subscale scores and the total HDS score were below .5 for all time periods. Age of symptom onset correlated significantly with language subscale for all time periods with correlation coefficients ranging from .28 to .42 and with praxis subscales for Time 2 ($r = .37$, $p < .01$) and Time 4 ($r = .37$, $p < .05$). Age of symptom onset correlated significantly with the total HDS score only at Time 2 ($r = .30$, $p < .01$). Gender did not correlate significantly with any of the subscales, except with orientation at Time 1 ($r = -.25$, $p < .05$). The place of residence did not correlate significantly with any of the subscales except with orientation ($r = .32$, $p < .01$) and language subscales ($r = .23$, $p < .01$) at Time 2. Education correlated significantly with all the subscales for Time 1, Time 2, and Time 3 except for the subscales of perception and calculation.

Table 5

Correlation Matrix at Time 1 among 7 HDS Subscale Scores, the Total HDS Score, and the Covariates: Age, Sex,

Education, and Place Assessed

	Orientation	Language	Memory	Praxis	Concentration	Perception	Calculation	Total
Orientation								
Language	.42***							
Memory	.55***	.45***						
Praxis	.33**	.76***	.36**					
Concentration	.43***	.57***	.42***	.61***				
Perception	.20	.60***	.39**	.72***	.45***			
Calculation	.33**	.50***	.23	.67***	.59***	.53***		
Total	.58***	.87***	.71***	.83***	.69***	.70***	.66***	
Age	-.08	.28*	-.08	.20	.17	.27*	.06	.20
Sex	-.25*	.11	-.22	-.06	-.07	-.01	-.18	-.11
Education	.27*	.36**	.27*	.28*	.34**	.12	.24	.36**
Residence	.16	.22	.12	.22	-.04	.21	.19	.24

* p < .05   ** p < .01   *** p < .001

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Table 6

Correlation Matrix at Time 2 among 7 HDS Subscale Scores, the Total HDS Score, and the Covariates: Age, Sex,
Education, and Place Assessed

	Orientation	Language	Memory	Praxis	Concentration	Perception	Calculation	Total
Orientation								
Language	.57***							
Memory	.73***	.53***						
Praxis	.54***	.75***	.58***					
Concentration	.68***	.76***	.68***	.71***				
Perception	.49***	.54***	.53***	.62***	.49***			
Calculation	.68***	.67***	.59***	.75***	.69***	.62***		
Total	.76***	.88***	.80***	.88***	.85***	.70***	.81***	
Age	.07	.42***	-.02	.37**	.32**	.10	.28*	.30**
Sex	-.17	.07	-.12	-.09	-.07	-.13	-.18	-.09
Education	.28*	.27*	.33*	.20	.28*	.23	.20	.32**
Residence	.32**	.23**	.18	.08	-.21	.09	.15	.21

* p < .05   ** p < .01   *** p < .001

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Table 7

Correlation Matrix at Time 3 among 7 HDS Subscale Socres, the Total HDS Score, and the Covariates: Age, Sex, Education, and Place Assessed

	Orientation	Language	Memory	Praxis	Concentration	Perception	Calculation	Total
Orientation								
Language	.43***							
Memory	.62***	.58***						
Praxis	.31**	.77***	.56***					
Concentration	.54***	.78***	.72***	.77***				
Perception	.39**	.79***	.58***	.75***	.71***			
Calculation	.45***	.66***	.60***	.74***	.75***	.62***		
Total	.56***	.91***	.79***	.89***	.89***	.82***	.80***	
Age	.10	.36**	-.003	.21	.27*	.10	.18	.25
Sex	-.10	.09	-.14	-.04	-.01	.07	-.19	-.04
Education	.27*	.37**	.27*	.28*	.34**	.12	.24	.36**
Residence	.16	.22	.12	.22	-.04	.21	.19	.24

* $p < .05$ ** $p < .01$ *** $p < .001$

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Table 8

Correlation Matrix at Time 4 among 7 HDS Subscale Scores, the total HDS Score, and the Covariates: Age, Sex, Education, and Place Assessed

	Orientation	Language	Memory	Praxis	Concentration	Perception	Calculation	Total
Orientation								
Language	.66***							
Memory	.70***	.67***						
Praxis	.55***	.90***	.58***					
Concentration	.75***	.87***	.79***	.77***				
Perception	.59***	.89***	.62***	.89***	.79***			
Calculation	.61***	.81***	.66***	.76***	.79***	.75***		
Total	.67***	.94***	.75***	.93***	.86***	.82***	.83***	
Age	.15	.37**	.05	.31*	.26*	.23	.24	.24
Sex	-.09	.10	-.05	.02	.02	.05	-.07	.03
Education	.13	.24	.31*	.14	.16	.16	.21	.20
Residence	.11	.06	-.05	-.06	-.03	-.05	-.13	-.04

* $p < .05$ ** $p < .01$ *** $p < .001$

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Analysis of Group Differences and Longitudinal Changes

Group Differences. The mean and standard deviations of the total HDS score and the scores for domains of language functions, praxis functions, memory functions, perception, concentration, calculation, and orientation for the sixty subjects who completed all four assessments are presented in Table 9. From the first assessment (Time 1) to the last assessment (Time 4), there was a 15% drop in total HDS score, 33% change in the language functions, 14.13% change in the domain of praxic functions, 50% change in the domain of memory functions, 18% in concentration score, 13% in perception score, 24% in the calculation score, and 20.2% change in the orientation score. Differences in scores between Time 1 and Time 4 were significant on all outcome measures for the whole group.

In this study, a repeated measures design was considered appropriate as the aim was to examine a single sample change in the cognitive functions as measured by the HDS over four assessment periods. As the same patient is tested in each time period, differences between time periods cannot be attributed to differences between groups of patients. In dementia, where large individual differences exist among patients, the removal of individual differences from the analysis is important.

Repeated Measure of Analysis of Variance (RM ANOVA) on Total HDS. In order to assess the degree of change in mean levels over time on the total HDS score in the two age groups (under 65 and over 65), a 2 (Age groups) x 4 (Time) Repeated Measures Univariate Analysis of Variance (RM ANOVA) was

Table 9

Mean and SD of HDS Total Score and for 7 Subscale Scores (N = 60) from Time 1 to Time 4 (at Inital Assessement and at Each of the Three Time Periods at 6 Month Intervals)

HDS Subscales	Time 1		Time 2		Time 3		Time 4		% change
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Orientation	7.18	2.32	6.47	2.39	6.10	2.16	5.73	2.56	20.20%
Language	44.83	7.51	43.29	8.83	41.52	10.20	30.03	13.45	33.00%
Memory	18.38	6.57	14.68	6.23	13.38	7.39	11.93	7.36	50.00%
Praxic	36.82	4.28	35.41	6.16	34.20	8.24	31.70	11.20	14.13%
Concentration	7.83	2.23	7.34	2.41	7.23	2.49	6.43	2.76	18.00%
Perception	9.33	1.24	8.93	1.51	8.43	1.95	8.08	2.66	13.00%
Calculation	8.47	2.49	7.42	3.05	6.87	3.52	6.47	3.84	24.00%
Total HDS Score	171.72	21.37	162.02	26.69	155.00	33.49	145.85	43.11	15.0%

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computed. The analysis showed a significant main effect of Age $F(1, 57) =$ 6.31, $p < .01$ for the total HDS score for the two age groups, with the younger age group having lower scores. The main effect of Time $F(1, 57) = 29.77$, $p < .001$ on the total HDS score was significant with differences being significant by univariate F between Time 1 and Time 2 only. The interaction between the two age groups and time was not significant. The younger age group scored lower on the total HDS and continued to score lower at Time 2. However this difference between the scores on the total HDS score for two age groups was not maintained at Time 3 (12 months) and Time 4 (18 months).

Repeated Measure Multivariate Analysis of Variance (RM MANOVA) on Seven Outcome Measures. In order to assess the degree of change in mean levels over time in the two age groups (under 65 years and over 65 years) on the seven subscales of the HDS (language functions, praxic functions, memory, perception, calculation, concentration, orientation), a 2 (Age groups) x 4 (Time) Repeated Measures Multivariate Analysis of Variance (RM MANOVA) was computed.

The Wilks' Lambda criterion showed a significant multivariate main effect of Age, $F(7, 51) = 2.44$, $p<.05$, and Time, $F(21, 37) = 1.9$, $p < .05$ on the seven outcome measures but not on the interaction of Age with Time, $F(21, 37) = 1.33$. The univariate tests for scores on the language functions $F(1,57) = 9.40$, $p <.01$, praxic functions $F(1,57) = 7.45$, $p < .01$, concentration $F(1,57) = 5.92$, $p < .05$, calculation $F(1,57) = 5.34$, $p<.05$, showed significant differences for the two age groups, with the younger age group having lower scores. Differences in

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the scores between the two groups on orientation, memory functions and perception were not significant. Univariate tests for the main effect of Time showed significant differences ($p < .001$) between Time 1 and Time 2, on all subscales, language functions $F_{(1, 57)} = 24.09$, $p < .001$, praxic functions $F_{(1,57)} = 19.71$, $p < .001$, memory $F_{(1, 57)} = 37.11$, $p < .001$, perception $F_{(1,57)} = 17.21$, $p < .001$, concentration $F_{(1,57)} = 20.96$, $p < .001$, calculation $F_{(1,57)} = 19.06$, $p < .001$. and orientation $F_{(1,57)} = 17.42$, $p < .001$. Although the multivariate effect for interaction between Age and Time was not significant, the univariate interaction of Age by Time showed significant differences for language function scores $F_{(1,57)} = 4.62$, $p < .05$, at Time 2 from baseline, and for praxic function scores $F_{(1,57)} = 6.20$, $p < .01$ at Time 4.

Model of Decline in Alzheimer Disease to Predict Rate of Decline

To allow for the prediction of cognitive decline in AD, a model taking into account covariates was built. Several types of matrices were tried and the selection of the best-fitting model for the data was based on the Bayesian Information Criterion (BIC). This criterion is used as an approximation when assessing which of several regression models is best supported by the data. A Bayes Factor provides the probability of obtaining the data set given that one model (e.g. model 1) is correct, divided by the same probability for another model (say model 2). If model 1 fits the data better, then the Bayes Factor will be greater than 1. An exact Bayes Factor requires input of prior distributions for every unknown parameter in the model, but this requirement is removed by the BIC approximation. BIC represents an asymptotic Bayes Factor, where the prior

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information is negligible compared to the information in the data. This is similar to using likelihood ratio tests, which are also based on asymptotic approximations. The use of BIC for model selection is preferred to the usual backwards and forwards model selection techniques, since it avoids over-fitting of the model to the data, which is often associated with the latter techniques. The final model selected was independent of the order in which the models are tested (Kass & Raftery 1995).

Several covariates and combinations of covariates were entered in the model selection analysis. Treating age of symptom onset, years of education, and severity of cognitive impairment as continuous variables and dummy coding the categorical covariates of gender (female = 0, male = 1), place of residence (home = 0, hospital/institution = 1), a Repeated Measures Analysis of Variance (RM ANOVA) was used as a Regression Model to analyze the data longitudinally. The age of onset of the disease was estimated by subtracting the variable "duration of symptoms in years" from the variable "the age of entry in the study."

Longitudinal analysis to measure rate of decline was calculated by two styles of regression analysis: RM ANOVA by restricted maximum likelihood method (REML) and least squares regression analysis (slope analysis). These two methods are different modeling strategies for the same data set, making use of all of the data. The RM ANOVA uses the covariance structure of the data to develop a model. It allows the investigation of the effects of various possible independent variables, but it does not allow for adjustment for time of symptom

onset. The least square regression analysis assumes independence of the errors within subjects to arrive at a single slope for each subject. This method allows the scores for each subject to be òback-projectedó to age of symptom onset (Time 0). The outcome measures of language functions, praxic functions and the total HDS scores are regressed from Time 0. Although both these analyses are similar, additional information is obtained from each.

Longitudinal Analysis

Repeated Measures Analysis of Variance (RM ANOVA) by Restricted Maximum Likelihood Method (REML) on Total HDS Scores, Language, and Praxic Scores. The decline in scores on the subscales measuring language and praxic functions and the total HDS were found to be most significant on MANOVA, and since these measures are clinically most meaningful in maintaining the quality of life, further RM ANOVA using the regression approach for analysis of variance by restricted maximum likelihood method (REML) were done on these three dependent measures. Of all the covariates and combinations that were tried, the best covariates as selected by BIC for building a model of decline in the total HDS scores and for language and praxic functions were, age at symptom onset, education, and place of residence. And from these, the age of symptom onset was the best predictor of decline. In the best model parameter, gender was not significant and therefore not included in the model.

Language Functions Score. For the domain of language functions, the covariate age of symptom onset when entered in the model, predicted a

significant coefficient of decline of .36 points (t = 4.30, df 55, p < .001) on the language subscales for every 6 months (.72 points annually), the covariate education when entered in the model contributed a significant coefficient of decline of .81 points (t = 3.73, df 55, p < .001) on the language subscales for each period of 6 months (1.62 points annually). The covariate place of residence when entered in the model, contributed a significant coefficient of decline of 3.88 points (t = 2.09, df 55, p < .05) for every 6 months on the language subscales (7.76 points annually). Gender did not contribute significantly to decline on the language subscales (Table 10).

Praxic Functions. For the domain of praxic functions, the covariate age of symptom onset when entered in the model, predicted a significant coefficient of decline of .13 points (t = 2.51, df 57, p < .01) for every 6 months on the praxic subscales (.26 points annually). The covariates gender, education and place of residence did not contribute in the prediction of decline (Table 11).

Total HDS Score. For the total HDS score, the covariate age of symptom onset predicted a significant coefficient of decline of .80 points (t = 3.25, df 54, p<.001) for every six months on the total HDS score (1.60 points annually). The covariate education contributed a significant coefficient of decline of 2.28 points (t = 3.70 df 54, p < .001) on the total HDS score for every 6 months period (4.56 points annually), and place of residence contributed a significant coefficient of decline of 12.07 points (t = 5.31, df 54 p < .05) (24.14 points annually). The covariate gender did not contribute significantly to decline (Table 12).

