DIAGNOSTIC APPROACHES AND MANAGEMENT ASPECTS OF EARLY DEMENTIA.

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DIAGNOSTISCHE BENADERINGEN EN MANAGEMENT ASPECTEN VAN VROEGE DEMENTIE.

Proefschrift

ter verkrijging van de graad van doctor

aan de Erasmus Universiteit Rotterdam

op gezag van de rector magnificus

Prof. Dr. C.J. Rijnvos

en volgens besluit van het College van Dekanen.

De openbare verdediging zal plaatsvinden op

woensdag 8 mei 1991 om 15.45 uur.

door

THERESIA JOHANNA MARIA VAN DER CAMMEN

geboren te Rotterdam

Promotiecommissie:

Promotoren:	Prof. Dr. F.J.G. Oostvogel Prof. Dr. W.J. Schudel
Overige leden:	Prof. Dr. A. Hofman Prof. Dr. M.A.D.H. Schalekamp

Gedrukt door: Drukkerij Haveka B.V., Alblasserdam.

Voor Johanna

CONTENTS

CHAPTER I: INTRODUCTION.

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Learning (the acquisition of new knowledge) and memory (the retention of knowledge) are abilities which have assumed increasing importance in the climb up the evolutionary tree. How organisms learn and remember is one of the most interesting problems in neuroscience (Morris et al 1988). The loss of these abilities in man is one of the most devastating clinical problems for individual sufferers, their carers and for society at large. The commonest cause of such loss is Alzheimer type dementia. This thesis discusses diagnostic approaches and management aspects of early dementia, especially of the Alzheimer type.

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Morris RGM, Kandel ER, Squire LR (1988) The neuroscience of learning and memory: cells, neural circuits and behaviour. Trends in Neuroscience 11: 125-127.

I.1 THE CONCEPT OF DEMENTIA: A HISTORIC OVERVIEW.

The concept of dementia that we know today, has evolved over many centuries, as was pointed out by Mahendra (1987) in his excellent review of the history of the concept. 'Dementia' corresponds to Latin 'dementatus' - that is, out of one's mind, crazed, applicable to any and all abnormal, unusual, incomprehensible or bizarre behaviour. Over 20 centuries the term has been adapted to suit conditions that were current in any given society. It is easy to understand that a concept now employed in most instances in relation to the elderly sick in de 20th century might not have had much meaning for the very different populations, patients and practitioners of the past.

For a start, living to be old was a distinctly unusual phenomenon in past centuries. Very few in the population survived to the senium, the period of life in which dementia becomes a calculable prospect rather than a chance occurrence. An estimate of those reaching the age of 65 in primitive society is around 3%; the lifespan, on the average, of a subject in the Roman Empire was less than 30 years; an Englishman in 1700 could hope to live a mean of 35 years; in 1840 the span of life in western Europe had risen to 40-43 years, and in the 1980s it is 76-80 years, women living to the higher age.

In those early days, while the small number of the elderly would have shown the common cognitive changes associated with normal old age, only a minute proportion would have become demented in a modern sense. It is easy to see how the features of pathologic old age in the few would have been swamped by the relatively larger number of the elderly showing subtler physiological changes (Mahendra 1987).

The account of earlier approaches to senility and attitudes to old age owes much to George Rosen's excellent paper (Rosen 1961). Rosen quotes Cicero's essay on old age in the 2nd century BC. The major preoccupation in this age was the practice of mental hygiene. Poets and philosophers, at least, wondered if an active mental life might not forestall or postpone the decrepitude of old age. Cicero wrote:

> 'It is our duty to resist old age; to compensate for its defects by a watchful care; to fight against it as we would fight against disease....
> Much greater care is due to the mind and soul; for they, too, like lamps, grow dim with time, unless we keep them supplied with oil....

> Intellectual activity gives buoyancy to the mind.... Old men retain their mental faculties, provided their interest and application continue... the aged remember everything that interests them....' (Rosen 1961)

Aurelius Cornelius Celsus (30 BC-AD 50), a Roman writer on medical subjects, introduced the terms 'delirium' and 'dementia' in his encyclopaedia 'De re medicina', published around AD 30 (Alexander & Selesnick 1966; Lipowski 1980; Lipowski 1981).
A century later, the term 'senile dementia' itself seems to have been first used by Aretaeus, the physician of Cappadocia. He mentions 'the dotage which is the calamity of old age ...dotage commencing with old age never intermits, but accompanies the patient until death; while mania intermits, and with care ceases altogether' (Rosen 1968; Alexander 1972). Aretaeus may have been the first to use the equivalent of the term 'senile dementia' - dotage - and to distinguish it from 'secondary' dementia (Menninger et al 1963).
In the 2nd century AD, when only a fraction of humanity was still destined to reach old age, Juvenal (AD 60-130) dealt with the subject of dementia with pessimism and bitterness in his tenth satire:

> 'But worse than all bodily failing is the weakening mind which cannot remember names of slaves, nor the face of a friend he dined with last evening, cannot remember the names of offspring begotten and reared....' (Lipowski 1981)

A couple of centuries later, in the 4th century AD, Oribasius, physician to the Emperor Julian, wrote of cerebral atrophy in his 'Digest of Medicine and Surgery'. This disease was thought to manifest itself by loss of intellectual capacity and weakness of movement (Rosen 1961, 1968).
With regard to depression, Rosen (1961) notes that in the 9th century AD Rhazes the Persian physician mentions melancholy as an inevitable condition in the lives of old and decrepit persons.
The Moslem writers of the Middle Ages seem to have had ideas similar to those of the Graeco-Romans on the nature of old age. The inevitable decrepitude and melancholic character of old age were commonplace ideas during the

Renaissance period but the principal sources remained the ancient authors or mediaeval writers indebted to classical thought (Rosen 1961; Mahendra 1987).
Robert Burton (1577-1640), the author of 'Anatomy of Melancholy', observed that 'after seventy years all is trouble and sorrow'. He had views on the relationship between old age and melancholy too, saying that old age was 'natural to all ...being cold and dry, and of the same quality as Melancholy is, must needs cause it, by diminution of spirits and substance....'
Shakespeare (1564-1616) has shown remarkable understanding of the psychological make-up of his fellow men, as is revealed by the words he puts into the mouths of many of the characters in his plays. He decribes 'senile decay' in 'As you like it':

'The sixth age shifts
Into the lean and slipper'd pantaloon,
With spectacles on nose and pouch on side;
His youthful hose, well sav'd, a world too wide
For his shrunk shank; and his big manly voice,
Turning again towards childish treble, pipes
And whistles in his sound. Last scene of all
That ends this strange eventful history,
Is second childishness and mere oblivion,
Sans teeth, sans eyes, sans taste, sans everything'.

(As You Like It)

Shakespeare notes the effect of ageing on the manifestations of mental disorders in 'King Lear'. Lear has been quoted as the prime example of involutional depressive illness (Trethowan 1988). He appears in the play as a melancholic, characteristically hell-bent on self-destruction. Later on, he demonstrates forgetfulness, as is revealed in his speech to his daughter Cordelia and his physician:

'Pray do not mock me:
I am a very foolish fond old man,
Fourscore and upward, not an hour more nor less;

And to deal plainly,
I fear I am not in my perfect mind.
Methinks I should know you, and know this man;
Yet I am doubtful: for I am merely ignorant
What place this is; and all the skill I have
Remembers not these garments; nor I know not
Where I did lodge last night.'

(King Lear)

Lear's forgetfulness suggests that degenerative changes leading to senile dementia are beginning to supervene, but as Trethowan (1988) has pointed out, Shakespeare did not portray the distressing state of the final stage of senile dementia in any of his plays. Perhaps the reason why Shakespeare, with his remarkable insights, did not go into the matter further, was that people in his day did not live as long as they do now. Furthermore, preferring sudden death by violence, he probably did not consider senile decay a very enlivening subject with which to entertain Elizabethan theatre audiences (Trethowan 1988).

The period between 1535 and 1860 is covered by Hunter and Macalpine's excellent source book (Hunter & Macalpine 1963). The authors include an account of William Salmon (1644-1713), a London practitioner who made his living from patients turned away from St Bartholomew's Hospital, an early indication perhaps of attitudes to the less glamorous branches of the medical profession. He described a patient with senile dementia under the heading, 'Defects of Imagination, Reason and Memory in a Man superannuated' whom he diagnosed as 'not mad' but 'decayed in his Intellectuals'. He observed the early stages when such patients complain of depression and hypochondriacal symptoms and drew attention to the diagnostic triad of emotional lability, loss of memory for recent events and perseveration, suggesting arteriosclerotic dementia (Hunter & Macalpine 1963). Between 1793 and 1838 the clinical recognition of senile dementia evolved rapidly. The first ripple was recognition as a medical entity by Cullen: 'Imbecility of judgement, by which men either do not perceive the relation of things or forget them due to diminished perception and memory when oppressed with age' (Cullen 1793; Torack 1983, p 26). Another astounding recognition occurred in 1793, 3.000 miles across the sea, from the brilliant

I.1 The concept of dementia: A historic overview.

Benjamin Rush:

> 'It would be sufficiently humbling to human nature if our bodies exhibited in old age the marks only of a second childhood; but human weakness descends still lower. I met with an instance of a woman between 80 and 90 who exhibited the marks of a second infancy, by such a total decay of her mental faculties as to lose all consciousness in discharging her alvine and urinary excretions. In this state of the body, a disposition to sleep succeeds the wakefulness of the first stages of old age'.
>
> (Rush 1793, p 311; Torack 1983, p 26).

In 1797, Philippe Pinel (1745-1826) threw the shackles off the inmates at Bicetre; some of these inmates were senile dements. Pinel coined the term 'demence' to indicate that condition in which 'there is no judgement either true or false. The ideas appear to be insulated and to rise one after the other without connection, the faculty of association being destroyed' (Pinel, translation by Davis 1977; Torack 1983).
It was, however, Jean Etienne Dominique Esquirol (1772-1840) working with Pinel who really defined senile dementia in an 1838 text:

> 'Senile dementia is established slowly. It commences with enfeeblement of memory, particularly the memory of recent impressions. The sensations are feeble; the attention, at first fatiguing, at length becomes impossible; the will is uncertain and without impulsion; the movements are slow and impractical'.
>
> (Esquirol 1838 and 1976, p 261; Torack 1983, p 26).

This 1838 description by Esquirol essentially completed the clinical characterization of senile dementia. Esquirol distinguished three varieties of dementia: acute, chronic and senile. The acute variety could be caused by fever or haemorrhage and it was curable. The chronic form could be due to such factors as masturbation and drunkenness, or it could follow mania or epilepsy, and it was seldom cured. Clearly, Esquirol included a wide range of psychiatric

disorders including delirium and functional illness in this conception. Although he was over-inclusive in his use of the term 'senile dementia', his description of cognitive changes in some of those he considered demented in the senium brings him close to the modern conception (Mahendra 1987). Esquirol was able to sum up the difference between the demented and the mentally handicapped in an 1838 epigram: 'The dement is a man deprived of the possessions he once enjoyed, he is a rich man who has become poor. But the defective has been penniless and wretched all his life' (Esquirol 1838; Mahendra 1987). By 1838, then, the clinical description of senile dementia was essentially completed.

The 19th century was dense with systems of classification and large heroic figures. The German titans - Neumann, Kahlbaum and Griesinger - believed that there was one mental disease - insanity - and that the various clinical syndromes were but stages of a unitary morbid process (Menninger et al 1963). Dementia was considered to be the terminal stage of the process. In 1837 the British psychiatrist Prichard divided dementia into primary and secondary forms and proposed that the illness could be divided into four stages, but the aetiology was still ascribed to moral rather than to physical causes (Lipowski 1981).

Emil Kraepelin (1856-1926) narrowed the scope of the word dementia. Clinical classification was a field of exceptional interest for Kraepelin. In the famous 6th edition of his textbook (published in 1899, translated by Defendorf in 1902) Kraepelin separated 'dementia praecox' (schizophrenia) from the other dementias (paralytic and organic), a decision that greatly narrowed the scope of the concept of dementia. In this 1899 edition, the chapter on 'involutional psychosis' included (A) melancholia, (B) presenile delusional insanity, and (C) senile dementia (Kraepelin 1899, translation by Defendorf 1902; Amaducci et al 1986).

Gradually, histological and clinical studies began differentiating arteriosclerotic vascular disease from neurosyphilitic general paresis on the one hand, and from senile psychoses on the other.

Blocq and Marinesco, in 1892, first described what we now know as senile plaques, although they were then called 'neuroglia nodules', in the brain of an elderly patient affected by epilepsy (Blocq & Marinesco 1892). In 1898, Redlich re-described these same lesions as 'miliary sclerosis' in the brain of two cases of senile cerebral atrophy associated with memory defects and mental confusion (Redlich 1898; Rosen 1961). It was Simchowitz who first proposed the term 'senile

plaque' in 1911 (Ferraro 1975). But it was Alzheimer in 1904, who reported their presence in cases of senile dementia. Since he believed that the major problem in cerebral atrophy was arteriosclerosis, however, and because he assumed that the plaques were glial tissue, he did not get excited. It was only in 1906, with the aid of the new Bielschowsky stain, that he identified something new: neurofibrillary tangles - and reported his findings to a meeting of the Southwest German Society of Alienists a year later (U'Ren 1987). Alzheimer's famous case, reported in 1907, was a 51-year-old woman who presented with morbid jealousy, loss of memory, capricious behaviour, spatial and temporal disorientation, persecutory ideas and speech difficulties. The focal symptoms were always mild but the dementia progressed and she was dead within 5 years. To the naked eye her brain appeared atrophied without obvious lesions on the surface, though the larger vessels seemed atherosclerosed. Microscopically, inside cells, numerous thick fibrils taking on silver stain were found. Up to a third of cells had a metabolic product deposited in the cell, and scattered throughout the cortex, especially in the upper layers, were found numerous 'miliary foci' due to the deposition of a peculiar substance. There was no infiltration of the blood vessels (Alzheimer 1907).

Thus, with the aid of the new Bielschowsky stain, Alzheimer had identified the neurofibrillary tangle. He was sure he had discovered a new disease entity, a form of dementia occurring in the presenium. Kraepelin was again sceptical about the distinction between senile and presenile dementia on the basis of age alone and commented: 'The anatomic findings suggest ... an especially severe form of senile dementia.' But Kraepelin finally accepted Alzheimer's argument and endorsed the existence of presenile dementia (a term actually proposed by Binswanger in 1898) in the 8th edition of his textbook in 1910 (Kraepelin 1910; Torack 1978). It remained for Simchowicz in 1910 to describe the granulovacuolar changes in the large pyramidal cells of the hippocampus to complete the triad of neuropathological changes we now associate with Alzheimer's disease, i.e., senile plaques, neurofibrillary tangles, and granulovacuolar changes (Ferraro 1975).

Initially, the diagnosis of Alzheimer's disease was dependent upon both clinical and pathological characteristics, but the specificity of the senile plaque was already being questioned. The specificity of the other element in the histopathological diagnosis, the neurofibrillary tangle, also became uncertain when

it was found outside dementing illness, as in amyotrophic lateral sclerosis and post-viral Parkinson's disease. Soon it became known that large numbers of normal people in the senium had some senile plaques and neurofibrillary tangles. In 1936, Jervis and Soltz advised that only clinical criteria would suffice for a diagnosis of Alzheimer's disease (Jervis & Soltz 1936).

In 1955, Roth showed that conditions such as affective disorder, late paraphrenia and confusional states were entities which were distinct from senile and arteriosclerotic dementia (Roth 1955). The neuropathological correlates of this finding were later established by Tomlinson et al (1968, 1970), who demonstrated that the changes in the brain in such conditions as physical illness, confusional states, depressive illness and paraphrenia were minimal and far removed from those in Alzheimer type dementia (see also chapter I.2).

Although by the turn of the century, as Mahendra (1987) has pointed out, the use of the word dementia had become much more specific than it had been earlier (dementia usually occurred in older age but sometimes earlier; its principal causes - syphilis, arteriosclerosis, Alzheimer's disease - could be identified and distinguished from each other; it was due to brain disease), the entire field of organic psychiatry fell into relative neglect during the last 80 years. This was caused, in large part, by the influence of Freud and his followers, who caused American psychiatry to swerve in the direction of psychological explanations for mental illness and toward psychotherapy. But is was also caused by the father of descriptive psychiatry himself, Kraepelin, whose brilliant descriptions and solid classifications seemed to leave little room for therapeutic efforts or optimism (U'Ren 1987).

In the last 25 years, and especially in the last 10 years, organic psychiatry has been on the move again, and the concept of dementia is once again the focus of research. The interest in dementia, in both the United States and Great Britain, has also been part of the larger development of geriatric medicine in those two countries (Adams 1975; Beck & Vivell 1984). Research into the aetiology and pathogenesis of the various dementias is at present a worldwide activity, with Alzheimer type dementia being one of the world's most intriguing research interests.

Vascular or arteriosclerotic dementia.

Leonardo da Vinci had recognized that arteriosclerosis occurred in blood vessels, but it was François Bayle who was the first, in 1677, to relate it to strokes (McHenry 1969). In 1694, George Baglivi attended the famous Malpighi when Malpighi was struck down by a stroke that affected the right side of his body. After 40 days, however, 'he got clear of the Apoplexy, and Palsie', but it was observed that he was left somewhat demented, 'impaired in Memory and Reason, with emotional weakness, melting into tears upon the slightest occasion' (Major 1945). On November 29 that year, Malpighi had a further apoplectic fit and died. A week later, Baglivi dissected his corpse. The heart was enlarged and there were about 2 pints of black clotted blood in the brain. The blood vessels of the brain were dilated and broke on all hands (Baglivi 1704). By the time the 6th edition of Kraepelin's textbook was published, it was established with some authority that arteriosclerosis could be distinguished from senile dementia and was associated with a form of insanity characterized by headache, vertigo, irritability, loss of memory, aphasia, circumscribed paralyses and periods of remission (Kraepelin 1899, translation by Defendorf 1902). The groundwork had been laid earlier by Alzheimer who, in 1894, had reported the characteristic microscopic changes associated with arteriosclerosis of the brain and, along with Kraepelin, had correlated them with the clinical findings (Kraepelin 1899, translation by Defendorf 1902; Mahendra 1987). Their description tallies closely with what we would call multi-infarct dementia nowadays.