Table 10

Repeated Measures Analysis of Variance (ANOVA) for Predictors of Rate of Change in Language Functions for

60 Subjects

Parameter	Estimate	SE	T	df	p
Intercept	11.26	6.42	1.75	55	
Age of symptom onset	0.36	0.08	4.30	55	.001**
Education	0.81	0.22	3.73	55	.001**
Place of Residence (Hopsital)	3.88	1.86	2.09	55	.05*

* p < .05   ** p < .001

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Table 11

Repeated Measures Analysis of Variance (ANOVA) for Predictors of Rate of Change in Praxic Functions for 60

Subjects

Parameter	Estimate	SE	T	df	p
Intercept	28.35	3.65	7.77	57	0.0001**
Age of symptom onset	0.13	0.05	2.51	57	0.01*

* p <.01   ** p < .001

Table 12

Repeated Measures Analysis of Variance (ANOVA) for Predictors of Rate of Change in Total HDS Score

Parameter	Estimate	SE	T	df	p
Intercept	91.72	19.38	4.73	54	.001**
Age of symptom onset	0.80	0.24	3.25	54	.001**
Sex	6.37	4.99	1.27	54	ns
Education	2.29	0.62	3.70	54	.001**
Place of Residence (Hospital)	12.07	5.31	2.27	54	.05*

* $p < .05$ ** $p < .001$

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Regression Analysis Through Estimate Of Slope (Annual rate of change)

Since the observed total HDS and subscale scores tend to decline linearly and cluster about a straight line, a least squares regression line was fitted to the data. Again using the BIC Model selection criteria, a general linear model was constructed to assess the contribution of the covariates in predicting decline in language and praxic functions of the HDS.

Least Squares Regression Analysis (Slope Analysis). To estimate the annual rate of cognitive change as measured by the HDS, a least squares regression analysis was used to calculate the slope of three dependent variables (DVs): the total HDS score, and the scores for language functions (a composite score of the five language subscales), and the scores for praxic functions (a composite score of four praxic subscales) for each of the 60 subjects who completed the four assessments. For each subject, the slope of change over time, expressed in terms of the 6-month follow-up intervals, was calculated.

As the level of severity of each of the subject who entered the study was different, all the subjects needed to be brought to a common starting point (the intercept) in the disease process and an estimated age of onset of the disease was calculated for each subject. This was done by subtracting the variable "estimated duration of symptom onset" from "the age of entry into the study" and then "back projecting" the scores of Time 1 to Time O, i.e. the time of disease onset. The scores in the domains of language functions and praxic functions and the total HDS score were then regressed on time from this estimated age of

onset to obtain the predicted score at Time 0. The regression coefficient or the slope from this predicted score at Time 0 gave the rate of change in the language, praxic, and total HDS score.

For each subject, the estimated slope of change over time, expressed in terms of the 6-month follow-up intervals, was calculated. The estimated slopes of each of the 60 subjects were used to compose histograms. Box and whisker plots were drawn to visualize the distribution of scores in the covariates (gender and place of residence), and in the dependent variables (language and praxic functions). The upper and lower boundaries of the boxes are the upper and lower quartiles. The box length is the interquartile distance and the box contains the middle 50% of the observed values. Scatter plots were drawn to assess the relationships between the covariates age at symptom onset and education, with language and praxic functions. Table 13 shows the mean value changes in dependent variables of language, praxic, and total HDS scores for 6-month unit changes in the independent variable of Time.

The regression analysis to estimate the annual rate of cognitive change in the total HDS score, as well as scores in the domain of language and praxic functions, show that the covariate, age of symptom onset, again predicted decline significantly in language functions (Table 14) and in praxic functions (Table 15). The covariates, education and place of residence (hospitalization), did not contribute significantly to the estimate of slope of decline on praxic functions. None of the covariates contributed to estimate of slope of decline in the total HDS score.

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Table 13

Means and SDs for Three Slopes of Language, Praxic, Total HDS

Variables	N	Mean	Std Dev.	Minimum	Maximum
Language	60	-1.94	3.48	-13.30	2.50
Praxic	60	-1.66	3.12	-13.50	2.20
Total HDS	60	-8.54	12.04	-48.70	7.00

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Table 14

Best Model Parameter Estimates for Regression Coefficient (B) of Dependent Variable Language from

Estimated Time of Onset

Dependant Variable	Mean	SD	T	df	P
Language Intercept	-1.05	2.20	-0.48	1	NS
Language Time 0	-0.12	0.01	-10.20	1	<.001
Age Symptom Onset	0.08	0.03	2.85	1	<.01

Table 15

Best Model Parameter Estimates for Regression Coefficient (B) of Dependent Variable Praxic from

Estimated Time of Onset

Dependant Variable	Mean	SD	T	df	P
Praxic Intercept	-1.05	2.20	6.79	1	<.001
Praxic Time 0	-0.12	0.01	-10.37	1	<.001
Age Symptom Onset	0.08	0.03	2.20	1	<.05

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The estimated slopes for the domains of language and praxic functions are shown in histograms (Figures 2 and 3), which are composed of single observations (slope) for each subject. The frequency of observations, across age, at each of the possible slope values is drawn on the Y axis with the value of the slope given on the X axis. The majority of the subjects tend to be centered at 0 slope. Figures 4, 5, and 6 are histograms that present visually the age distribution of the sample (n = 60), the distribution of age at first symptom onset, the distribution of the education level of the sample. The Y axis on each of the histograms shows the frequency of occurrence.

The scatter plot for the estimated slope for age at first symptom onset and language functions is shown in Figure 7, and the scatter plot for the estimated slope for age at symptom onset and praxic functions is shown in Figure 8. The X axis indicates the age in years, and the Y axis the value of the slope. The flatter slopes for the older age groups indicate slower decline in language and praxic functions.

The scatter plot for the estimated slope for education and language is shown in Figure 9 and the scatter plot for the estimated slope for education and praxic functions is shown in Figure 10, where the X axis indicates education levels in years and the Y axis the value of the slope. In Figure 11 the scatter plot shows the relationship between the slopes for language functions on the Y axis and praxic functions on the X axis. There are no significant differences of the slope estimates for language and praxic functions. Even though the praxic functions slope is higher than the language
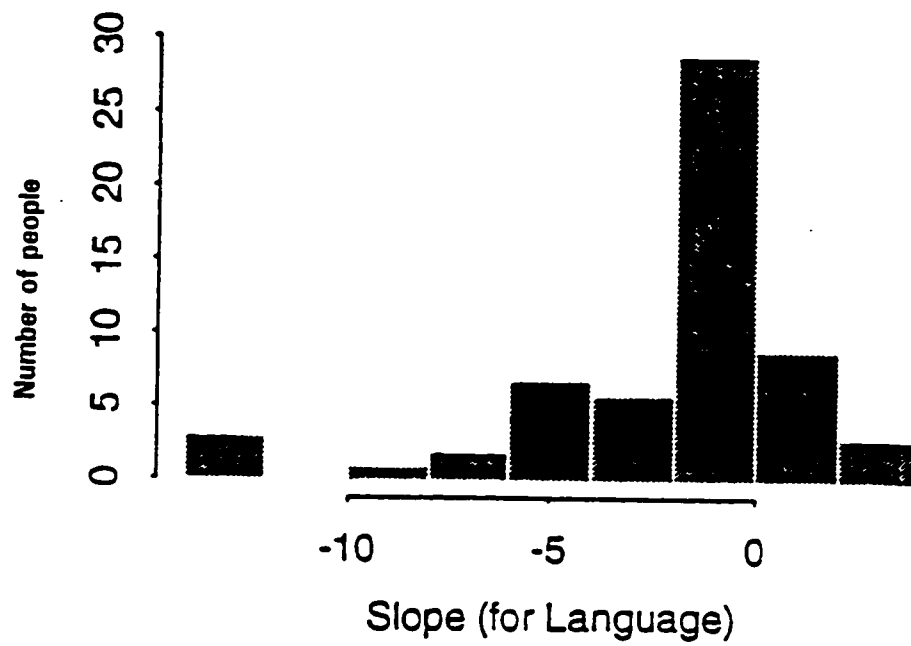
Figure2. Histogram of estimated slope of decline for language functions based on single observations from each subject (N = 60).
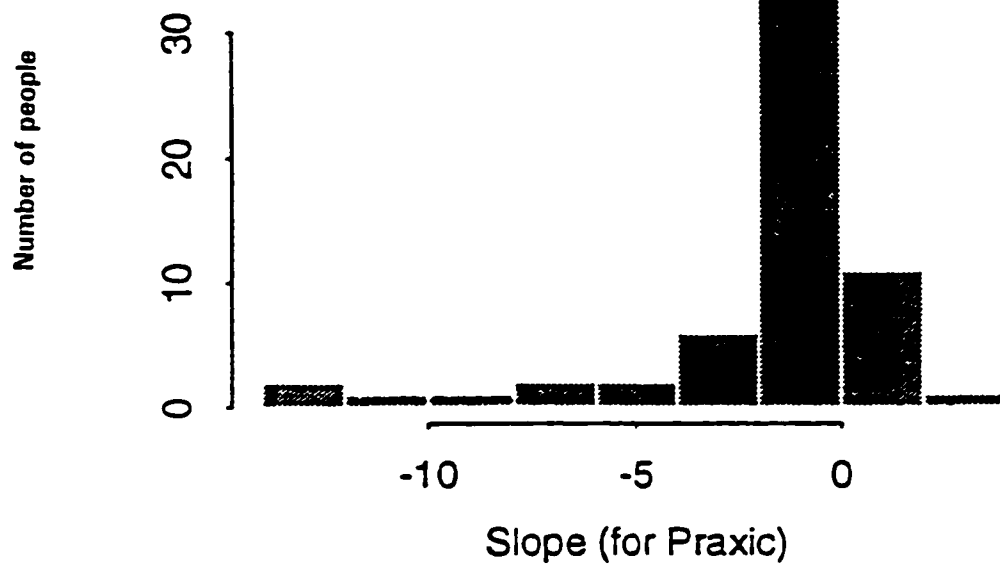
Figure 3. Histogram of estimated slope of decline for praxic functions based on single observations from each subject (N = 60).
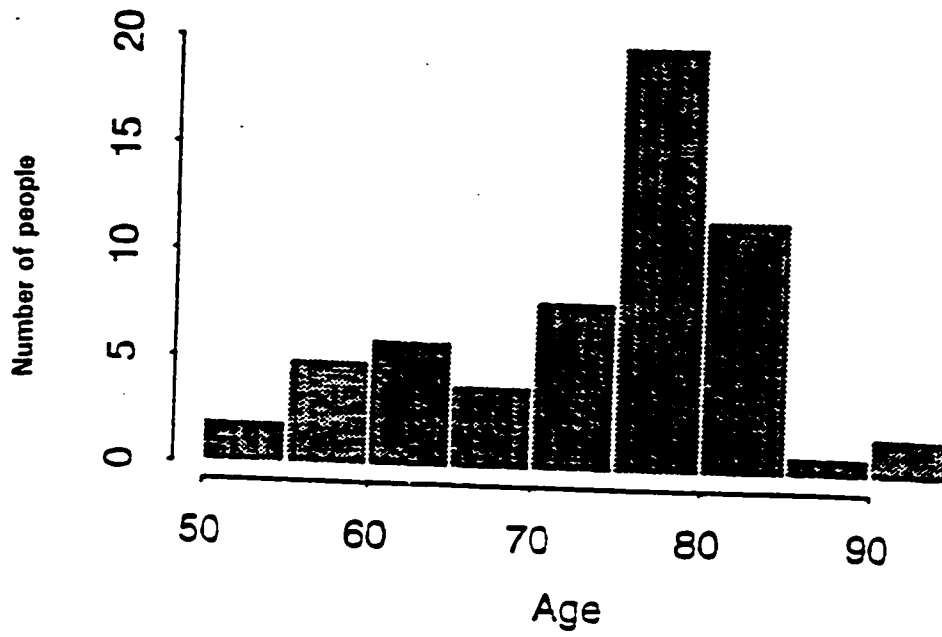
<u>Figure 4</u>. Histogram of age distribution based on single observations from each subject (N = 60).
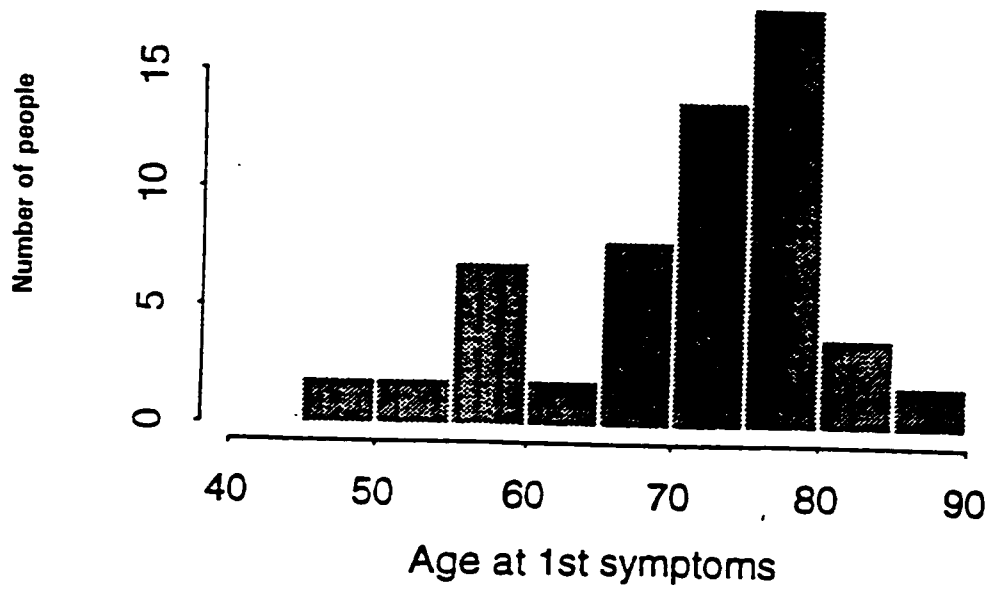
Figure 5. Histogram of age at first symptom onset distribution based on single observations from each subject (N = 60).
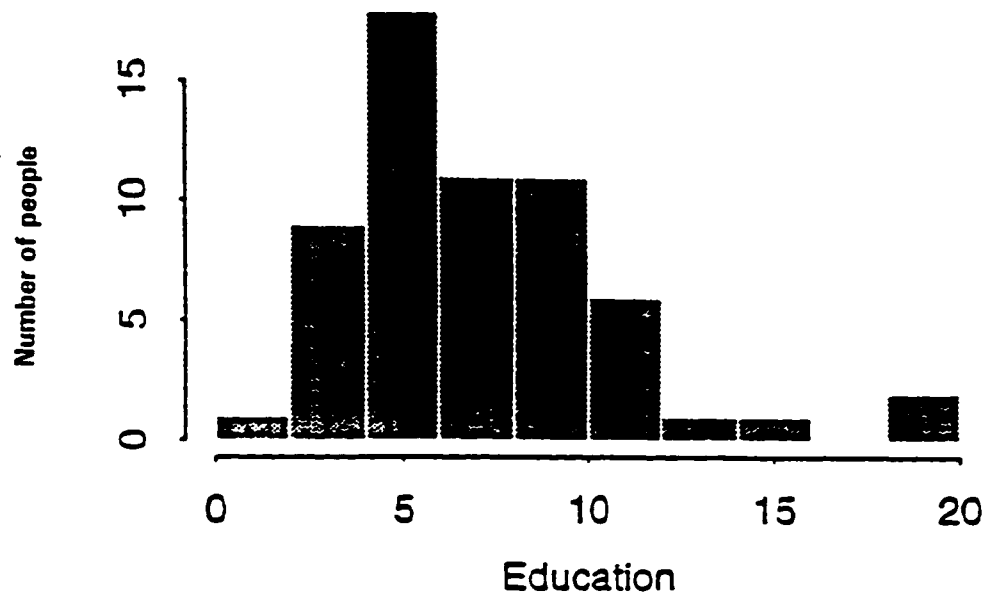
Figure 6. Histogram of distribution of education level based on single observations from each subject (N = 60).
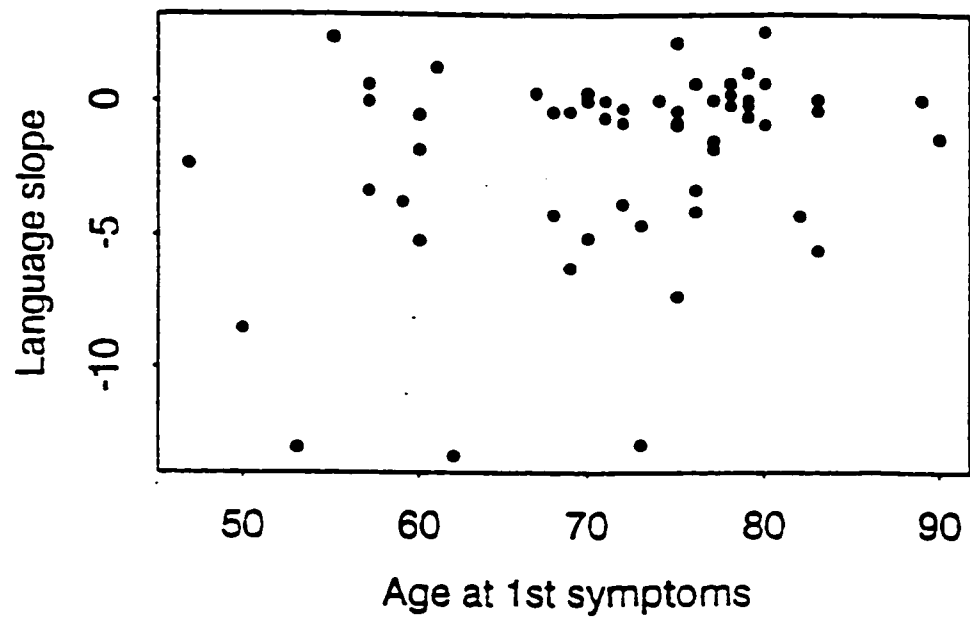
Figure 7. Scatter plot for estimated slope of age at 1st symptom onset on language functions.
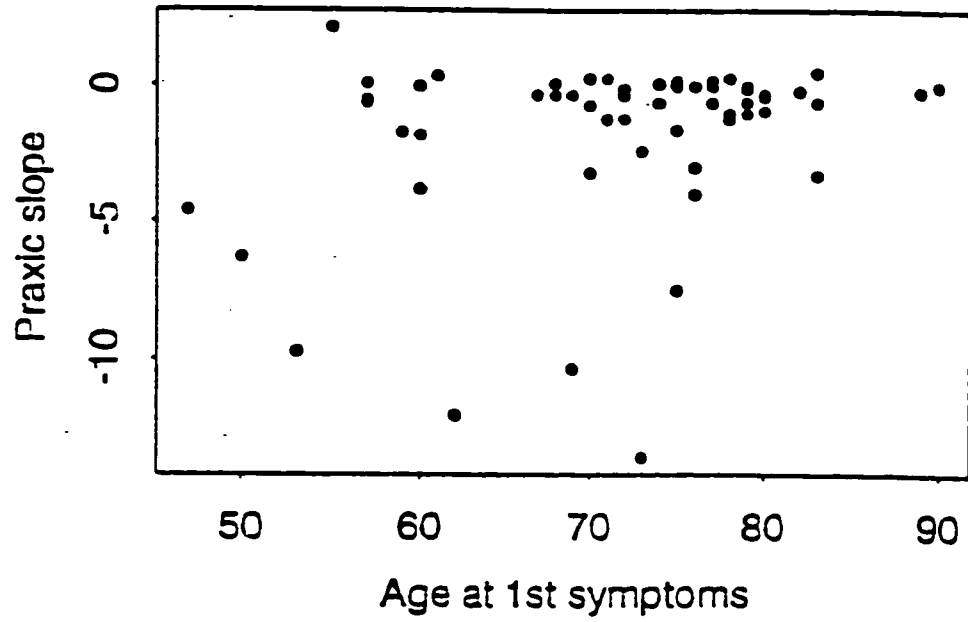
Figure 8. Scatter plot for estimated slope of age at 1st symptom onset on praxic functions.
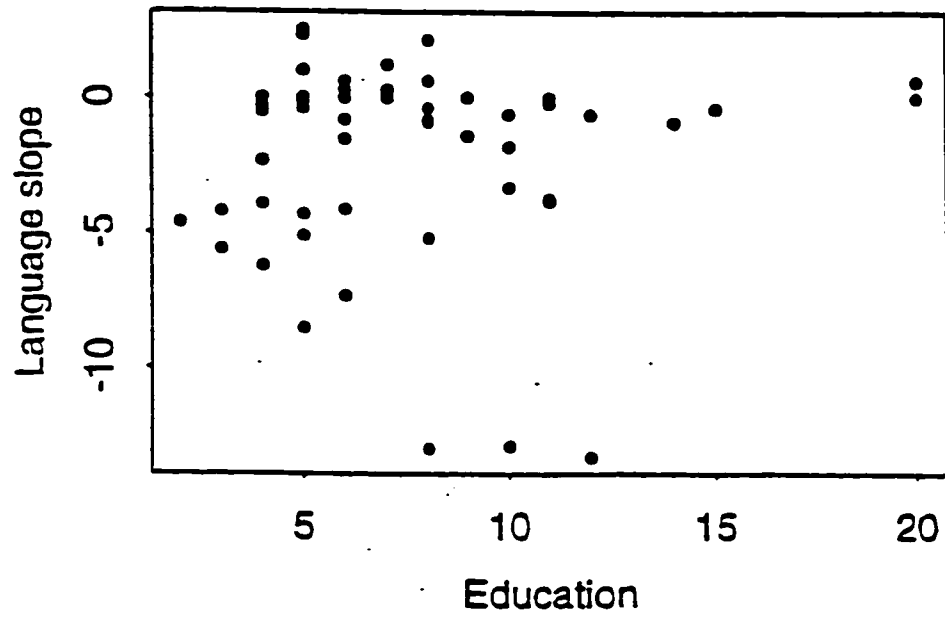
Figure 9. Scatter plot for estimated slope of education on language functions.
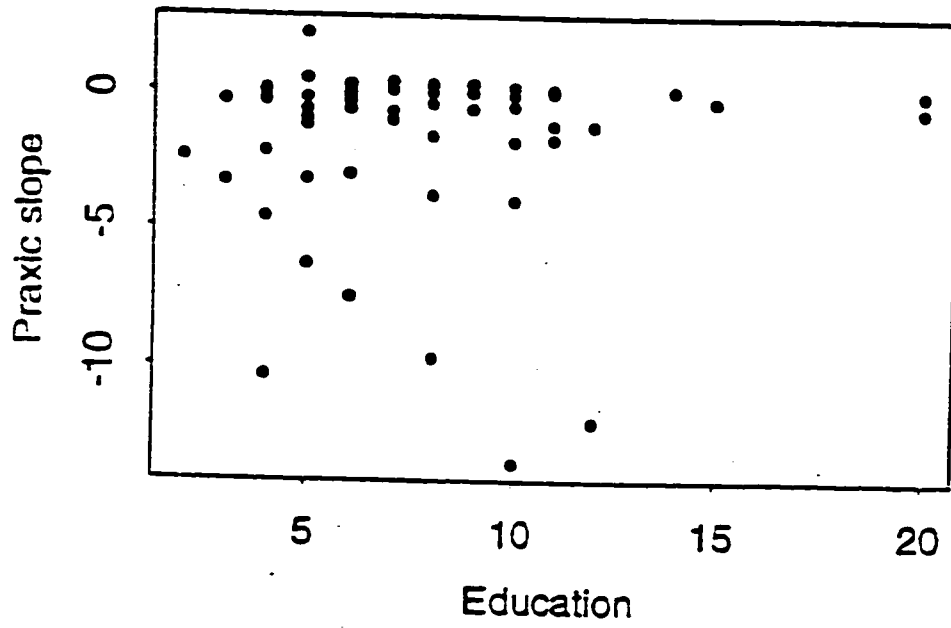
Figure 10. Scatter plot for estimated slope of education on praxic functions.
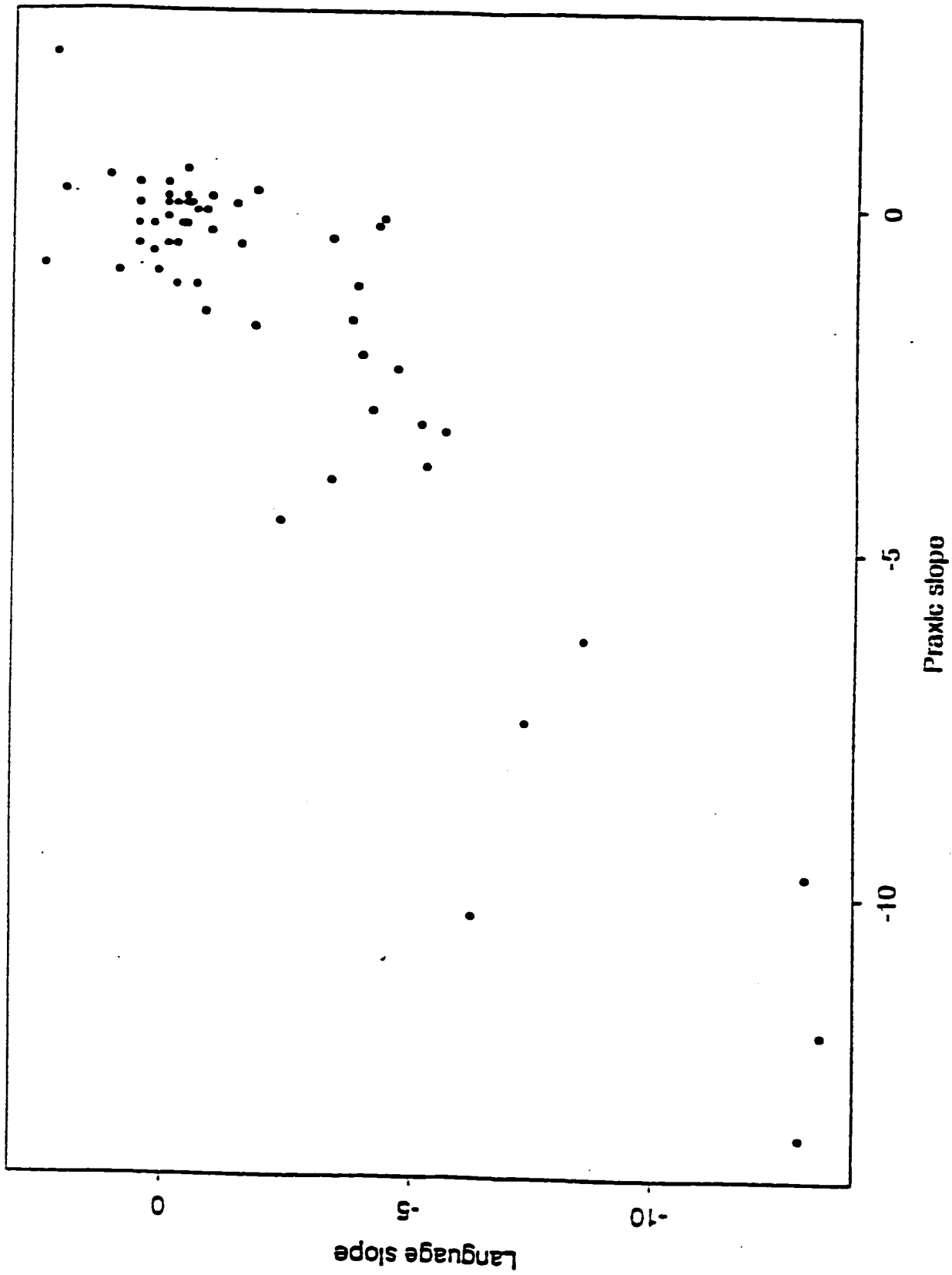
Figure 11. Scatter plot for relationship between language and praxic functions.

functions slope, a paired t-test comparing the slopes gave a non-significant value of t = 1.41, df=59. In Figure 12 the estimated language functions slope for each subject is represented by single lines. The time, in 6-month periods, is indicated on the X axis where Time 0 is the estimated time of onset to which the score of each subject is "anchored". The initial language function score is then regressed from this Time 0. Since each patient had a different time of onset of AD (Time0) from the time of assessment (their own Time 1), the regression lines do not all start from Time 0. The start of each regression line indicates the length of time into the disease process at the time the subject was first assessed. The Y axis indicates the scores on the dependent measure, i.e. the language functions. Figure 13 shows the estimated slope and initial score for the praxic functions.

The relationship between covariate gender and the clinical variables of language (Figure 14) and praxic functions (Figure 15) are presented in box and whisker plots. There is a greater spread in the scores for language functions than for the praxic functions for males, and more males than females have a negative slope especially for the language functions. The relationship between the covariate place of residence (home and hospital/institution) and the clinical variable of language (Figure 16) and praxic functions (Figure 17) are presented in box and whisker plots.