A possible aetiological role for transmissible agents in the dementia syndrome?

The role of transmissible agents slowly inducing brain disease and dementia was discovered with the advent of the twentieth century.

In 1904, Alzheimer described the histopathology of general paresis (Alexander & Selesnick 1966).

In 1905, Fritz Schaudinn discovered the spirochaete (Treponema pallidum) causing syphilis in primary lesions. In 1913, Noguchi and Moore demonstrated the spirochaete in the brains of patients with general paresis due to syphilis (Alexander & Selesnick 1966).

In 1920 Creutzfeldt, and in 1921 Jakob, described cases of dementia with

pyramidal and extrapyramidal signs. Creutzfeldt's case is now excluded from the group of spongiform encephalopathies, among which the disease is classified. Jakob's original five slides were reviewed more than 50 years after they were made by Masters and Gajdusek, who found that two of Jakob's five cases represented the earliest proven examples of subacute spongiform encephalopathy (Masters & Gajdusek 1982). The disease, which is occasionally familial, is rare and the neuropathological findings are those of a degenerative disease of the nervous system, in which there is a tendency for nerve cells to vacuolate and to die, for astrocytes to swell and to proliferate, and for the grey matter to reflect the neuronal and glial changes by developing a spongy look (Corsellis 1979).

In 1957, Gajdusek and Zigas identified the condition called kuru, a degenerative disease of the central nervous system with a genetic bias leading to cerebellar ataxia, in certain tribes in the Eastern Highlands of Papua-New Guinea (Gajdusek & Zigas 1957). But it was not until 1965, through the work of Gajdusek, that 'kuru became the first heredofamilial chronic degenerative disease of the central nervous system of man demonstrated to be a virus-induced slow infection with incubation periods measured in years and with a progressive accumulated pathology restricted to the gray matter of the brain and spinal cord leading to death' (Gajdusek & Gibbs 1968; Gibbs & Gajdusek 1978). By 1968, the transmissible nature of Creutzfeldt-Jakob disease had been established and it was placed, together with kuru and scrapie, within the group of 'transmissible subacute spongiform encephalopathies', thought to be due to an unconventional group of 'slow viruses' (Cohen 1983; Gajdusek & Gibbs 1968; Gibbs & Gajdusek 1978).

Recent research has shown that prion protein gene analysis can help to determine the full clinical and neuropathological phenotype in familial cases of human spongiform encephalopathy, and thus, the term 'prion dementia' or 'prion disease' has been introduced (Collinge et al 1990).

With regard to the durability of scrapie virus, it was recently demonstrated that the virus can survive for 3 years when exposed to natural environmental conditions, and that most residual infectivity remains in the originally contaminated soil, with little leaching (Brown & Gajdusek 1991). These results have implications for environmental contamination by scrapie and by similar agents, including those of bovine spongiform encephalopathy and Creutzfeldt-Jakob disease (Brown &

Gajdusek 1991).

Discussion.

The definition of Alzheimer type dementia was essentially completed by 1910. Neurofibrillary tangles and granulovacuolar degeneration described by Alzheimer and Simchowicz in 1906 and 1910, respectively, were the major morphological additions to the senile plaque. However, the essential question on its aetiology was not resolved then, and it remains unresolved today. Is Alzheimer type dementia the seventh stage of life as described by Shakespeare or is it a true age related disease?

Recent evidence indicates that there is more than one cause of Alzheimer type dementia. In some instances, the disorder is caused by a genetic defect on chromosome 21. In other instances, the disorder results from other mono- or polygenic genetic defects, from non-genetic agents, or from mixed genetic and environmental factors (St. George-Hyslop et al 1990).

The most recent evidence suggests that some cases of Alzheimer type dementia could be caused by mutations in the amyloid precursor protein (APP) gene of chromosome 21, with the resulting beta-amyloid peptide deposition as the central event in the pathogenesis of the disorder (Goate et al 1991).

It is not impossible that slow viruses which have not yet been discovered might be implicated in the aetiology of Alzheimer type dementia. There is also renewed interest in the possible causal role of heavy metals and poisonous solutions.

The interesting point to note is that, throughout the evolution of the concept of Alzheimer type dementia, its main differential diagnosis has been with depression and multi-infarct dementia, a situation that persists until today.

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I.2 CURRENT CONCEPTS OF DEMENTIA, DEFINITIONS, DIAGNOSTIC CRITERIA AND DIFFERENTIAL DIAGNOSIS.

The evolution of the definition of dementia.

As we have seen in the first part of this chapter, the concept of dementia has evolved over many centuries.

Whilst, therefore, the term dementia may have meant many things to many men over many centuries, the last few decades have seen a development towards a consensus definition of dementia.

Dementia is a functional, not a pathological term. The term describes a clinical syndrome that can be produced at any age by numerous causes (see Table I.2.1), although most cases are associated with degenerative disease of the central nervous system (Haase 1977). Of these, Alzheimer type dementia is by far the most common cause. It has been estimated that, of all cases of dementia, 60 to 70 per cent are of the Alzheimer type, and 10 to 15 per cent are due to multi-infarct dementia; another 10 to 15 per cent are due to a combination of Alzheimer type dementia and multi-infarct dementia, often referred to as 'mixed dementia' (Sourander & Sjogren 1970; Tomlinson et al 1970; Jellinger 1976; Wells 1977; Smith & Kiloh 1981). In perhaps as many as 5 per cent of cases of dementia, its cause remains unknown, even after extensive post mortem studies (Katzman 1986). The remaining 5 per cent suffer from various other, less common but nevertheless important and in some cases potentially reversible conditions (see Table I.2.1). The brain is affected in different ways; the final expression is widespread neuronal failure and dementia. In series that were evaluated before cranial computed tomography was available (Vitaliano et al 1984), brain tumours in either the midline or the so-called silent areas - especially the right frontal and temporal lobes - were found in 4 to 5 per cent of cases of dementia (Katzman 1986). However, in a recent study, in which assessment included cranial computed tomography, a high diagnostic error rate was found between the clinical diagnosis and the findings at autopsy, with Alzheimer type dementia being overdiagnosed (13 clinical diagnoses, of which only six were confirmed at autopsy), and with multi-infarct dementia being underdiagnosed (16 cases diagnosed at autopsy, with only 10 having been correctly diagnosed during life) (Homer et al 1988).

Another recent study (Duyckaerts et al 1990) compared the impressions and analyses of investigators from 11 different laboratories on 2 slides from each of 6 cases with varying quantities of neuropathological changes found in Alzheimer

I.2 Current concepts of dementia, definitions, diagnostic criteria and differential diagnosis.

Table I.2.1
Causes of the dementia syndrome

Common causes
Alzheimer type dementia
Multi-infarct dementia
Mixed Alzheimer type dementia and multi-infarct dementia

Less common causes
Head trauma
Huntington's chorea
Parkinson's disease
Pick's disease
Progressive supranuclear palsy
Progressive myoclonus epilepsy
CNS-infections (AIDS, Creutzfeldt-Jakob disease, postencephalitic and syphilis)
Normal pressure hydrocephalus
Space occupying lesion(s)

Medical disorders which may present with a dementia syndrome
Endocrine disorders: hypo/hyperthyroidism, Cushing's syndrome, hypopituitarism
Metabolic disorders: hyponatraemia, hypercalcaemia
Neoplasms: multiple intracerebral metastases, meningeal carcinomatosis
Nutritional disorders: pernicious anaemia, pellagra, thiamine deficiency
Toxic disorders: drugs, alcoholism, heavy metals, chemicals

Psychiatric disorders which may mimic dementia
Depression
Acute confusional state (delirium)
Schizophrenia

Other situations which may mimic dementia
Sensory deprivation due to hearing or visual disabilities
Social isolation
Severe psychosocial stress
Insomnia
Severe pain

type dementia and normal ageing. The material came from 6 selected female patients, who had died aged over 75, and who had been examined in detail and assessed by the Blessed Dementia Rating Scale during life. Two were severely demented, 2 mildy demented and 2 were considered to be normal. Unstained paraffin-embedded slides were sent to the different investigators, the choice of the staining techniques being left to each laboratory. A quantitative evaluation of the changes was requested in 2 specified areas of the hippocampus and in the first temporal gyrus. Subjective scores of severity of brain changes and a final guess about the pre-mortem intellectual status (demented or not) were asked. The 11 replies were analyzed. A total of 14 different staining techniques were used. Absolute values of density differed much from one investigator to another, for senile plaques as well as for neurofibrillary tangles. Statistical analysis showed that concordance might be improved by the use of corrective factors which would standardize the scales of measurement. The observers guessed correctly the intellectual status of the 2 most affected cases and often disagreed for the intermediate and normal cases. It was concluded that quantitative assessment is useful in cases with few lesions and mild Alzheimer type dementia, but that the neuropathological diagnostic procedures have to be more strictly standardized before quantitative histopathological criteria can be reliably transferred from one laboratory to another, especially when mildly affected cases are involved (Duyckaerts et al 1990).