When age was treated as a dichotomous variable, the repeated measures MANOVA did not show any significant interaction on the seven
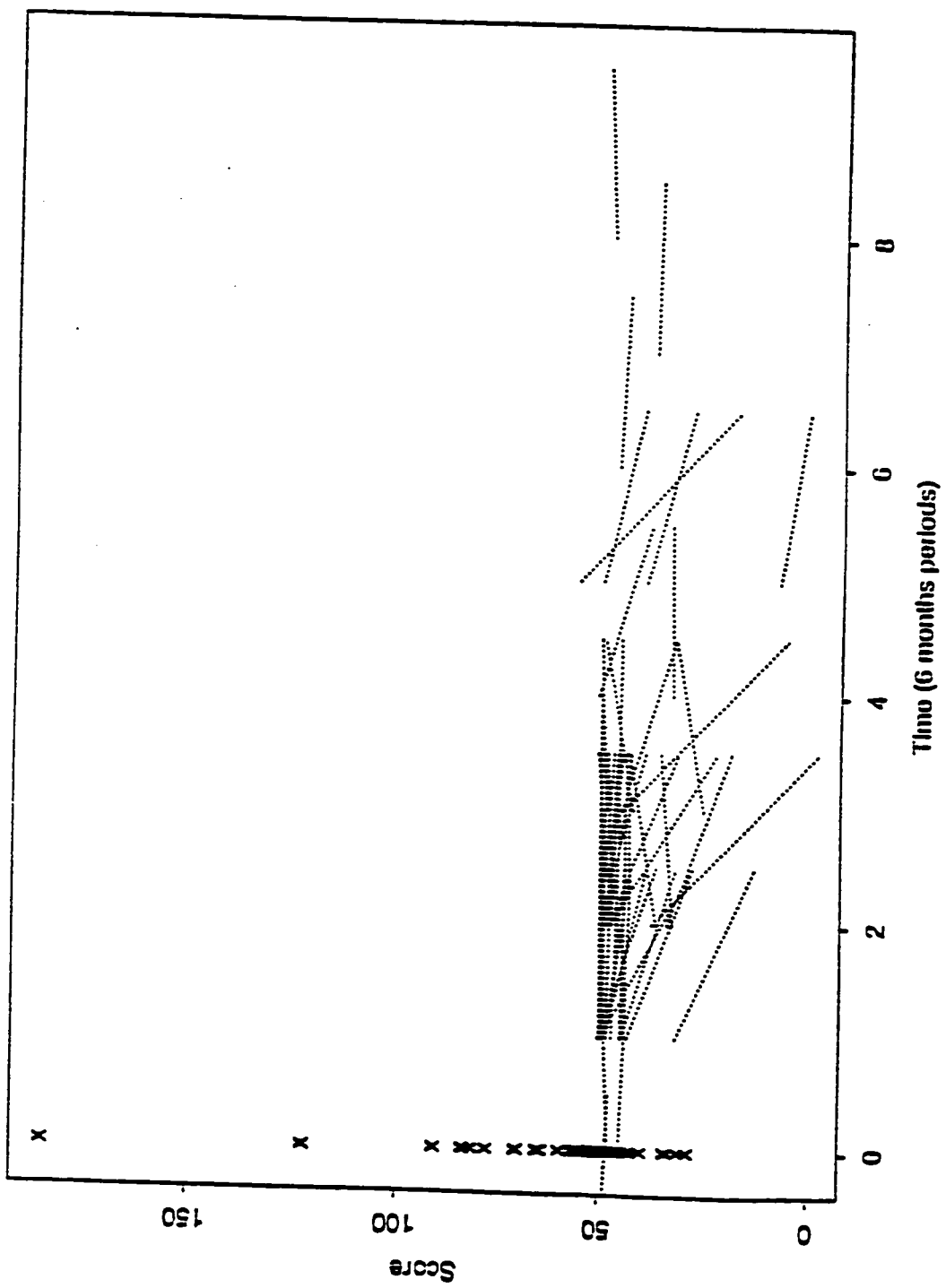
Figure 12. Estimate of slope and initial score for language functions.

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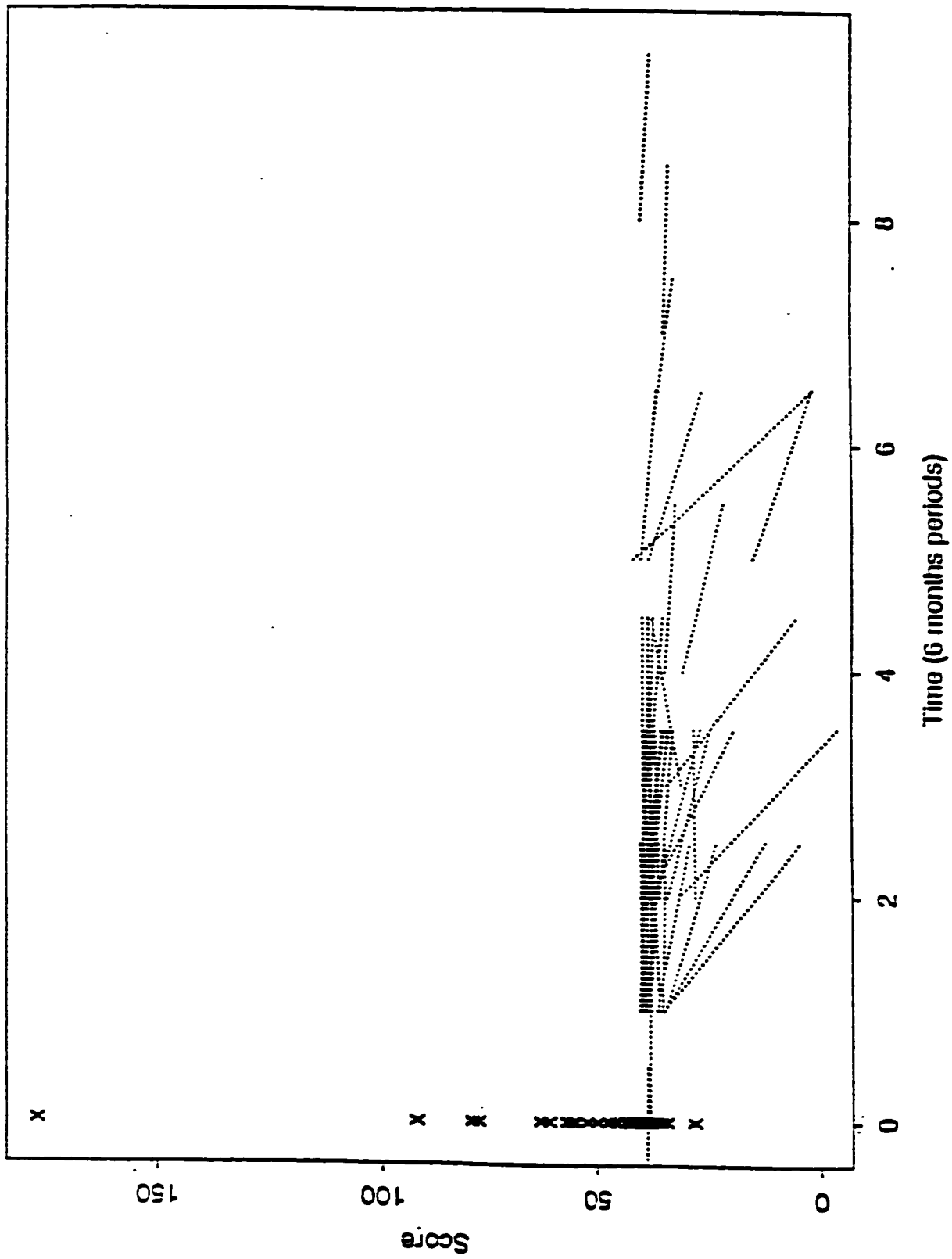
Figure 13. Estimate of slope and initial score for praxic functions.

Language slope by sex
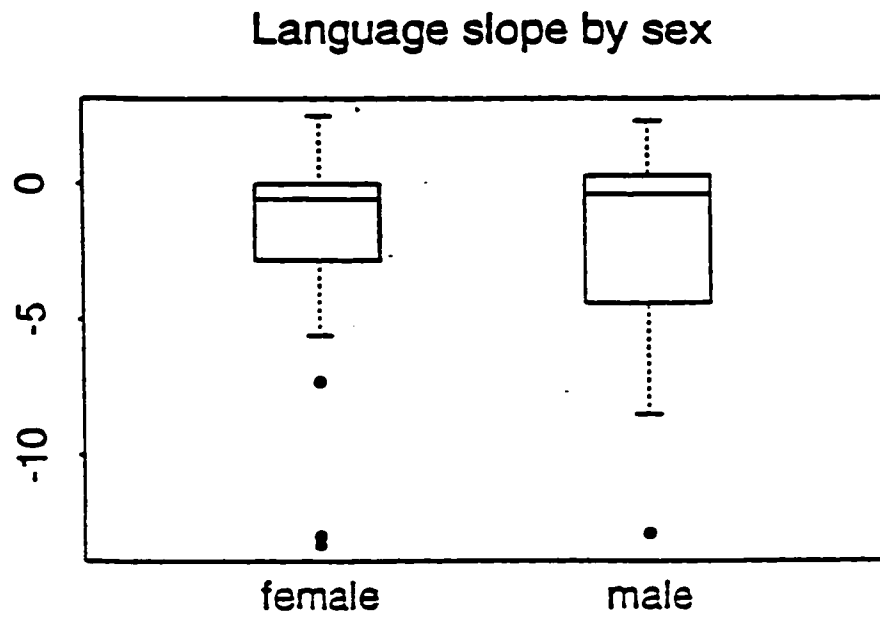
Figure 14. Box and whisker plot for language slope by sex.
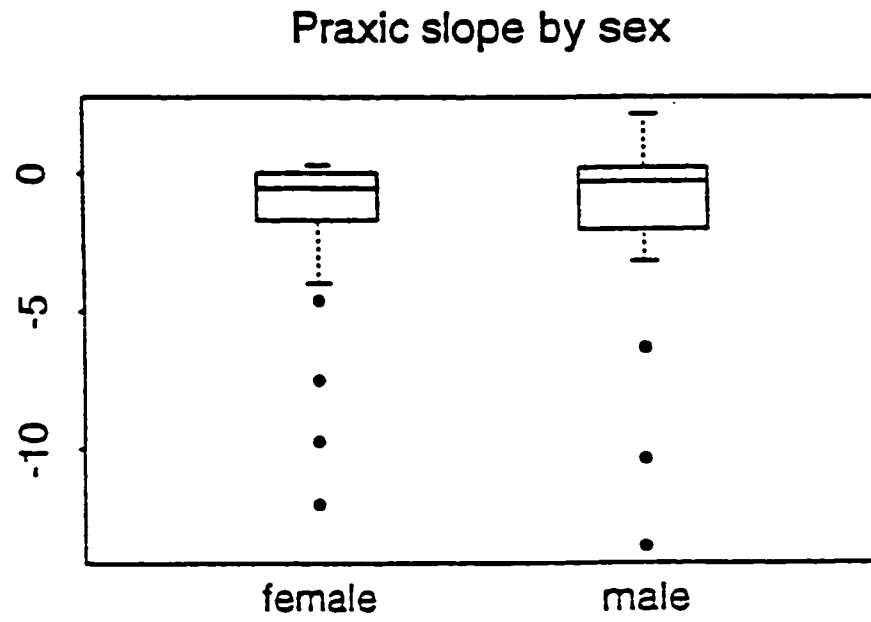
Praxic slope by sex

Figure 15. Box and whisker plot for praxic slope by sex.

Language slope by 'hospital'
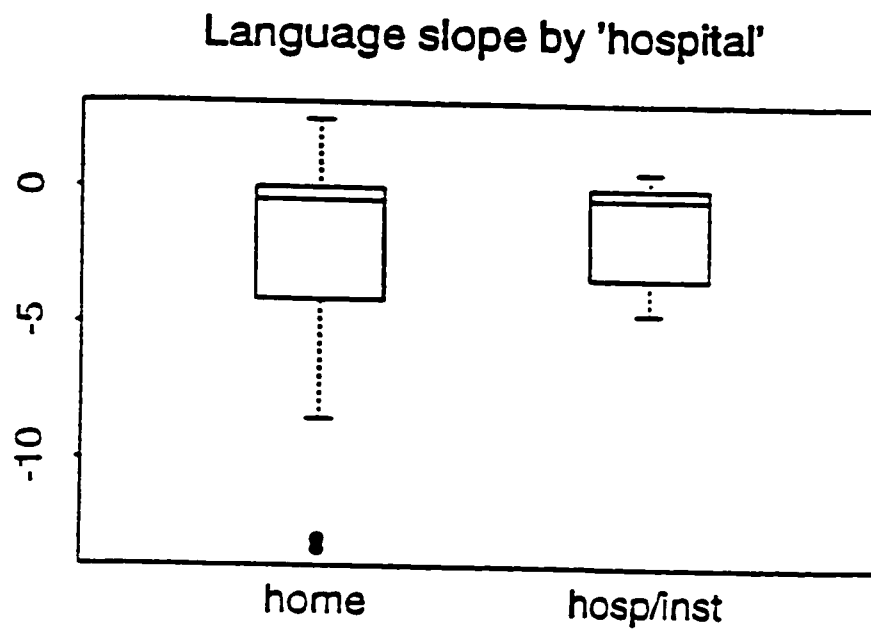
Figure 16. Box and whisker plot for language slope by (hospital) place of residence.

Praxic slope by 'hospital'
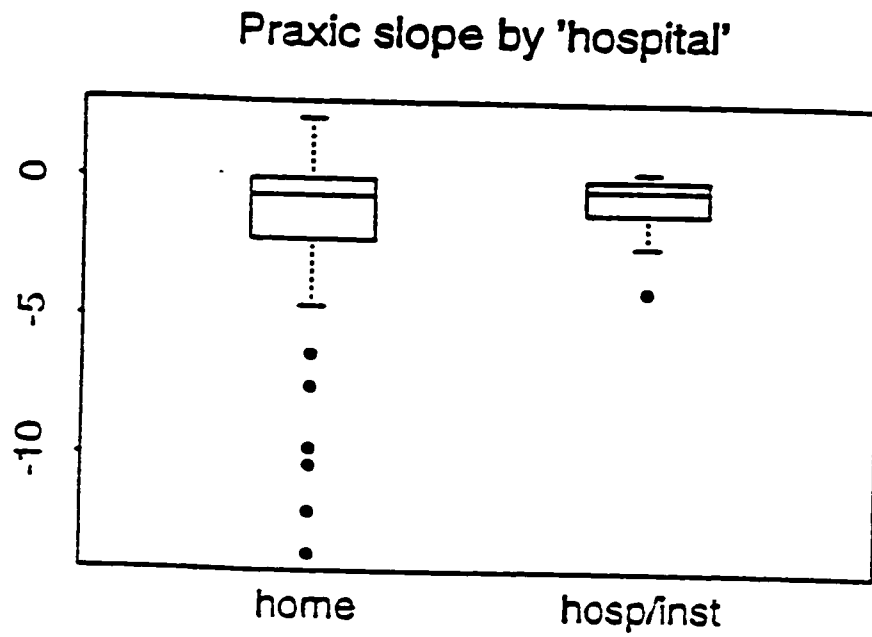
Figure 17. Box and whisker plot for praxic slope by (hospital) place of residence.

outcome measures between age of symptom onset and time. A RM ANOVA on total HDS showed significant changes. However when treating age as a continuous variable and using the RM ANOVA as a regression model, age at symptom onset was found to be a significant predictor of decline of total HDS score, as well as for the domains of language and praxic functions.

Discussion

Once the clinical signs of cognitive impairment are first noticed, practical questions are generally posed to clinicians by families, for prognosis for care plans as well as to identify risk factors which can influence this decline. This research was undertaken to answer some of those questions. It was hypothesized that using the HDS, patients whose age of onset of the clinical symptoms is under 65 would decline faster on the total HDS Score, than those whose age of symptom onset is over 65. It was further hypothesized that the two age groups will decline at a different rate on the HDS subscales measuring the 7 domains of orientation, language, memory, praxic, concentration, perception and calculation, with the younger age group showing a faster decline.