The list of causes of dementia grows constantly, with dementia secondary to the acquired immunodeficiency virus (Shaw et al 1985) being the most recent addition.

The concept of dementia was defined by the neuropathological studies of Corsellis (1962) and the clinical and neuropathological studies of Roth at al between 1952 and 1970 (Roth & Morrissey 1952; Roth 1955; Blessed et al 1968; Tomlinson et al 1968; Roth & Myers 1969; Tomlinson et al 1970). The modern era of knowledge about Alzheimer's disease and dementia really began in 1955, when Roth demonstrated that mental changes could be caused by a variety of both 'functional' and 'organic' diseases (Roth 1955). In 1955, Roth defined senile dementia as 'a condition with a history of gradual and continuously progressive failure in the common activities of everyday life and a clinical picture dominated by

failure of memory and intellect and desorganisation of the personality, where these are not attributable to specific causes such as infection, neoplasm, chronic intoxication or a cerebrovascular disease known to have produced cerebral infarctions'. In this description, Roth accentuates the slowly progressive loss of independence and adaptation and already implies exclusion criteria similar to those used in the 1980 version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) (American Psychiatric Association 1980).

Corsellis (1962) was the first to use Roth's 1955 criteria in a study of the correlation between the clinical picture and the brain changes found at autopsy. He found a considerable correlation between the clinical diagnosis and the degree of the neuropathological brain changes (both degenerative and vascular). Roth and his colleagues continued this work (Blessed et al 1968; Tomlinson et al 1968, 1970).

In 1968, Blessed et al reported a prospective study of elderly persons whose mental status, as determined during life, correlated with changes in the brain that were detected at autopsy. Most of the subjects with dementia fell into one of two categories - a larger group with the characteristic brain changes of Alzheimer type dementia and a smaller group with vascular disease and multiple infarcts (strokes). Within the group with the Alzheimer type brain changes, there was a strong correlation between mental test scores and functional scores (as measured on the Blessed Dementia Rating Scale), obtained one to 11 months before death, and the number of neuritic plaques found in the cerebral cortex. Within the group with multiple infarcts (strokes), there was also a relation between the amount of cerebral hemisphere tissue that was destroyed or infarcted and the presence of dementia. The degree of atherosclerosis in the cerebral blood vessels was not itself related to the presence or absence of dementia (Blessed et al 1968). This study established the importance of the quantitative relationship between clinical features of senile dementia and the extent of the pathological changes in the brain. The same group of investigators compared brain changes found at autopsy of 28 non-demented elderly people and 50 elderly patients with severe senile dementia either of the degenerative or of the vascular type (Tomlinson et al 1968, 1970). They found a striking difference in the number of neuritic plaques, neurofibrillary tangles, granulovacuolar changes and Hirano bodies between the

Table I.2.2: List of definitions.

* **Senile plaques** are neuritic plaques with a complex structure containing amyloid, degenerating synaptic terminals and neurites; they are easily stained with dyes such as Bielschowsky silver and are round and vary between 5 and 100 micrometer in size with a central dense core which contains amyloid; surrounding this core is a crown of radiating, intensely argentophilic structures up to 5 micrometer in diameter - these are thought to contain the remains of degenerating mitochondria and numerous lamellar lysosomes, which seem to be derived from the mitochondria; paired helical filaments are also found to be prominent in most plaques.
* **Neurofibrillary tangles** are abnormal neurones in which the fibrillar components of the nerve cell body condense into twisted, convoluted masses in the cytoplasm; the tangle is mainly made up of highly stable paired helical filaments, each pair being about 20 nanometer at its widest and having a narrow twist about every 80 nanometer along its length.
* **Granulovacuolar degeneration** is the third neuropathological change associated with Alzheimer type dementia; this change is restricted to neurones in the medial temporal structures and consists of multiple vacuoles of 5-6 micrometer in the cytoplasm of the neurones; each vacuole contains a single central 1-2 micrometer granule; clusters of vacuoles may cause the neurones to bulge and displace the nucleus.
* **Hirano bodies** are elongated eosinophilic structures in the hippocampus; usually they are immediately adjacent to the hippocampal pyramidal neurones, but they may be found away from neurones; they appear as paracrystalline, ovoid or spheroid bodies and are brightly eosinophilic on light-microscopic examination; electron microscope examination shows them to be sheets of membrane-bound ribosomal particles derived from partially degraded rough endoplasmic reticulum.

The neuropathological diagnosis of Alzheimer type dementia is based on the presence of large numbers of senile plaques, neurofibrillary tangles, granulovacuoles, and Hirano bodies in the medial temporal structures including the hippocampus; senile plaques and neurofibrillary tangles in the general cortex; and neurofibrillary tangles in the brain stem.

(Adapted from: Tomlinson & Kitchener 1972; Mahendra 1987, p 128-129; Scholtz 1987, p 128-129; Dawson 1988)

non-demented elderly and those with Alzheimer type dementia (see Table 1.2.2 for definitions). The group of 28 non-demented elderly consisted of 16 females and 12 males with an age range of 65 to 92 years and a mean age of 75 years. At autopsy, their brains were free of evidence of Alzheimer type dementia, although in some, neuritic plaques, neurofibrillary tangles and granulovacuolar changes could be demonstrated (see Table I.2.3; Tomlinson et al 1968). However, these were never of the profusion found in the brains of the patients with Alzheimer type dementia (Tomlinson et al 1970).

Table I.2.3
Plaque counts, Alzheimer's neurofibrillary change and granulovacuolar degeneration in 28 non-demented old subjects.

Senile plaques		Alzheimer's neurofibrillary change		Granulovacuolar degeneration (25 cases)	
None	6	not found	11	not found	11
<1/field	5	present in hippocampus only	14	present in less than 4 cells in whole section	8
1-5/field	9	present in hippocampus and general cortex	1		
6-13/field	8	present in general cortex only (hippocampus not examined in 1)	2	present in considerable numbers	6
Total	28		28		25

Mean plaque count 3.3

Tomlinson BE, Blessed G, Roth M (1968) Observations on the brains of non-demented old people. J Neurol Sci 7: 331-356. Reproduced with kind permission of B.E. Tomlinson and Elsevier Science Publishers B.V., Amsterdam, The Netherlands.

Table I.2.4
Comparison of senile plaques in 28 non-demented and 50 demented cases.

	None	<1/field	1-5/field	6-13/field	14-17/field	18 and over	Mean
Non-demented (28)	6	5	9	8	0	0	3.3
Demented (50)	8	2	3	11	9	17	14.7

Tomlinson BE, Blessed G, Roth M (1970) Observations on the brains of demented old people. J Neurol Sci 11: 205-242. Reproduced with kind permission of B.E. Tomlinson and Elsevier Science Publishers B.V., Amsterdam, The Netherlands.

Table 1.2.5:
Comparison of neurofibrillary tangles in 27 non-demented and 50 demented cases.

	Non-dements	Dements
Not found	11	14
Few in hippocampus only	6	8
Moderate in hippocampus only	9	9
Severe in hippocampus	0	19
Present in general cortex	3	31

Tomlinson BE, Blessed G, Roth M (1970) Observations on the brains of demented old people. J Neurol Sci 11: 205-242. Reproduced with kind permission of B.E. Tomlinson and Elsevier Science Publishers B.V., Amsterdam, The Netherlands.

Table 1.2.6
Comparison of granulovacuolar degeneration in hippocampal pyramidal cells in 28 non-demented and 50 demented cases.

	Non-dements	Dements
None found	11	9
Present in small numbers	8	8
Present in considerable numbers	6	8
Present in large numbers	0	24
Not examined	3	1
Total	28	50

Tomlinson BE, Blessed G, Roth M (1970) Observations on the brains of demented old people. J Neurol Sci 11: 205-242. Reproduced with kind permission of B.E. Tomlinson and Elsevier Science Publishers B.V., Amsterdam, The Netherlands.

Table I.2.7
Brain changes in Alzheimer type dementia versus normal ageing.

Alzheimer type dementia	Normal ageing
- senile plaques throughout the general cortex	- senile plaques absent or scanty
- large numbers of neurofibrillary tangles in medial temporal structures, including the hippocampus; also frequently present in the general cortex	- neurofibrillary tangles absent or scanty; if present, usually confined to the hippocampus
- granulovacuolar degeneration and Hirano bodies in hippocampus frequent	- much less frequent
- severe cholinergic deficit present	- absent
- marked reduction of brain weight: brains from patients with Alzheimer type dementia weigh $\pm$ 10-15% less than those from age-matched non-demented persons	- 7-10% reduction of brain weight by the ninth decade

Note: The important feature is that the brain changes in Alzheimer type dementia appear in combination and profusion.

(Adapted from Van der Cammen et al 1991)

The group of 50 demented patients consisted of 16 females and 34 males with an age range of 56 to 92 years and a mean age of 76.4 years. The patients came from mental hospital wards and from geriatric wards in a general hospital. All had a clinical diagnosis of dementia; in addition, the Blessed Dementia Rating Scale was used to assess the severity of the dementia. In 25 of the 50 demented patients, brain changes of the Alzheimer type were found, and were considered the only possible explanation for their dementia (Tomlinson et al 1970). The brains of the remaining 25 demented patients showed evidence of 'arteriosclerotic' dementia (9 cases), 'mixed' dementia, i.e., a combination of Alzheimer type

dementia and 'arteriosclerotic' dementia (9 cases), early Alzheimer type changes (5 cases), Wernicke encephalopathy (1 case), and dementia of traumatic origine (1 case) (Tomlinson et al 1970).

Tomlinson et al then compared the brain changes found in the 28 non-demented and the 50 demented elderly (see Tables I.2.4, I.2.5, and I.2.6; Tomlinson et al 1970).

Based on the evidence obtained by these two studies, the conclusion was drawn that the difference between Alzheimer type dementia and Alzheimer type changes found in normal ageing is quantitative. In Alzheimer type dementia the brain changes should be present in combination and profusion (see Table I.2.7; adapted from Van der Cammen et al 1991).

In the early 1960s, Kidd (1963) and Terry et al (1964) had demonstrated that the ultrastructural changes in the brains of elderly persons with Alzheimer type dementia and in those with Alzheimer's disease (i.e., the presenile condition) were identical. Together, the findings by Blessed et al (1968) and Terry et al (1964) eventually led to the recognition of Alzheimer's disease and senile dementia of the Alzheimer type as a single entity (Katzman 1976; see also Katzman et al 1978; Katzman 1981, 1986).

In 1964, the term 'chronic brain syndrome' came into use to refer to the dementia syndrome. Kay et al (1964a) used this term in a study of dementia in elderly community subjects living in Newcastle. Six mutually exclusive categories were used to identify the patients:

1. Chronic Brain Syndrome. Unequivocal evidence of either senile or arteriosclerotic dementia was present in nearly every case. The initial diagnosis was firm and 'mild' cases were excluded.
2. Suspected Chronic Brain Syndrome. Persons were suspected of chronic brain syndrome for many reasons such as failing to answer questions coherently, showing a defect of recent memory or giving a poor response to a standardized memory questionnaire and showing an apparent deterioration of behaviour, habits and personality. However, the picture was either not sufficiently severe, or the impairment not sufficiently widespread or the evidence of progression was doubtful.
3. Persons with evidence of cerebrovascular insufficiency without dementia. These

subjects had signs or symptoms suggestive of cerebrovascular involvement, vertebro-basilar insufficiency, evidence of hemiparesis or field defects or hypertension with dizziness and transient disturbances of consciousness. In all cases, the memory and intellect were well preserved.

4. Other Organic Psychosyndromes (other Organic Brain Syndromes). This group included subjects with intercurrent delirious states, myxoedematous retardation and chronic recurrent hypoglycaemic condition.
5. Functional syndromes (Functionals). This group contained mainly subjects suffering from affective symptoms of at least moderate severity.
6. 'Normals'. This group not only consisted of those subjects without significant psychiatric symptoms but also included those showing only deviant personality traits.

The term 'chronic brain syndrome' is now being used less frequently, as better definitions and classifications of dementia have since been developed. However, I have included this terminology because the original Newcastle studies are still frequently referred to nowadays, as their prevalence values for dementia (all types) correlate well with today's and their follow-up data remain a useful source for comparison (Kay et al 1964a, 1964b, 1968; Bergmann et al 1971; Kay 1972; Kay & Bergmann 1980; see also chapter IV).

In 1976, Isaacs and Caird suggested the term 'brain failure' to describe the clinical syndrome of 'global deterioration of intellect, cognition, behaviour, and emotion', based on the analogy with other clinical syndromes such as 'heart failure', but without success (Isaacs & Caird 1976).

In the early 1980s, the definition of dementia became the focus of attention of various working parties, which resulted in new working models. One of the best definitions of dementia was proposed in 1981 by the Royal College of Physicians' Committee on Geriatrics which defined dementia as 'the global impairment of higher cortical functions including memory, the capacity to solve the problems of day-to-day living, the performance of learned perceptuo-motor skills, the correct use of social skills and control of emotional reactions, in the absence of gross clouding of consciousness'. In addition, it was pointed out that 'the condition is often irreversible and progressive' (Report of the Royal College of Physicians on Organic Mental Impairment in the Elderly 1981, p 8). In the Report, it is made

clear that an operational approach was used in order to arrive at this definition. Recently, more extensive diagnostic criteria have been developed, i.e., the DSM-III and DSM-III-R, NINCDS-ADRDA and ICD-10, which I will now discuss.

The diagnostic criteria from DSM-III and DSM-III-R.

A major step in the classification of the dementias, including Alzheimer type dementia, occurred with the publication of the American Psychiatric Association's third version of a diagnostic and statistical manual (DSM-III) in 1980 and its revised edition DSM-III-R in 1987 (American Psychiatric Association 1980, 1987). Dementia belongs to the general category of 'Organic Brain Syndromes', which consists of nine subcategories in the DSM-III (1980), and of eleven subcategories in the DSM-III-R (1987). DSM-III-R requires for the diagnosis of dementia to be made that there is a demonstrable evidence of impairment in both short- and long-term memory, associated with at least one other symptom of dementia (see Table I.2.8). In addition, DSM-III-R includes criteria for severity of dementia. The hierarchical structure of the DSM-III and DSM-III-R is clear.

In DSM-III and DSM-III-R, inclusion and exclusion criteria are used, and patients do not have to meet all the criteria mentioned. Consequently, the group of patients which is identified as belonging to the category dementia is not homogeneous, and in clinical practice examples can be found of diagnostic error if one relies on DSM-III-R criteria without using one's clinical insight. For instance: according to the DSM-III-R criteria, a patient with memory impairment, reduced social abilities and personality changes would qualify for a diagnosis of dementia, whereas in clinical practice this type of change is known to occur occasionally in depressed or recently bereaved elderly individuals. These examples demonstrate the need to use one's clinical judgement in order to reduce diagnostic error in future studies of dementia. Moreover, if DSM-III-R had included the prerequisite that such disturbances should have been present for a certain length of time before a confident diagnosis of dementia can be established, the chance of diagnostic error as demonstrated by the above cases would have been reduced.

With regard to the criteria for severity of dementia, one could comment that the attempt made in DSM-III-R to indicate stages of severity is admirable. However, without an operational definition of dementia severity, terms such as 'mild',

Table I.2.8: DSM-III-R CRITERIA FOR THE DIAGNOSIS OF DEMENTIA.

Dementia

A Demonstrable evidence of impairment in short- and long-term memory. Impairment in short-term memory (inability to learn new information) may be indicated by inability to remember three objects after five minutes. Long-term memory impairment (inability to remember information that was known in the past) may be indicated by inability to remember past personal information (e.g., what happened yesterday, birthplace, occupation) or facts of common knowledge (e.g., past 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 function, 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 function), and 'constructional difficulty ' (e.g., inability to copy three-dimensional figures, assemble blocks, or arrange sticks in specific designs).
4) personality change, i.e., alteration or accentuation of premorbid traits.

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

D Not occurring exclusively during the course of Delirium.

E Either 1) or 2):

1) there is evidence from the history, physical examination, or laboratory tests of a specific organic factor (or factors) judged to be etiologically related to the disturbance.
2) in the absence of such evidence, an etiologic organic factor can be presumed if the disturbance cannot be accounted for by any non-organic mental disorder, e.g., Major Depression accounting for cognitive impairment.

Criteria for severity of Dementia:

Mild: Although work or social activities are significantly impaired, the capacity for independent living remains, with adequate personal hygiene and relatively intact judgment.
Moderate: Independent living is hazardous, and some degree of supervision is necessary.
Severe: Activities of daily living are so impaired that continual supervision is required, e.g., unable to maintain minimal personal hygiene; largely incoherent or mute.

(American Psychiatric Association 1987).

Table I.2.9: DSM-III-R CRITERIA FOR THE DIAGNOSIS OF AMNESTIC SYNDROME.

Amnestic syndrome
According to the diagnostic criteria from DSM-III-R the amnestic syndrome is characterized as follows:

A Demonstrable evidence of impairment in both short- and long-term memory; with regard to long-term memory, very remote events are remembered better than more recent events. 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 President, well-known dates).