There is no generally accepted best way to calculate longitudinal change in naturalistic studies (Stern et al 1994). Therefore, in order to ensure that the conclusions drawn from this research do not depend upon the choice of a single analytic method, the hypotheses were tested using two different approaches: 1 where age was treated as a dichotomous variable, and the sample divided into two groups: the age of onset under 65 , and the age of onset over 65, and 2 where age was treated as a continuous variable. Using the second approach it was possible to adjust the scores of all the patients enrolled in the study to their age of onset. This allowed for meaningful comparisons of levels of cognitive impairments. The annualized deterioration in HDS of every patient being studied was based on their own specific baseline HDS score

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which would be representative of the disease severity.

The results of the repeated measures univariate analysis for the total HDS revealed an interesting relationship between time and age. It suggests that over an 18- month period, the early-onset AD is characterized by a more rapid clinical decline of 39.14 points on the total HDS scores as opposed to the late-onset AD patients who decline by 22.13 HDS points over the same follow-up period. The early-onset age group was cognitively more impaired than the late-onset group at all time periods with the difference increasing with time from 12.27 points at Time 1 to 30.21 points at Time 4. However the interaction between the 2 age groups and time was not significant. The trend may become significant with a larger sample size.

In the analysis with age as a dichotomous variable, the significant main effects of age and time, with no significant interaction between age and time, indicate that age of onset predicts poor performance but not the rate of decline. The repeated measures analysis, which does not take into account the "zero time" which is the age of onset of the disease process, showed that the younger age group was poorer in cognitive performance regardless of time. However in AD, on average, all patients are declining on cognitive performance with highly variable individual rates of decline. Some patients may have a zero slope and some a positive slope for brief time periods. Hence the rate of decline of a patient is likely to be influenced by the point of entry in the study. When two patients with identical disease course enter the study at different times, one early in the disease course and the second later in the disease course, the

length of time in the disease will obscure the effects of age on rate of decline. A patient whose cognitive decline is slow may be discovered to have AD later than a patient whose cognitive decline is faster, indicating a false relationship between age and rate of decline. By treating age as a continuous variable and adjusting the score of each patient to the starting point of the disease process, a better understanding of the relationship between age and decline was developed. In the slope analysis, each patient's score was regressed to Time 0, which was the estimated time of disease onset. By this method many patients obtained zero or flat slopes which tended to cluster in the beginning of the disease process while those who were entered in the study later in the disease process when the dementia had progressed had steeper slopes. This finding suggests that the rate of decline depends on both the severity of the disease as well as the age of onset.

The current results are also characterized by a differential pattern of impaired and preserved cognitive abilities between the two groups. The total HDS score which is a combination of all the subscale scores, is dependent on the contribution each of the subscales make to overall cognitive impairment. More detailed insight into the relationship between age of symptom onset of AD and the subscales of orientation, language, memory, praxis, concentration, perception and calculation was gained from the multivariate analysis Patients with early-onset AD were more impaired than late-onset patients at baseline on all measures except memory functions. These findings are in line with those reported elsewhere (Jacobs et al 1994; Dastoor & Cole 1988), where late-

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onset patients were significantly more likely to have memory as a presenting symptom while early-onset patients were more likely to have language or other performance difficulties. The most likely explanation as to why memory does not differentiate significantly between the early onset and late onset groups may be that as memory deficit is the cardinal symptom in dementia, once memory is affected its steady decline is maintained irrespective of age. The present results however do not support the findings of Bayles (1991) who after controlling for the effects of dementia severity on language performance scores of confrontation naming, auditory comprehension, writing from dictation and reading comprehension did not find a relationship between early age of onset of AD and greater language impairment.

The variable progression of AD and the lack of substantial evidence for clinical subtypes to account for the diversity in the course of the disease has made it difficult for clinicians to provide patients and their families with an accurate prognosis. This in turn has prompted the search for factors that can reliably predict the course of the disease in individuals with AD.

The need to develop an annual rate of change (ARC) in the different domains of the dementia syndrome has significant clinical as well as practical and financial implications. With increasing costs of providing services and maintaining the demented individual, either at home or in an institution, who may be in varying stages of cognitive impairment, there is a concerted effort, to try new pharmacological agents to slow the progression of the disease with the eventual aim of delaying or even reversing its course. As a treatment era

begins to emerge for AD, it is more and more imperative that the disease progression, as well as the factors which affect this progression be studied despite the absence of placebo controlled trials of the future. Documentation of its progress and prediction of its course is also necessary in counseling families and helping them plan their own lives as AD imposes substantial economic and emotional costs upon the care-givers. (Ostbye & Crosse, 1994)

Huff et al (1987) and Katzman et al (1988) examined the progression of AD symptomatology longitudinally and found conflicting results. Huff using the summary score of the Blessed Test (IMC) and following the patients for 3 months had found a more rapid decline in the late-onset group whereas Katzman who followed the patients for a minimum of 1 year and a maximum of 6 years found no difference in the annual rate of change on the Blessed Test (IMC) between the groups. A limitation of both of these studies is the variability in length of follow-up which may have contributed to the results. When Lucas, et al (1993), followed AD patients for 1 year on the Blessed Test (IMC), significantly faster decline was observed in the early-onset patients. Using the total HDS score the present prospective longitudinal study does not provide conclusive evidence of more rapid cognitive decline in patients with onset of AD symptoms prior to age 65.

Risk Factors in the Decline of Cognitive Functions in Total HDS Score, Language Scores and Praxic Scores

Total HDS Score. As each AD patient is an individual with a different history and psycho social background, there is no "typical" AD patient. There

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are a minority of patients who show substantial change over time as opposed to others who show no change. To consider the contribution of individual differences in patients, as potential risk or protective factors, a modeling approach was used in this study. A model which utilizes actual scores and is a function of time, requiring knowledge of the start of the disease, was built to predict decline in the overall level of cognitive functions and in the critical clinical neuropsychological functions of language and praxis. Knowing the age of disease onset, the level of cognitive impairment at the starting point of the disease, can be estimated. This would allow patients with different levels of cognitive decline to be entered in the study from a common distribution.

From the several covariates entered in the model to assess the extent to which the rate of decline in AD is affected, age of symptom onset, education, and place of residence predicted significant decline in the total HDS. Age of symptom onset gave a predicted beta coefficient of 1.60 points of decline for each year of symptom onset. Applying this to a case study, a patient whose age of symptom onset is 70 years and whose present total HDS score is 170, can expect to have a score of 162.00 points at age 75 years (1.60 x 5 years = 8.00 points). In contrast a patient whose age of symptom onset is 60 years and whose present HDS score is 170, can expect to have a score of 146.00 total HDS points (1.60 x 15 = 24.00 points) by age 75. At age 75 the severity of cognitive impairment as measured by the HDS scores in these two patients will not be the same even though the level of impairment was similar at initial contact.

The clinician can indicate to the family that an early age of symptom onset is a risk factor for a steeper decline in cognitive functions over time.

Higher level of education was found to be a protective factor for AD by allowing the patients to manage the deficits for a longer period and hence delay the clinical manifestations of the disease. In the model for the general cognitive decline as measured by the total HDS, a significant beta coefficient of 4.56 points per each year of education (2.28 points per 6 months) was predicted. When applied to the same case study: the score on the total HDS in a patient with 10 years of education, will be 22.90 points higher than for a patient with 5 years of education (4.58 x 5 years of difference in education = 22.90). Education was positively correlated with the total HDS score for all time periods.

In the general model of factors to predict decline another risk factor the place of residence, yielded a beta coefficient of 12.07 per 6 months (24.14 points annually) for institutional living (hospitalized), implying that patients institutionalized would decline faster than those not institutionalized (at home). This adds strength to the findings of Gold, Dastoor & Zieren (1996) that initial total HDS score predicted institutionalization. Patients are generally placed in an institution when the clinical and behavioural symptoms become so severe that they cannot be managed at home, and higher levels of cognitive impairment indicate lower scores on the HDS. Gender was not a contributing factor in the model of decline for Alzheimer Disease.

Language Function Score. Language is one of the main cognitive processes affected in AD (McKhann, Drachman, Folstein, Katzman, Price &

Stadlan 1984), beginning with decreases in verbal fluency and difficulty in word finding. Breakdown in language functioning is generally seen early in the disease and is almost universal in the later stages. As the disease progresses both receptive and expressive language abilities deteriorate, often reaching a level of impairment in later stages that precludes cognitive testing. (Lee 1991).

The language function tasks administered in this study included confrontation naming, auditory and verbal comprehension, reading, writing to dictation and abstraction. The composite score on language and level of education were significantly correlated (r = .36) at baseline assessment but not at Time 4 (r = .24).

From the several co-variates entered in the model to assess the extent they can predict decline in the language functions of the HDS, age of symptom onset, education and place of residence were found to be most significant. Gender was not considered a risk factor. A significant beta coefficient of .72 points (.36x2) was calculated for every year of difference in symptom onset between patients. Applying this predicted beta coefficient to the previous case study, a patient whose age of symptom onset of AD is 70 years and whose present composite language score is 45 would expect to have a language score of (.72 x 5 years = 3.60) 41.40 at age 75 years. In contrast a patient whose age of onset is 60 years and whose present composite language score is also 45 can expect to have a language score of 34.20 (.72 x 15 years = 10.80) at age 75 years. The level of language impairment with the progression of the disease will be more severe with the younger age of onset. The findings

of this research concur with Yesavage, Brooks, Taylor & Tinklenberg (1993), Boller et al (1991), Kraemer, Tinklenberg & Yesavage (1994), that language functions decline faster in the younger onset age group. Early age of symptom onset can predict change in language performance.

A higher level of education was a protective factor for maintaining the language scores of the HDS. A significant beta coefficient of 1.62 for every year of difference in the education level of the patient, would yield a difference of 8.10 points between a patient with 5 years of education or 10 years of education. The covariate education and language function scores of the HDS had modest positive correlations at all time periods.

A patient who is already in an institution on average will score 7.76 points (3.88 per 6 months) lower on the composite language score than a patient not hospitalized. This adds strength to the findings of Gold, Dastoor & Zieren (1996) that initial total HDS score predicted institutionalization.

The results of this study suggests that education (linguistic ability) can be considered as a risk factor or a protective factor in dementia. Patients with more years of education tend to have flatter slopes (less decline) on language functions whereas patients with less education have steeper slopes of decline. This supports the findings of Snowdon (Snowdon et al 1996), from the Nun study, the findings of the 1996 Canadian Study of Health and Aging on the risk factors in AD, the findings from studies in Shanghai (Zhang, Katzman, Jin & Salmon 1990), and Netherlands (Friedland 1993), that more education may be a protective factor against AD. The support for education as a protective factor

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for decline in language functions is further strengthened by steeper slopes for patients with less education. The mean education level of 8 years of the present research sample is modest, in comparison to the education levels in the studies quoted above. The regression analysis indicates that patients with education levels of 5 years and less had steeper negative slopes than those with education levels more than 10 years The research confirms that less education was a significant risk factor in the prediction of decline even for a sample with relatively low levels of education.

From the covariates entered in the model to predict decline, gender was not considered to be a risk factor for decline in the language functions, however the larger negative slope for males may be indicative of language functions deteriorating faster in males than in the females. This finding supports the general conception that language functions are developed earlier in females and by corollary deteriorate slower in females.

Placement in an institution was also found to be a risk factor in predicting impairment of language functions, as the significant beta coefficient of 3.88 points per 6 months would lower the language score of the HDS by 7.76 points annually.

Praxic Function Score. Apraxia is a cortical deficit frequently encountered in AD which increases in severity as the disease progresses, generally being present in 70% of the cases in late stages of the disease. The tests for apraxia used in this study , namely ideomotor apraxia, ideational apraxia, spatial constructional ability and drawing ability, distinguish between a

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conceptual system that includes knowledge of tools and how to use them, and a production system containing knowledge of motor action programs and how to translate them into skilled movements. Early age of symptom onset was a significant predictor of decline in praxic functions where a significant beta coefficient of .26 (.13 x 2) points was calculated for every year of symptom onset. Applying this predicted beta coefficient to the previous case study, a patient whose age of symptom onset of AD was 70 years with a score of 35, would expect to have a score of 33.70 points (.26 x 5 years = 1.30 points) on the praxic functions at age 75. On the other hand the patient with age of symptom onset of AD at 60 years and a score of 35 points on praxic functions can expect to have a score of 31.10 points at age 75 (.26 x 15 = 3.90 points). With the spread of the slope for praxic functions being even for both men and women, gender was not a risk factor in predicting decline in the praxic functions.

Using these beta coefficients, the clinician can predict the differences in the rate of decline between patients depending on their age of symptom onset. Early in the course of the disease when the severity of the disease is mild subjects tend to have a gentler decline of functions, while later in the disease course the slopes tend to become steeper.

Clinical Relevance

An important question to consider from this study is how do these statistical changes translate into clinical relevance. How do these findings affect the life of the patient and caregiver? A better understanding of the rate of progression of cognitive and functional deterioration and the covariates that

predict the rate of decline in dementia will help improve our knowledge of the natural history of the disease and help identify differential patterns of decline to facilitate the clinician in counseling patient and family. Knowledge of the rate of deterioration, based on the covariates as risk or protective factors, will help in the management of legal and financial matters, for effective planning and delivery of care, as well as allow clinicians to give appropriate advice on response expectation to therapeutic drug trials to patients and caregivers. Knowledge of the natural progression of the disease can help modify the stress and help cope with the frustrations that arise from the current uncertainties of AD and allow family members to better anticipate problems before they fully develop.

In this study only cognitive measures are used to determine rate of progression. The results of the study indicate that from all the covariates entered in the model, age of symptom onset, education, and place of residence affected cognitive decline significantly as measured by the total HDS score. The specific clinical features of language and praxic functions are affected differently by the covariates. Language functions could be predicted by the age of symptom onset and education whereas only age of symptom onset could predict decline for praxic functions. The results suggest that early age of onset has a greater impact on deficits of language and praxic function which can be considered as risk factors for more rapid cognitive decline in total HDS score, as well as in the scores for language and praxic functions. The patients above age 65 decline slower than those below the 65 age group. The finding that age

of onset and education are predictors for decline on the HDS are important for the design of clinical trials and other longitudinal studies in AD. Interventions designed to slow or arrest the progression of AD must consider the age of onset. As HDS is less subject to floor and ceiling effects than other psychometric tests, it could be a good addition in the arsenal of tests in clinical trials as a linear measure of progression.

The model developed in this study suggests that cognitive deterioration as measured by the HDS, will be faster on the total HDS scores and in the language functions scores, in a patient with an early age of symptom onset, with less education and living in an institution. The corollary also applies that patients with preserved language functions, and late age of symptom onset will not deteriorate as rapidly. The decline in the praxic functions can only be predicted by age of symptom onset.