B Not occurring exclusively during the course of Delirium, and does not meet the criteria for Dementia (i.e., no impairment in abstract thinking or judgment, no other disturbances of higher cortical function, and no personality change).

C 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.

(American Psychiatric Association 1987).

'moderate' and 'severe' may mean different things to different researchers and clinicians, leading to different levels of dementia severity being detected in different studies. Moreover, this type of inclusion might create a false idea of exactitude.

Both DSM-III and DSM-III-R include criteria for amnestic syndrome (see Table I.2.9). These criteria include impairment in both short- and long-term memory in the absence of other indications of dementia.

The next step in the DSM-III-R consists of establishing whether or not a patient belongs to the category of 'Primary Degenerative Dementia' (see Table I.2.10). The course of the disorder (insidious onset with a generally progressive deterioration) and the lack of other causes of dementia (as established by history, physical examination, and laboratory tests) establish the diagnosis of 'Primary Degenerative Dementia of the Alzheimer Type'. The amount of deterioration and the length of time during which this deterioration takes place are not specified.

The DSM-III-R then continues with the division of 'Primary Degenerative Dementia

Table I.2.10: DSM-III-R CLASSIFICATION OF DEMENTIAS ARISING IN THE SENIUM AND PRESENIUM

Primary Degenerative Dementia of the Alzheimer Type
The diagnostic criteria from DSM-III-R for this condition are threefold:
A. Dementia.
B. Insidious onset with a generally progressive deteriorating course.
C. Exclusion of all other specific causes of Dementia by history, physical examination, and laboratory tests.

Types

Primary Degenerative Dementia of the Alzheimer Type, Senile Onset (after age 65)
290.30 with delirium
290.20 with delusions
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

Multi-Infarct Dementia
A. Dementia.
B. Stepwise deteriorating course with 'patchy' distribution of deficits (i.e., affecting some functions, but not others) early in the course.
C. Focal neurologic signs and symptoms (e.g., exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity, etc.).
D. Evidence from history, physical examination, or laboratory tests of significant cerebrovascular disease that is judged to be etiologically related to the disturbance.

Types

Multi-Infarct Dementia
290.41 with delirium
290.42 with delusions
290.43 with depression
290.40 uncomplicated

(American Psychiatric Association 1987)

Table I.2.11: DSM-III-R CRITERIA FOR THE DIAGNOSIS OF DEMENTIA NOT OTHERWISE SPECIFIED.

290.00 Senile Dementia Not Otherwise Specified
Dementias associated with an organic factor and arising after age 65 that cannot be classified as a specific Dementia, e.g., as Primary Degenerative Dementia of the Alzheimer Type, Senile Onset, or Dementia Associated with Alcoholism.

290.10 Presenile Dementia Not Otherwise Specified
Dementias associated with an organic factor and arising before age 65 that cannot be classified as a specific Dementia, e.g., Primary Degenerative Dementia of the Alzheimer Type, Presenile Onset.

(American Psychiatric Association 1987).

of the Alzheimer Type' in 'Senile Onset', i.e., onset after age 65, and 'Presenile Onset', i.e., onset at age 65 and below (see Table I.2.10), based on the arbitrary cutoff point of the patient's age. Finally, the DSM-III-R gives criteria for the diagnosis of 'Multi-infarct Dementia' (see Table I.2.10) and for 'Dementia Not Otherwise Specified' (see Table I.2.11).

Despite some defects, the criteria proposed in DSM-III-R may prove a much needed barrier to the over-diagnosis of Alzheimer type dementia, and the initial characterization provides an excellent description of the problems subsumed under the term dementia. At present, the diagnostic criteria from DSM-III-R are the most frequently used, and the clinician-researcher is able to construct groups of patients as homogeneous as possible, by using the procedures and criteria of the manual. However, since DSM-III and DSM-III-R provide only general diagnostic guidelines, it is possible that different groups of researchers or schools disagree on the classification of patients. The major area of uncertainty remains the differential diagnosis of Alzheimer type dementia with multi-infarct dementia and depression.

The NINCDS-ADRDA criteria for clinical diagnosis of Alzheimer disease.

Another approach to the clinical diagnosis of Alzheimer type dementia was published in 1984, when the National Institute of Neurologic and Communicative

Table I.2.12: NINCDS-ADRDA CRITERIA FOR CLINICAL DIAGNOSIS OF ALZHEIMER DISEASE.

Probable Alzheimer Disease
Criteria

A. Dementia established by clinical examination and documented by the Mini-Mental State Examination (Folstein et al 1975), Blessed Dementia Scale (Blessed et al 1968), or some similar examination, and confirmed by neuropsychological tests
B. Deficits in two or more areas of cognition
C. Progressive worsening of memory and other cognitive functions
D. No disturbance of consciousness
E. Onset between ages 40 and 90, most often after age 65
F. Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficit of memory and cognition.

The diagnosis of Probable Alzheimer Disease is supported by:
- Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia).
- Impaired activities of daily living and altered patterns of behavior.
- Family history of similar disorders, particularly if confirmed neuropathologically.
- Laboratory results: normal lumbar puncture; normal pattern of non-specific changes in EEG, such as increased slow-wave activity; evidence of cerebral atrophy on CT-scan with progression documented by serial observation.

Features which make the diagnosis of Probable Alzheimer Disease uncertain or unlikely include:
- Sudden, apoplectic onset.
- Focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness.
- Seizures or gait disturbances at the onset or very early in the course of the illness.

Possible Alzheimer Disease can be diagnosed
- On the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders, and in the presence of variations in the onset, course and presentation
- In the presence of a second systemic disorder which is sufficient to cause dementia, and which is not considered to be the cause of dementia
- In research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable causes

Definite Alzheimer Disease
- Probable Alzheimer Disease
- Histopathologic evidence (autopsy, biopsy)

(McKhann et al 1984)

Disorders and Stroke (NINCDS) and the Alzheimer Disease and Related Disorders Association (ADRDA) produced criteria for the diagnosis of probable, possible and definite Alzheimer disease (see Table I.2.12; McKhann et al 1984). The NINCDS-ADRDA criteria can be understood as a further specification within the DSM-III-R category of 'Primary Degenerative Dementia of the Alzheimer Type'. Identical with DSM-III-R, one significant criterion was the exclusion of other disorders that could account for the dementing state but the NINCDS-ADRDA list was more complete. The NINCDS-ADRDA criteria emphasized diagnosis based on symptoms and signs readily demonstrable in the clinical setting. Moreover, the general category of 'Alzheimer Disease' was divided into three subcategories: 'Probable, Possible and Definite Alzheimer Disease'. First of all, the work group produced a list of clinical criteria for the diagnosis of 'Probable Alzheimer Disease'. In addition to the clinical criteria, the committee provided a list of findings to support the diagnosis of 'Probable Alzheimer Disease' and another list of features which make this diagnosis uncertain or unlikely (see Table I.2.12). The combination of both lists provides a valuable aid for the identification of patients with 'Probable Alzheimer Disease'. Furthermore, a diagnosis of 'Possible Alzheimer Disease' was allowed, based on an incomplete symptom picture or the presence of a second disease process complicating the clinical picture but not considered to be the cause of the demented state. Finally, a third category, 'Definite Alzheimer Disease', demands histologic demonstration of appropriate neuropathological findings from biopsy or autopsy.

The NINCDS-ADRDA criteria were published without validation but were immediately accepted as a strong guide for both clinical and research approaches to Alzheimer type dementia (McKhann et al 1984; Benson 1989). The point to note is that, contrary to DSM-III-R, the arbitrary division in presenile and senile Alzheimer type dementia has not been included in the NINCDS-ADRDA criteria. The NINCDS-ADRDA criteria are different from the DSM-III-R in some other respects as well: (1) right from the start the aim is to diagnose one disease, i.e., 'Alzheimer Disease' and (2) they clearly state that, without histopathological evidence, the diagnosis is not definite (although this is of course an assumption in the DSM-III-R). However, the recent study by Duyckaerts et al (1990) has clearly demonstrated that, in the neuropathologist's laboratory, inter-investigator

agreement is presently achieved only for the severe cases of Alzheimer type dementia, and further standardization of the neuropathological procedures is required to achieve concordance for mild cases of Alzheimer type dementia and for brain changes found in normal ageing. Nevertheless, it is to be expected that stringent application of the NINCDS-ADRDA diagnostic criteria will result in a reduction of the prevalence of Alzheimer type dementia.

The Tenth Revision of the International Classification of Diseases (ICD-10).

In 1984, the World Health Organization commenced work on the mental disorders chapter for the Tenth Revision of the International Classification of Diseases (ICD-10), in collaboration and consultation with some 150 experts from all the geographical regions, representing among themselves a variety of points of view, research and clinical traditions, and cultures (WHO 1988). The official adoption of ICD-10 by the World Health Assembly took place early in 1990 and its practical implementation in the Member States has been scheduled for 1993. The mental disorders chapter has been designed with the explicit aim to serve not only as a guide to the statistical reporting on morbidity, but also as a clinical and research manual and, possibly, as a teaching tool (Jablensky 1989).