A major contribution of this study is to add strength to the role of risk factors in accelerating decline with every year of symptom onset. Knowledge of this information would help caregivers plan for the future in a realistic fashion

Limitations

The generalizability of the results and conclusions of the present study are bound by the study's limitations. The representativeness of the population sampled warrants mention. It is generally felt that subjects identified for the study from medical facilities, particularly from specialty clinics, in teaching hospitals may not be representative of individuals with AD in the general population. Patients who cannot be treated in the office of the GP are sent to

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specialty clinics. This was observed in the study sample as well where there was a ratio of 2:1 women to men which is representative of the general population at this age group where there are significantly more women. However in contrast, in the younger age group there were significantly more men. This can be explained by the fact that younger men who are still in the work force when they begin to show signs of cognitive deficit, come to the attention of their employers, who request an assessment to a specialty clinic prior to a decision for early termination of their employment.

The study results are applicable only with the use of the Hierarchic Dementia Scale and when the diagnosis of AD is accurately made. Analyzing the pattern of scores on each of the individual subscales which make up the composite scores of language and praxic functions could be beneficial in the understanding of the contribution each component of the functions make to cognitive decline in AD.

Estimation of age of symptom onset from family reports is another limitation of the study. The date of the first report of memory impairment was used as the time of onset that was subtracted from the patient's age at testing to obtain perceived age of onset of AD. For some memory impairment may not be the first symptom noticed which may have distorted the age of onset. It is also impossible to verify caregivers' report of symptoms. To obtain an accurate age of symptom onset, normal subjects over the age of 55 years would have to be followed longitudinally with repeated cognitive assessments for several years. The cost in terms of time and manpower would not make this a very viable

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approach for a doctoral thesis. The relatively short duration of the follow-up for practical reasons is another limitation, specially since the pilot study indicated that difference between the age groups become more pronounced after 24 months of onset. Given the large variability within patient scores over time, with 60 subjects who completed the four assessments, only very large effects could be found and any subtleties would likely be subject to further study with a larger number of patients.

Conclusion

In conclusion this study has developed a model of decline in AD which confirms a number of hypothesized risk factors as well as a set of protective factors. The age of symptom onset is the most significant risk factor for AD which also significantly predicts the rate of decline on the language and praxic functions. The HDS has again proven to be a sensitive instrument in showing change over time in several neuropsychological functions.

The current study provides longitudinal evidence that the pattern and rate of decline of cognitive function in AD as measured by the HDS differ as a function of age of symptom onset.

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APPENDIX A

48 Months Decline on the HDS Total Score in a Study of
13 Subjects, N=7 (<65 years); N=6 (>65 years)

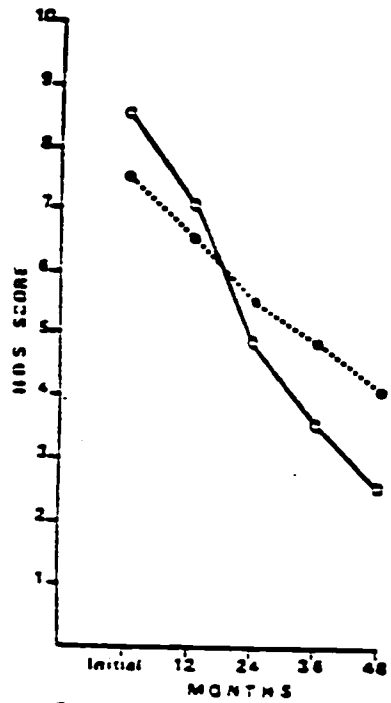# TOTAL HDS

Fig.1 TOTAL HDS

●——● Late onset (72.0 yrs.)
○——○ Early onset (56.1 yrs.)

APPENDIX B

48 Months Declin on the HDS in a Study of
13 Subjects, N=7 (<65 years); N=6 (>65 years) on Language Functions

LANGUAGE FUNCTIONS
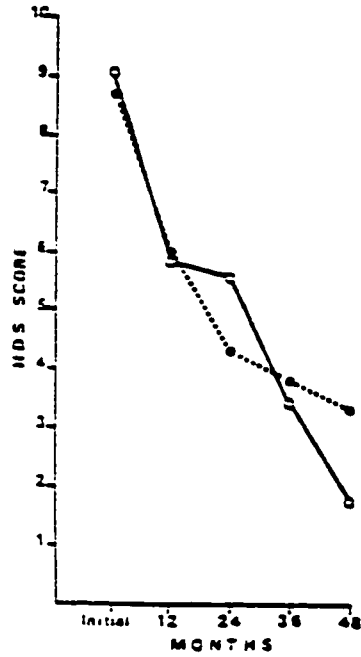
Fig. 2 WRITING

Fig. 3 READING

Fig. 4 DENOMINATION

●———● Late onset (78.0 yrs.)

○———○ Early onset (56.1 yrs.)

Ref: Dastoor, D.P. & Cole, M.G. (1988) Age-related patterns of decline in dementia as measured
        by the Hierarchic Dementia Scale. The American Journal of Alzheimer's Care and Related
        Disorders Research 28-35.

APPENDIX C

48 Months Declin on the HDS in a Study of
13 Subjects, N=7 (<65 years); N=6 (>65 years) on Praxic Functions
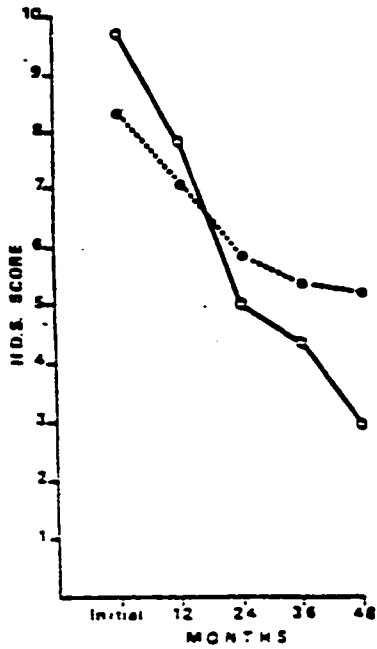
Fig. 5 PRAXIC GRAPHIC
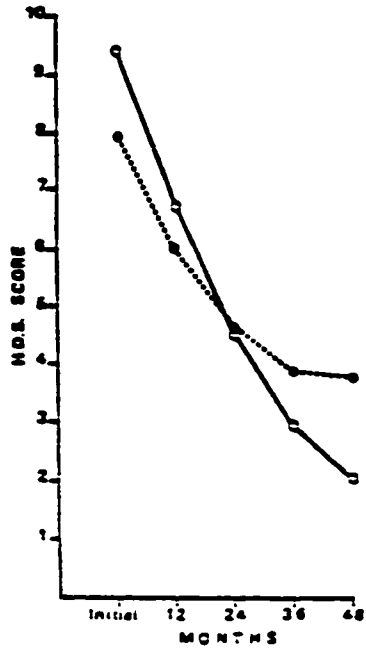
Fig. 6 PRAXIC CONSTRUCTIONAL
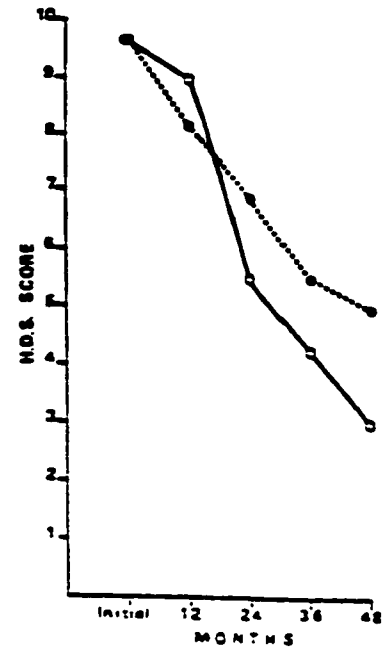
Fig. 7 PRAXIC IDEATIONAL

Fig. 8 PRAXIC IDEOMOTOR

Fig. 9 GNOSIS

Late onset (78.0 yrs.)

Early onset (56.1 yrs.)

Ref: Dastoor, D.P. & Cole, M.G. (1988) Age-related patterns of decline in dementia as measured by the Hierarchic Dementia Scale. The American Journal of Alzheimer's Care and Related Disorders Research 28-35.

APPENDIX D

48 Months Declin on the HDS in a Study of
13 Subjects, N=7 (<65 years); N=6 (>65 years) on Cognitive Functions
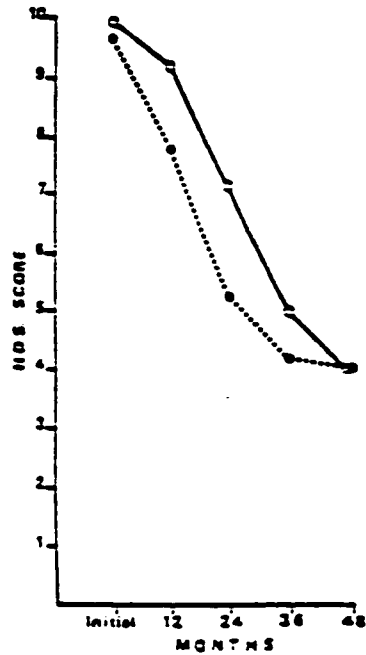
COGNITIVE FUNCTIONS
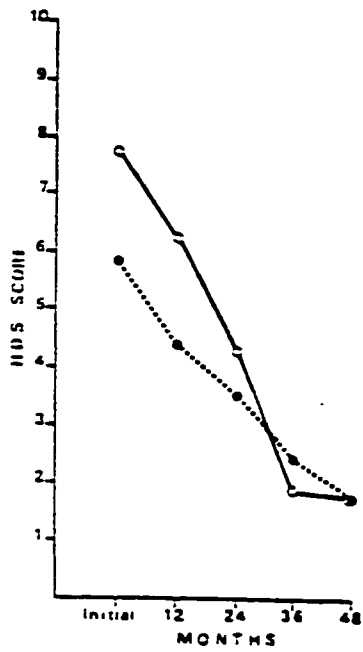
Fig. 10 ORIENTATION
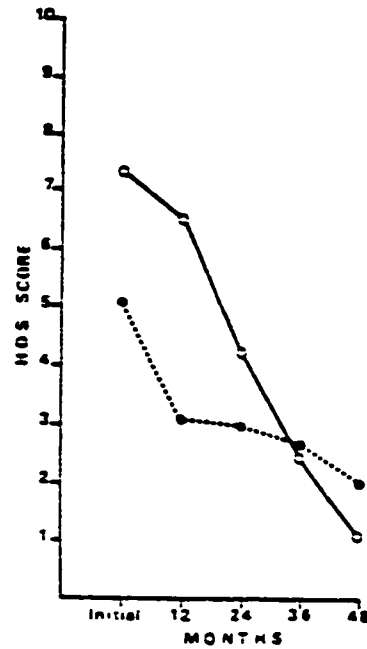
Fig. 11 SIMILARITIES
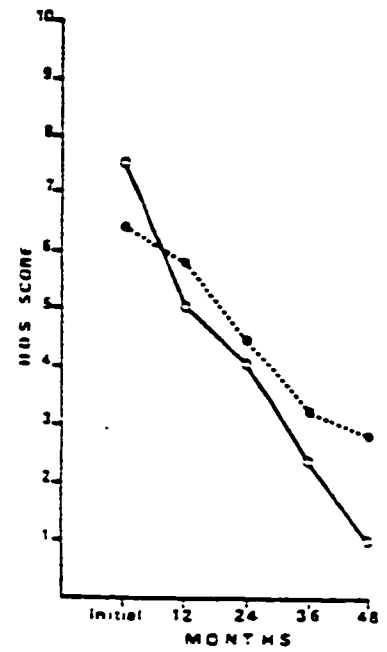
Fig.-12 CALCULATION
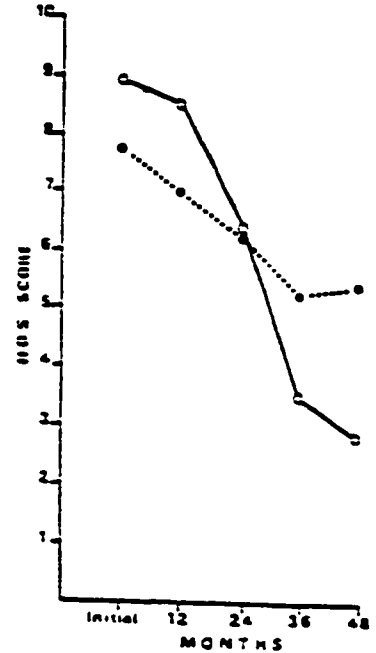
Late onset (78.0 yrs.)

Early onset (56.1 yrs.)

Ref: Dastoor, D.P. & Cole, M.G. (1988) Age-related patterns of decline in dementia as measured by the Hierarchic Dementia Scale. The American Journal of Alzheimer's Care and Related Disorders Research 28-35.

APPENDIX E

48 Months Declin on the HDS in a Study of
13 Subjects, N=7 (<65 years); N=6 (>65 years) on Amnestic Functions

AMNESTIC FUNCTIONS
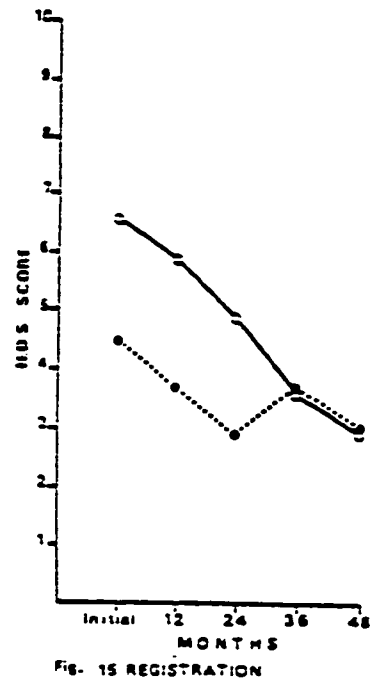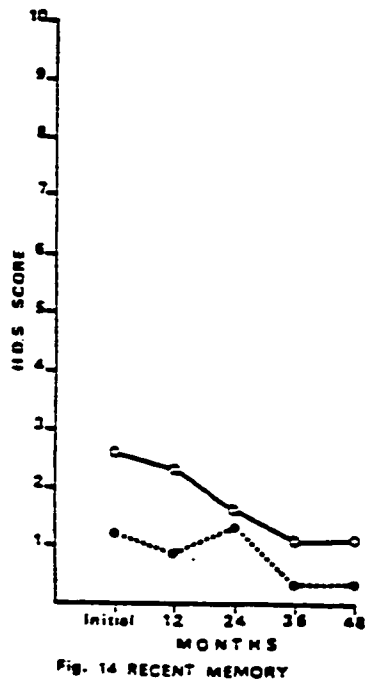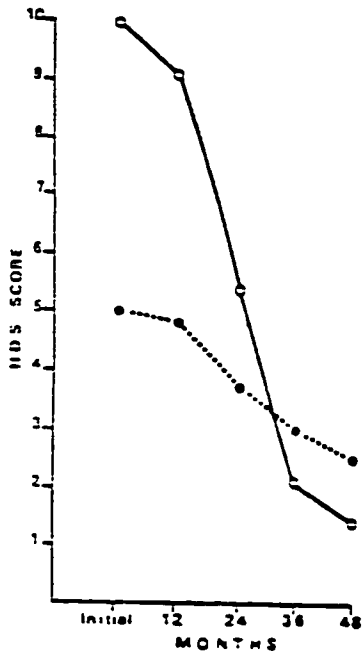
Fig. 13 REMOTE MEMORY

Fig. 14 RECENT MEMORY
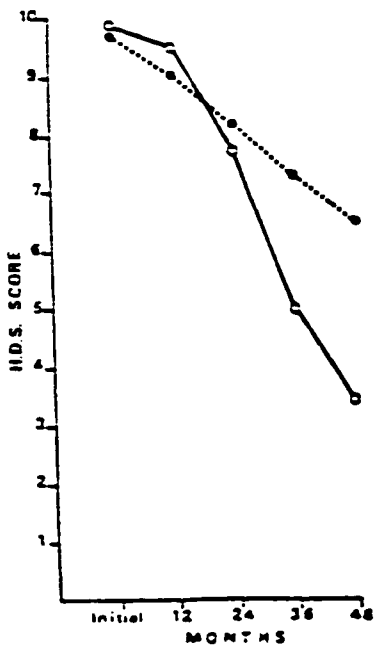
Fig. 15 REGISTRATION

●——● Late onset (78.0 yrs.)

○——○ Early onset (56.1 yrs.)

Ref: Dastoor, D.P. & Cole, M.G. (1988) Age-related patterns of decline in dementia as measured by the Hierarchic Dementia Scale. The American Journal of Alzheimer's Care and Related Disorders Research 28-35.

APPENDIX F

NINCDS/ADRDA Criteria for Clinical Diagnosis of
Alzheimer's Disease

NINCDS/ADRDA Criteria for Clinical Diagnosis of
Alzheimer's Disease

(I)   The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease
includes:

Dementia established starts by clinical examination and documented by
    Mini-Mental Test, Blessed Dementia Scale or some similar
    examination and confirmed neuropsychological tests;
Deficits in two or more areas of cognition;
Progressive worsening of memory and other cognitive functions;
No disturbance of consciousness;
Onset between ages 40 and 90, most often after age 65 and absence of
    systemic disease or other brain diseases that in themselves could
    account for the progressive deficits in memory and cognition.

(II)   The diagnosis of PROBABLE Alzheimer's disease is supported by:

Progressive deterioration of specific cognitive functions such as
    language (aphasia), motor skills (apraxia), and perception
    (agnosia);
Impaired activities of daily living and altered patterns of behavior;
Family history of similar disorders, particularly if confirmed by
   neuropathologically, and laboratory results of: normal lumbar
    puncture as evaluated by standard techniques;
Normal patterns or nonspecific changes in EEG, such as increased
    slow-wave activity, and evidence of cerebral atrophy on CT with
    progression documented by serial observations.

(III) Other clinical features consistent with the diagnosis of PROBABLE
       Alzheimer's disease after exclusion of causes of dementia other than
       Alzheimer's disease includes:

Plateaux in the course of the progression of the illness;
Associated symptoms of depression, insomnia, incontinence delusions,
    illusions hallucinations, catastrophic verbal, emotional or physical
    outbursts, sexual disorders and weight loss;
Other neurologic abnormalities in some patients, especially with more
    advanced disease and including motor signs such as increased
    muscle tone, myoclonus or gait disorder;
Seizures in advanced disease;
CT normal for age.

(IV)   Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

Sudden onset;
Focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and in coordination early in the course of the illness;
Seizures or gait disturbances at the onset or very early in the course of the illness.

(V)   Clinical diagnosis of POSSIBLE Alzheimer's disease:

May be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric or systemic disorders sufficient to cause dementia and in the presence of variations in the onset, in the presentation or in the clinical course;
May be made in the presence of a second systemic or brain disorder sufficient to produce dementia which is not considered to be the cause of the dementia; and should be used in research studies when a single gradually progressive sever cognitive deficit is identified in the absence of other identifiable cause.

(VI)   Criteria for Diagnosis of DEFINITE Alzheimer's disease are:

The clinical criteria of probable Alzheimer's disease and histopathologic evidence obtained from a biopsy or autopsy.

(VII)   Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

Familial occurrence;
Onset before age of 65;
Presence of trisomy-21;
Coexistence of other relevant conditions such as Parkinson's disease.

APPENDIX G

Criteria for the Diagnosis of Alzheimer's
Disease DSM III R

CRITERIA FOR THE DIAGNOSIS OF ALZHEIMER'S DISEASE DSM III R

Diagnostic Criteria for Dementia

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

B. At least one of the following:

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

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

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

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

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

D. Not occurring exclusively during the course of Delirium

E. Either (1) or (2):

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

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

APPENDIX H

Diagnostic CriteriA for Primary Degenerative Dementia
of the Alzheimer Type DSM IIIR

TYPE

Primary Degenerative Dementia of the Alzheimer Type, Senile Onset (after age 65)

290.30	with delirium,
290.20	with delusion,
290.21	with depression,
290.00	uncomplicated

Primary Degenerative Dementia of the Alzheimer Type, Presenile Onset (age 65 and below)

290.11	with delirium
290.12	with delusions
290.13	with depression
290.10	uncomplicated

APPENDIX I

Geriatric Depression Scale

Geriatric Depression Scale

Choose the best answer for how you felt over the past week

		YES	NO
1.	Are you basically satisfied with your life?	___	___
2.	Have you dropped many of your activities and interests?	___	___
3.	Do you feel that your life is empty?	___	___
4.	Do you often get bored?	___	___
5.	Are you hopeful about the future?	___	___
6.	Are you bothered by thoughts you can't get out of your head?	___	___
7.	Are you in good sprits most of the time?	___	___
8.	Are you afraid that something bad is going to happen to you?	___	___
9.	Do you feel happy most of the time?	___	___
10.	Do you often feel helpless?	___	___
11.	Do you often get restless and fidgety?	___	___
12.	Do you prefer to stay at hone, rather than go out and new things?	___	___
13.	Do you frequently worry about the future?	___	___
14.	Do you feel you have more problems with your memory than most people?	___	___
15.	Do you think it is wonderful to be alive now?	___	___
16.	Do you often feel downhearted and blue?	___	___
17.	Do you feel pretty worthless the way you are now?	___	___
18.	Do you worry a lot about the past?	___	___
19.	Do you find life very exciting?	___	___
20.	Is it hard for you to get started on new projects?	___	___
21.	Do you feel full of energy?	___	___
22.	Do you feel your situation is hopeless?	___	___
23.	Do you think most people are better off than you are?	___	___
24.	Do you frequently get upset over little things?	___	___
25.	Do you frequently feel like crying?	___	___
26.	Do you have trouble concentrating?	___	___
27.	Do you enjoy getting up in the morning?	___	___
28.	Do you prefer to avoid social gatherings?	___	___
29.	Is it easy for you to make decisions?	___	___
30.	Is your mind as clear as it used to be?	___	___

NB: NO answers on questions 1, 5, 7, 9, 15, 19, 21, 29, and 30, and
     YES answers on the others count for one point each.

TOTAL SCORE:

APPENDIX J

L'Echelle Gériatrique de Dépression

ÉCHELLE GÉRIATRIQUE DE DÉPRESSION

1. Etes-vous satisfait(e) de votre vie? ☐ oui ☐ non

2. Avez-vous renoncé à un grand nombre de vos activités? ☐ oui ☐ non

3. Avez-vous le sentiment que votre vie est vide? ☐ oui ☐ non

4. Vous ennuyez-vous souvent? ☐ oui ☐ non

5. Envisagez-vous l'avenir avec optimiste? ☐ oui ☐ non

6. Etes-vous souvent préoccupé(e) par des pensées qui reviennent
   sans cesse? ☐ oui ☐ non

7. Etes-vous de bonne humeur la plupart du temps? ☐ oui ☐ non

8. Craignez-vous un mauvais présage pour l'avenir? ☐ oui ☐ non

9. Etes-vous heureux(se) la plupart du temps? ☐ oui ☐ non

10. Avez-vous souvent besoin d'aide? ☐ oui ☐ non

11. Vous sentez-vous souvent nerveux(se), au point de ne pouvoir
    tenir en place? ☐ oui ☐ non

12. Préférez-vous rester chez vous plutôt que de sortir? ☐ oui ☐ non

13. L'avenir vous inquiète-t-il? ☐ oui ☐ non

14. Pensez-vous que votre mémoire est plus mauvaise que celle
    de la plupart des gens? ☐ oui ☐ non

15. Pensez-vous qu'il est merveilleux de vivre à notre époque? ☐ oui ☐ non

16. Avez-vous souvent le cafard? ☐ oui ☐ non

17. Avez-vous le sentiment d'être désormais inutile? ☐ oui ☐ non

17.	Avez-vous le sentiment d'être désormais inutile?	☐ oui	☐ non
18.	Ressassez-vous beaucoup le passé?	☐ oui	☐ non
19.	Trouvez-vous que la vie est passionnante?	☐ oui	☐ non
20.	Avez-vous des difficultés à entreprendre de nouveaux projets?	☐ oui	☐ non
21.	Avez-vous beaucoup d'énergie?	☐ oui	☐ non
22.	Désespérez-vous de votre situation présente?	☐ oui	☐ non
23.	Pensez-vous que la situation des autres est meilleure que la vôtre, que les autres ont plus de change que vous?	☐ oui	☐ non
24.	Etes-vous souvent irrité par des détails?	☐ oui	☐ non
25.	Eprouvez-vous souvent le besoin de pleurer?	☐ oui	☐ non
26.	Avez-vous du mal à vous concentrer?	☐ oui	☐ non
27.	Etes-vous content de vous lever le matin?	☐ oui	☐ non
28.	Refusez-vous souvent les invitations pour sortir?	☐ oui	☐ non
29.	Vous est-il facile de prendre des décisions?	☐ oui	☐ non
30.	Avez-vous l'esprit aussi clair qu'autrefois?	☐ oui	☐ non

APPENDIX K

Consent Form

Consent Form

RATE AND PREDICTORS OF DECLINE IN DEMENTIA OF THE ALZHEIMER TYPE AS MEASURED BY THE HIERARCHIC DEMENTIA SCALE

The main objective of this research is to study how quickly or slowly the different symptoms of Alzheimer's disease change and to see if the change is due to any special factors e.g. age and the type of symptoms which appear first. When this research is completed, it is hoped that we will be able to measure the annual rate of change. This will help people suffering from dementia to plan their life for the next few years.

This work will be used by Mrs Dastoor, for a Doctorate thesis in Psychology at Concordia Univesity. Mrs Dolly Dastoor is an experienced psychologist working since many years in Douglas Hospital.

I _____ am being followed at the Memory Clinic. As part of this regular clinical program, I _____ undergo periodic reevaluations which include neuropsychological assessments i.e. psychological tests which measure memory, concentration, language and other functions of the brain.

As part of the doctoral research (Ph.D), Dolly Dastoor is interested in utilizing part of the neuropsychological information from my medical chart. My name and identifying details will not be used, my annonymity will be preserved and the information will remain confidential. I _____ can withdraw consent for the use of the data at any time and that my refusal will in no way compromise my on-going treatment.

I _____ can ask for additional information concerning my participation in this research from Dolly Dastoor Tel: 761-6131 ext 23920

I _____ understand the research proposal that has been explained to me. By signing this form, I _____ am authorizing Dolly Dastoor, to use part of the information from my medical chart of the Memory Clinic at Douglas Hospital.

Date: Client or Mandator or Tutor
                                                      Signature :

Date: Witness :
                                                   Signature:

APPENDIX L

Consent Form (French)

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FORMULE DE CONSENTEMENT

Les signes précurseurs et la progression dans lademence de type Alzheimer
mesurés par l'échelle de démence hiérarchisée

Le but premier de cette recherche est d'étudier l'évolution de la maladie d'Alzheimer en observant la vitesse auxquels les divers symptômes de la maladie changent et d'établir si ces changements sont liés à divers facteurs tels, l'âge du patient et les symptômes qu'il a manifesté au début de la maladie. Bref, par le biais de cette recherche, nous souhaitons établir la vitesse auquel la maladie évolue annuellement. Il importe que cette question soit étudiée car elle permettra aux personnes atteintes de démence de planifier leur avenir.

Cette recherche sera utilisée par Madame Dolly Dastoor dans le cadre de ses études de doctorat en psychologie à l'Université Concordia. Notons que Madame Dastoor travaille comme psychologue à l'hôpital Douglas depuis plusieurs années.

A l'heure actuelle, vous êtes suivi par la Clinique de mémoire. Dans le cadre de ce programme clinique, vous subissez des réévaluations périodiques qui comprennent, entre autres, des évaluations neuropsychologiques (i.e. des examens psychologiques qui servent à évaluer votre capacité de mémoire, votre concentration, vos fonctions langagières ainsi que d'autres fonctions du cerveau).

Dans le cadre de son projet de recherche, Madame Dastoor cherche à utiliser une partie des données neuropsychologiques que l'on retrouve dans votre dossier médical. Si vous accordez votre consentement à participer à sa recherche, votre anonymat sera assuré car en aucun temps votre nom sera dévoilé et aucunes informations pouvant révéler votre identité seront utilisées. De plus, vous pourrez retirer en tout temps votre consentement à participer à la recherche et cette décision compromettra en aucune façon votre traitement en cours.

Si vous désirez un complément d'information, quant à votre participation au projet, n'hésitez pas de communiquer avec Madame Dolly Dastoor au 761-6131 poste 23920.

Par la présente, je/_____ comprends ce qui m'a été expliqué quant au projet de recherche. En signant cette formule, j'autorise Madame Dolly Dastoor à recueillir une partie des données que l'on retrouve dans mon dossier médical à la Clinique de Mémoire à l'Hôpital Douglas.