The classification of organic mental disorders in ICD-10 contains ten major rubrics (see Table I.2.13; Jablensky 1989). According to the ICD-10 criteria, the syndrome of dementia is defined by 'evidence of a decline in both memory and thinking which is of a degree sufficient to impair functioning in daily living', in a setting of clear consciousness; for a confident diagnosis to be established, such disturbances should have been present for at least six months. Deterioration in higher cortical functions (aphasia, agnosia, apraxia), as well as personality changes with conspicuous loss of spontaneity, are regarded as supportive evidence but not as necessary features.

The research criteria (but not the clinical guidelines) provide anchor points for a grading of the severity of functional impairment into mild, moderate and severe, separately for memory and intellectual capacity. The overall grading of the severity of the dementia is based on the sphere of functioning that is more severely impaired.

Table I.2.13: Organic mental disorders in ICD-10.

The classification of organic mental disorders in ICD-10 contains 10 major (3-character) rubrics:

F00 Dementia in Alzheimer disease
F01 Vascular dementia
F02 Dementia in disease classified elsewhere, containing dementia in Pick's disease, dementia in Creutzfeldt-Jakob disease, dementia in Huntington's disease, dementia in Parkinson's disease, dementia in HIV-infection
F03 Dementia unspecified
F04 Organic amnestic syndrome other than induced by alcohol or drugs
F05 Delirium, other than induced by alcohol or drugs
F06 Other mental disorders due to brain disease, damage or dysfunction, or to physical disease
F07 Personality and behavior disorder due to brain disease, damage or dysfunction
F08 Other organic or symptomatic mental disorder
F09 Unspecified organic or symptomatic mental disorder

(Jablensky 1989)

'Dementia in Alzheimer disease' (code F00) is defined, in addition to the presence of the syndrome of dementia, by a set of criteria shown in Table I.2.14. According to ICD-10, the diagnosis of 'Dementia in Alzheimer disease' can be supported by neuropathological examination (evidence of neurofibrillary tangles and plaques inexcess of those found in normal ageing of the brain). However, ICD-10 allows for a confident clinical diagnosis to be made, if there is clear evidence of cognitive deterioration from a previous level of functioning lasting for six months or more (if the period is shorter, the diagnosis is tentative) (Sartorius 1988; Jablensky 1989). ICD-10 criteria include a subtyping of 'Dementia in Alzheimer disease' on the basis of a dual criterion including age at onset and clinical presentation. Code F00.1 denotes 'Dementia in Alzheimer disease, senile onset', or Type I; code F00.2 is used for presenile onset, or Type II. The age dividing the two forms of the disorder is specified at 65 in both the research criteria and the clinical guidelines, but the latter add the qualification that the senile onset is 'usually in the late 70s or thereafter'.

Table I.2.14
Proposed ICD-10 criteria for 'Dementia in Alzheimer disease' (code F00).

- evidence of the syndrome of dementia as defined by a decline in both memory and thinking which is of a degree sufficient to impair functioning in daily living, in a setting of clear consciousness; for a confident diagnosis to be established, such disturbances should have been present for at least six months;
- insidious onset with a slow deterioration;
- absence of clinical or laboratory evidence that the syndrome could be explained by other systemic or brain disease;
- absence of a sudden, apoplectic onset, and of focal neurological signs.

Several further features are specified as supporting the diagnosis, without being necessary elements:
(1) aphasia, agnosia, apraxia, or other evidence of higher cortical function involvement;
(2) amotivation, apathy, aspontaneity, and disinhibition of social behavior;
(3) evidence of cortical atrophy
(4) parkinsonism, logoclonia (i.e., repeated stuttering of syllables), and epileptic seizures.

F00.1 Dementia in Alzheimer disease, senile onset, or Type I.
F00.2 Dementia in Alzheimer disease, presenile onset, or Type II.

(Jablensky 1989)

The second criterion, clinical presentation, requires 'evidence of a very slow, gradual onset and progression' and predominance of memory impairment for a diagnosis of Type I (senile onset), and relatively rapid onset and progression, as well as multiple disturbances of higher cortical functions for a diagnosis of Type II (presenile onset).
The present version of the research criteria gives no specific instruction on how to handle discrepant cases, i.e., patients in whom there is no correspondence between the age at onset and the configuration of the clinical picture described as either Type I or Type II. By implication, however, the criterion of age takes precedence in such instances (Sartorius et al 1988; Jablensky et al 1989).
The addition of the prerequisite that disturbances should have been present for at least six months before a diagnosis of dementia can be established, distinguishes the ICD-10 criteria from DSM-III-R and NINCDS-ADRDA in an advantageous way.

I.2 Current concepts of dementia, definitions, diagnostic criteria and differential diagnosis.

The merging of presenile and senile dementia of the Alzheimer type.

The question had to be answered if the separation of dementia before and after the age of 65 had any validity, if senile and presenile dementia had distinction beyond age. It was initially held that Alzheimer's disease, like the other eponymously named dementias (Huntington's chorea, Pick's disease and Creutzfeldt-Jakob disease) was a presenile condition, differing qualitatively from senile dementia of the Alzheimer type. However, large clinicopathological series reported over the 20th century have demonstrated that the pathologies of Alzheimer's disease (i.e., the presenile condition) and senile dementia of the Alzheimer type are not qualitatively different*. Basically, the findings by Blessed et al (1968) and Terry et al (1964) eventually led to the recognition of Alzheimer's disease and senile dementia of the Alzheimer type as a single entity. Katzman recommended in 1976 that Alzheimer's disease and senile dementia of the Alzheimer type be considered a single entity and, therefore, have a unique name, i.e., 'dementia of the Alzheimer type' (Katzman 1976; see also Katzman et al 1978; Katzman 1981, 1986). This suggestion has since been supported by other authors (American Psychiatric Association 1980, 1987; McKhann et al 1984; Sartorius et al 1988; Jablensky 1989). Based on this evidence, I will use the term 'Alzheimer type dementia' from this point onwards, throughout this thesis, for both presenile and senile onset cases. However, as Amaducci et al (1986) have recently pointed out, the controversy about the separation of the presenile and senile form of Alzheimer type dementia continues, and the issue is still extensively debated.

Although many have come to the conclusion that Alzheimer's disease and senile dementia of the Alzheimer type are part of the same spectrum of disease, it cannot be excluded that future research may justify the subcategorization of what we now consider a single condition.

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* Grünthal 1927; Rotschild & Kasanin 1936; Newton 1948; Neumann & Cohn 1953; Corsellis 1962; Kidd 1963; McMenemey 1963; Terry et al 1964; Blessed et al 1968; Sourander & Sjogren 1970; Tomlinson et al 1970; Constantinidis 1978; Terry 1978.

Differences in early versus late onset cases of Alzheimer type dementia.
Katzman's opinion (Katzman 1976) that Alzheimer's disease and senile dementia of the Alzheimer type should be considered a single entity has been included in DSM-III and DSM-III-R, NINCDS-ADRDA and ICD-10 definitions, although in all three definitions the age of 65 years remains a separately mentioned cut-off point. The ICD-10 criteria include a subtyping of 'Dementia in Alzheimer disease, senile onset', or Type I, and 'Dementia in Alzheimer disease, presenile onset', or Type II. There is now reason to believe that a distinction may be made, albeit in more quantitative terms, i.e., the rate of progression of the disease, between Alzheimer type dementia arising in 'younger' and 'older' patients. One of the differences claimed is that Alzheimer type dementia in the younger or presenile patient might be a more severe affliction.

Table I.2.15:
CLINICAL AND NEUROBIOLOGICAL CHARACTERISTICS OF TWO SUBTYPES OF ALZHEIMER DISEASE.

	AD-1	AD-2	Reference
Age of onset	Old age	Middle age	1
Clinical course	Insidious	Rampant	2
Parietal lobe impairment	++	+++	3
Motor signs	+	++	2
Ventricular enlargement	+	++	4
Neurofibrillary tangles	+++	++++	5
Loss of locus coeruleus neurones	+	+++	1
Loss of nucleus basalis neurones	?	+++	6
Loss of cortical ChAT	+	+++	7

Reference: Bondareff W (1983) Age and Alzheimer disease. Lancet 1: 1447.
Reproduced with kind permission of William Bondareff and The Lancet.

Refs.:
1. Bondareff et al (1981); 2. Roth (1980); 3. McDonald (1969); 4. Jacoby & Levy (1980); 5. Constantinides (1978); 6. Tagliavini & Pilleri (1983); 7. Rossor et al (1981).

Sourander and Sjogren (1970) showed that reduction in brain weight and presence of neurofibrillary tangles were more severe in presenile onset cases than in senile onset cases of Alzheimer type dementia, with better preserved physical status in the younger patient. It is now thought that there are 2 forms, if not types, of Alzheimer dementia: one running a severe course with a rapidly fatal outcome, occurring in early onset cases; the other running a less severe course with a less poor prognosis, occurring in late onset cases (see Table I.2.15; Bondareff 1983).