_____   _____
Date   Signature du client, du mandataire ou du tuteur
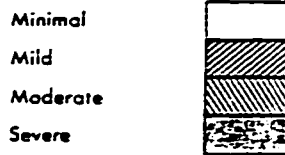

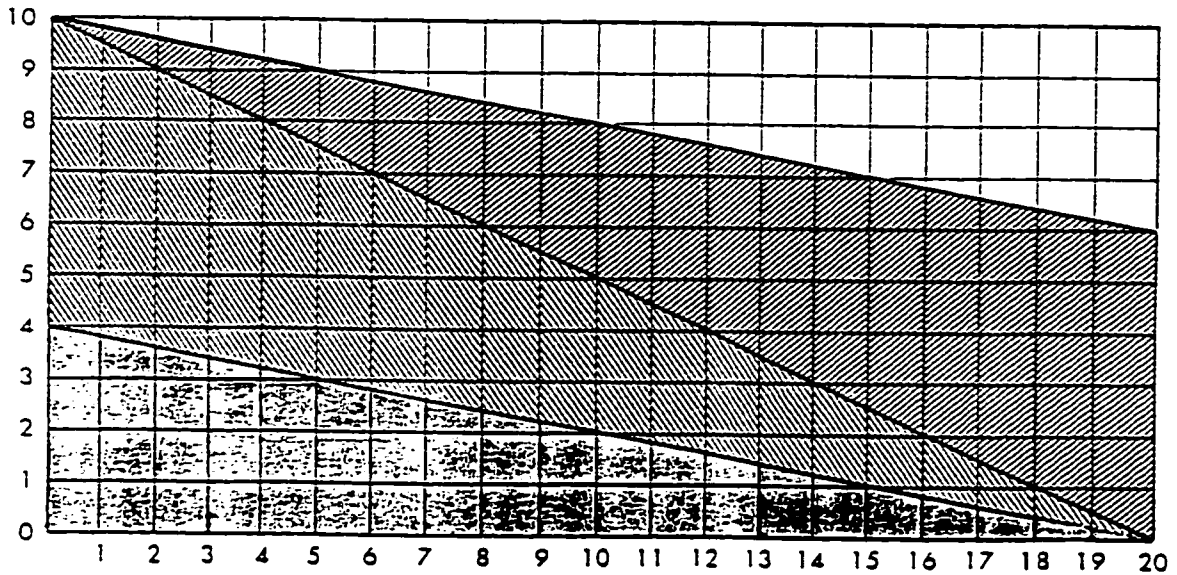_____   _____
Date   Signature d'un témoin

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APPENDIX M

Hierarchic Dementia Scale

HIERARCHIC DEMENTIA SCALE
(Colé and Dastoor)

Identification _____

Examiner _____

Date of Exam _____

Score _____

Minimal
Mild
Moderate
Severe

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1. Orienting

10. No impairment
8. Shakes Examiner's Hand
6. Reacts to Auditory Threat
4. Reacts to Visual Threat
2. Reacts to Tactile Threat

2. Prefrontal

10. None
8. Tactile Prehension
6. Cephalobuccal Reflex
4. Orovisual Reflex
2. Oral Tactile Reflex

3. Ideomotor

10. Reversed Hands
9. Double Rings
8. Double Fingers
7. Opposed Hands
6. Single Ring
5. Single Finger
4. Clap Hands
3. Wave
2. Raise Hands
1. Open Mouth

4. Looking

10. Finds Images
8. Searches for Images
6. Grasps content of Picture
4. Scans Picture
2. Looks at Picture

5. Ideational

10. Imaginary Match and Candle
9. Imaginary Nail and Hammer
8. Imaginary Scissors
7. Imaginary Comb
6. Match and Candle
5. Nail and Hammer
4. Scissors
3. Comb
2. Put on Shoes
1. Open Door

6. Denomination

10. No Errors
9. Nominal Aphasia — Parts
8. Nominal Aphasia — Objects
7. Use of Parts
6. Use of Objects
5. Conceptual Field — Parts
4. Conceptual Field — Objects
3. Sound Alike — Parts
2. Sound Alike — Objects
1. Deformed Words

7. Comprehension

Verbal:
5. Close eyes and touch left ear
4. Clap hands three times
3. Touch your right eye
2. Touch your nose
1. Open mouth

Written:
5. Close eyes and touch left ear
4. Clap hands three times
3. Touch your right eye
2. Touch your nose
1. Open mouth

8. Registration

10. Spoon, candle, scissors, button, whistle
8. Spoon, candle, scissors, button
6. Spoon, candle, scissors
4. Spoon, candle
2. Spoon

9. Gnosis

10. Superimposed Words
9. Superimposed Images
8. Digital Gnosis
7. Right-Left — Examiner
6. Right-Left — Self
5. Body Parts — Examiner
4. Body Parts — Self
3. Touch (pinch)   5 cm
2. Touch (pinch)   5 — 15 cm
1. Response to Touch (pinch)

10. Reading

10. Paragraph
8. Paragraph with error (s)
6. The cat drinks milk
4. Receive
2. M

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11. Orientation

    10. Date
    8. Month
    6. Year of Birth
    4. Morning or Afternoon
    2. First Name

12. Construction

    10. Four Blocks Diagonal
    8. Four Blocks Square
    6. Two Blocks Diagonal
    4. Two Blocks Square
    2. Form Board Circle

13. Concentration

    10. Serial 7's (100, 93, ...)
    9. Serial 3's (30, 27, ...)
    8. Months of Year Backwards
    7. Days of Week Backwards
    6. 93 − 85
    5. 10 − 1
    4. Months of Year Forwards
    3. Days of Week Forwards
    2. 1 − 10
    1. Actual Counting

14. Calculation

    10. 43 − 17
    9. 56 ÷ 19
    8. 39 − 14
    7. 21 ÷ 11
    6. 15 − 6
    5. 18 ÷ 9
    4. 9 − 4
    3. 8 ÷ 7
    2. 2 − 1
    1. 3 ÷ 1

15. Drawing

    10. Cube
    9. Cube (difficulty with perspective)
    8. Two Rectangles
    7. Circle and Square
    6. Rectangle
    5. Square
    4. Circle Inside Circle
    3. Circle
    2. Line
    1. Scribble

16. Motor

    10. No Impairment
    9. Increased Muscle Tone — Repeated
    8. Increased Muscle Tone — Initial
    7. Loss of Rhythm
    6. Loss of Associated Movements
    5. Contractures of Legs
    4. Kyphosis
    3. Vertical Restriction of Eye Movement
    2. Non-ambulatory
    1. Lateral Restriction of Eye Movement

17. Remote Memory

    10. Amount of pension
    8. Number of grandchildren
    6. Year of marriage or of first job
    4. Father's Occupation
    2. Place of Birth

18. Writing

Form:

    5. Flowing Style
    4. Loss of Flow
    3. Letters Misshappen
    2. Repetition or Substitution of Letters
    1. Scribble

Content:

    5. No Error
    4. Word Substitution
    3. Missing Preposition
    2. Missing Verb or Noun
    1. Missing 3 or 4 Words

19. Similarities

    10. Airplane — Bicycle
    8. Gun — Knife
    6. Cat — Pig
    4. Pants — Dress
    2. Orange — Banana

20. Recent Memory

    10. All Five
    8. Any Four
    6. Any Three
    4. Any Two
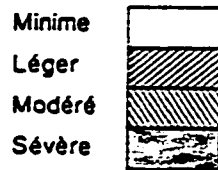   2. Any One

APPENDIX N

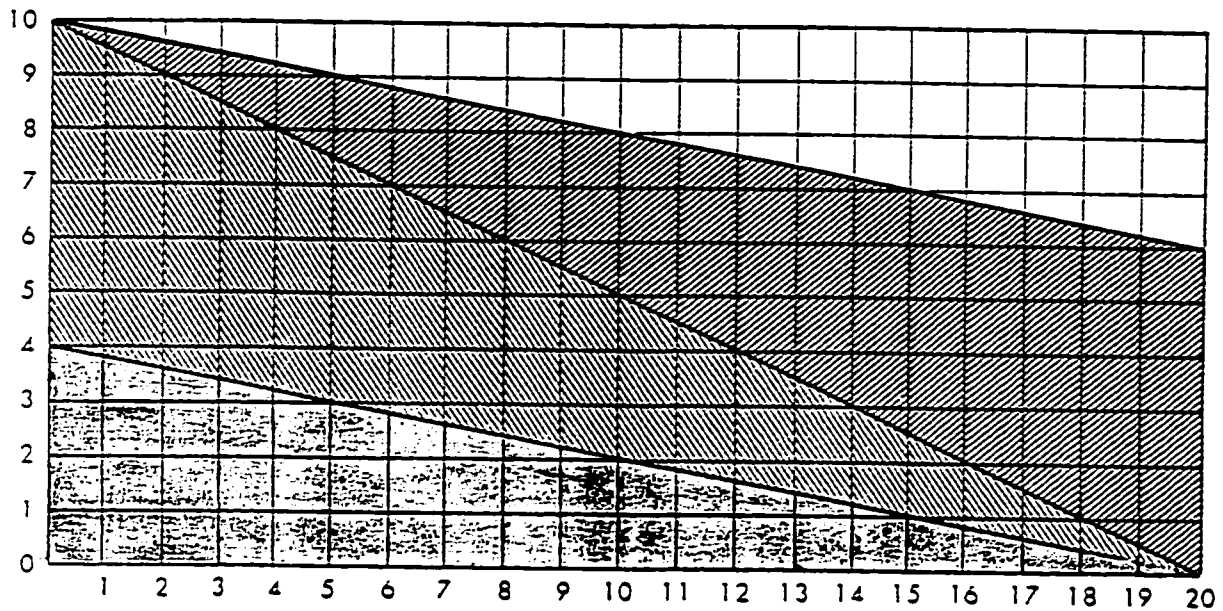## L'Echelle de Démence Hiérarchisée

ÉCHELLE DE DÉMENCE HIÉRARCHISÉE
(Cole et Dastoor)

Client _____

Évaluateur _____

Date de l'examen _____

Pointage Total _____

Minime

Léger

Modéré

Sévère

1. RÉACTIVITÉ

10. Sans détérioration
8. Serre la main de l'évaluateur
6. Réagit au stimuli auditif
4. Réagit au stimuli visuel
2. Réagit au stimuli tactile

2. PRÉ-FRONTALE

10. Aucun réflexe pathologique présent
8. Préhension tactile
6. Réflexe céphalobuccal présent
4. Réflexe orovisuel présent
2. Réflexe oro-tactile présent

3. IDÉOMOTRICE

10. Mains renversées
9. Anneaux doubles
8. Doigts doubles
7. Mains opposées
6. Anneau simple
5. Doigt simple
4. Tappage de main
3. Salutation
2. Levée de la main
1. Ouverture de la bouche

4. ORIENTATION VISUELLE

10. Trouve l'objet
8. Cherche l'objet
6. Comprend le contenu de l'image
4. Balayage de l'image
2. Regard sur l'image

5. IDÉOMOTRICE FONCTIONNELLE

10. Allumette et chandelle imaginaires
9. Clou et marteau imaginaires
8. Ciseaux imaginaires
7. Peigne imaginaire
6. Allumette et chandelle
5. Clou et marteau
4. Ciseaux
3. Peigne
2. Remettre de soulier
1. Ouverture de la porte

6. DÉNOMINATION

10. Aucune erreur
9. Aphasie nominale (partie)
8. Aphasie nominale (objet)
7. Usage des parties d'objets
6. Usage des objets
5. Champ conceptuel (partie)
4. Champ conceptuel (objet)
3. Résonne comme (partie)
2. Résonne comme (objet)
1. Mots déformés (crayon, peigne, chandelle)

7. COMPRÉHENSION

Verbal
5. Fermez vos yeux et touchez l'oreille gauche
4. Tapez les mains trois fois
3. Touchez votre oeil droit
2. Touchez votre nez
1. Ouvrez la bouche

Écrit
5. Fermez vos yeux et touchez l'oreille gauche
4. Tapez les mains trois fois
3. Touchez votre oeil droit
2. Touchez votre nez
1. Ouvrez la bouche

8. ENREGISTREMENT

10. Cuillère, chandelle, ciseaux, bouton, sifflet
8. Cuillère, chandelle, ciseaux, bouton, sifflet
6. Cuillère, chandelle, ciseaux, bouton, sifflet
4. Cuillère, chandelle, ciseaux, bouton, sifflet
2. Cuillère, chandelle, ciseaux, bouton, sifflet

9. GNOSIE

10. Mots superposés
9. Images
8. Gnosie digitale
7. Gauche-droite - évaluateur
6. Gauche-droite - soi
5. Partie du corps - évaluateur
4. Partie du corps - soi
3. Localisation (8 cm)
2. Localisation (5-15 cm)
1. Réponse au toucher

10. LECTURE

10. Paragraphe
8. Paragraphe avec erreur (s)
6. Le chat boit du lait
4. Recevoir
2. M

11. TEMPORELLE

- 10. Date
- 8. Mois
- 6. Année de Naissance
- 4. Matin ou après-midi
- 2. Prénom

12. CONSTRUCTION

- 10. 4 blocs - diagonal
- 8. 4 blocs - carré
- 6. 2 blocs - diagonal
- 4. 2 blocs - carré
- 2. Forme circulaire

13. CONCENTRATION

- 10. Soustraction en série de 7 (100, 93, ...)
- 9. Soustraction en série de 3 (30, 27, 24, ...)
- 8. Mois de l'année à l'envers
- 7. Jours de la semaine à l'envers
- 6. 93 à 85
- 5. 10 à 1
- 4. Mois de l'année
- 3. Jour de la semaine
- 2. 1 à 10
- 1. Compter des objets

14. CALCUL

- 10. 43 - 17
- 9. 56 + 19
- 8. 39 - 14
- 7. 21 + 11
- 6. 15 - 6
- 5. 18 + 9
- 4. 9 - 4
- 3. 8 + 7
- 2. 2 - 1
- 1. 3 + 1

15. DESSIN

- 10. Cube
- 9. Cube (difficulté de perspective)
- 8. Deux rectangles
- 7. Cercle et carré
- 6. Rectangle
- 5. Carré
- 4. Cercle concentrique
- 3. Cercle
- 2. Ligne
- 1. Griffonnage

16. MOTRICE

- 10. Sans déficit
- 9. Tonus musculaire augmenté - répété
- 8. Tonus musculaire augmenté - initial
- 7. Perte de rythme
- 6. Perte de mouvement associé
- 5. Contraction de la jambe
- 4. Kyphose
- 3. Restriction verticale des mouvements oculaires
- 2. Non-ambulatoire
- 1. Restriction latérale des mouvements oculaires

17. MÉMOIRE LOINTAINE

- 10. Montant de la pension
- 8. Nombre de petit-enfants
- 6. L'année du mariage (ou 1er emploi)
- 4. L'occupation du père
- 2. Le lieu de naissance

18. ÉCRITURE

Forme:
- 5. Style fluide
- 4. Perte de fluide
- 3. Déformation de lettres
- 2. Répétition ou substitution de lettres
- 1. Gribouillage

Contenu:
- 5. Sans erreur
- 4. Substitution de mot
- 3. Préposition manquante
- 2. Verbe ou mot manquant
- 1. Deux mots ou plus manquants

19. SIMILARITÉ

- 10. Avion - bicyclette
- 8. Fusil - couteau
- 6. Chat - cochon
- 4. Culotte - robe
- 2. Orange - banane

20. MÉMOIRE RÉCENTE

- 10. tous les 5
- 8. 4
- 6. 3
- 4. 2
- 2. 1

Traduit par Alain Lagacé, mai 1988.