Tagliavini and Pilleri (1983) have demonstrated that the percentage of neuronal loss in the basal nucleus of Meynert in patients with Alzheimer type dementia was related to age at death, with massive neuronal loss occurring in those dying at an 'early' age (see Figure I.2.1; Tagliavini and Pilleri 1983).

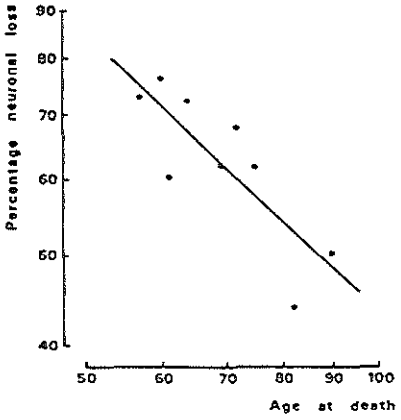
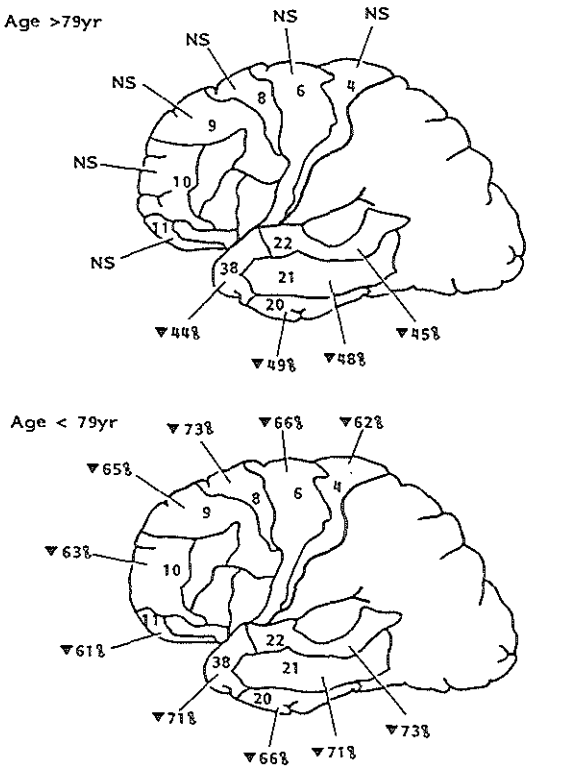


Figure I.2.1
Percentage neuronal loss (log scale) as a function of age at death (log scale) in nine cases of Alzheimer's disease.
From: Tagliavini F & Pilleri G (1983) Neuronal counts in basal nucleus of Meynert in Alzheimer disease and in simple senile dementia. Lancet 1: 469-470.
Reproduced with kind permission of the authors and The Lancet.

Furthermore, Rossor et al have demonstrated a difference in neurotransmitter deficits between 'younger' and 'older' groups of patients with Alzheimer type dementia (Rossor et al 1981; Rossor 1982). Rossor (1982) has described the 'cholinergic hypothesis' of Alzheimer type dementia as follows: 'Damage to the ascending cholinergic system is an important determinant of the functional deficits observed in Alzheimer type dementia'. Rossor and his colleagues demonstrated that acetylcholine, probably the main transmitter involved in higher neuronal activity, is reduced due to appreciable reductions in the activity of the enzyme choline acetyltransferase (ChAT, which synthesises acetylcholine) in the cerebral cortex of patients with Alzheimer type dementia. This cholinergic deficit, as assessed by ChAT activity, affects especially the hippocampus, amygdala and temporal cortex. The earlier the age at death the more severe this cholinergic abnormality - in patients dying after the age of 80 the frontal lobe was found to be unaffected (see Fig. I.2.2; Rossor 1982). The reduction in ChAT activity was found to correlate both with the density of cortical senile plaques and with the severity of dementia at the time of death whereas there were no obvious correlations with other markers. In addition to the cholinergic deficit, cortical concentrations of noradrenaline, gamma-aminobutyric acid (GABA) and somatostatin were found to be reduced in patients with Alzheimer type dementia; again these deficits were more obvious in early onset cases (Rossor et al 1981; Rossor 1982; Rossor et al 1982, 1984).

The finding that frontal lobe abnormality may represent the more severe type of Alzheimer dementia (see Figure I.2.2; Rossor 1982) was recently confirmed by a neuropsychological study demonstrating that there was a statistically significant difference in scores obtained on neuropsychological tests measuring frontal lobe function between patients with rapidly progressive Alzheimer type dementia and patients with slowly progressive Alzheimer type dementia (Mann et al 1989). This study by Mann et al (1989) suggests that the diagnosis of Alzheimer type dementia may indeed subsume two distinct subgroups: one characterized by slow clinical progression and neuropsychological evidence of mainly parietal lobe dysfunction, the other by fast clinical progression with symptoms associated with functional abnormalities in both parietal and frontal lobes.



The figures are percentage reductions from age-matched control values. Reduced activity is seen in the temporal lobe at all ages but the frontal lobe deficit is confined to the younger group.

Figure I.2.2
ChAT activities in Alzheimer's disease.
From: Rossor MN (1982) Neurotransmitters and CNS Disease: Dementia. Lancet 2: 1200-1203.
Reproduced with kind permission of Martin N. Rossor and The Lancet.

The study failed to find a significant difference in age at symptom onset, sex, education and global intellectual functioning as measured by the Full Scale IQ on the Wechsler Adult Intelligence Scale-Revised (WAIS-R) between the rapid progress group and the slow progress group. The fact that the two groups did not differ significantly in age at symptom onset suggests that frontal lobe

dysfunction may well be the hallmark for rate of progression of Alzheimer type dementia.

The Dutch view.

On 4 November 1988, the National Organization for Quality Assurance in Hospitals in the Netherlands held a consensus development conference in order to reach agreement on definition, diagnostic criteria and clinical and ancillary investigations required for the diagnosis of dementia. The conference resulted in a Dutch consensus, whereby dementia was defined as a clinical syndrome, which should be diagnosed by clinical methods. Its manifestation is primarily behavioural. It is characterized by a decline of two or more cognitive capacities, including memory, occurring without alteration of consciousness, and of sufficient severity to interfere with the patient's usual daily activities. It was agreed that at present the DSM-III-R diagnostic criteria for dementia are the most acceptable, with the exception of one, i.e., evidence or presumption of an etiologic organic factor, because this criterion is not compatible with the syndromal character of the dementia syndrome. Consensus was also reached about the following statements. The diagnosis of dementia syndrome is not valid in the presence of delirium. For clinical reasons it is considered important to distinguish between the conditions of cortical and subcortical dementia. Pseudodementia is an out-of-date concept. Epidemiological data on dementia are important for the diagnosis and prognosis in individual cases. In all patients with signs of the dementia syndrome, physical, neurological, psychiatric, and neuropsychological examinations should be performed, preferably according to a standardized protocol. The causal role of drugs in the dementia syndrome and in delirium in the aged cannot be overemphasized. For the differential diagnosis of the disease states that produce the dementia syndrome, standardized laboratory tests should always be performed, but with individual modifications. Electroencephalogram (EEG) and CT (or nuclear magnetic resonance {NMR})-scan are appropriate in certain cases, e.g., when the history points towards the possibility of a space occupying lesion in the brain, when there are focal neurological symptoms and signs and when the dementia syndrome has developed over a short period (Consensus Diagnostiek bij het Dementiesyndroom 1989; Schulte 1989).

Discussion.

Within the past decade, a number of changes in the diagnostics of dementia have taken place that have influenced the diagnosis of Alzheimer type dementia. First of all, we have seen that the various definitions, classifications and diagnostic criteria for dementia have become more precise, facilitating the distinction between the various types of dementia. In addition, grading of dementia severity has been attempted by the inclusion of guidelines in some of the classifications (DSM-III-R and the research criteria of ICD-10). In some definitions, a diagnosis of possible Alzheimer type dementia has been allowed with the aim to facilitate early diagnosis (NINCDS-ADRDA); in some, a time factor of 6 months has been included as a prerequisite for a confident diagnosis, in an attempt to reduce the chance of diagnostic error (ICD-10).

Although the merging of the original, well-established presenile Alzheimer's disease with the much more frequent but less clearly demarcated senile dementia of the Alzheimer type has by now been generally accepted, the age of 65 years remains a cut-off point separately mentioned in most classifications (DSM-III-R, NINCDS-ADRDA, ICD-10); recent studies suggest that there is indeed a difference between early and late onset cases of Alzheimer type dementia (Rossor et al 1981; Rossor 1982; Rossor et al 1982, 1984; Bondareff 1983; Tagliavini & Pilleri 1983). The recent study by Mann et al (1989) suggests that frontal lobe pathology rather than age at onset may well be the hallmark for rate of progression of Alzheimer type dementia.

Throughout the years, one fact has remained unchanged: in almost all definitions of dementia, memory impairment remains one of the most important diagnostic criteria; in the diagnostic criteria from DSM-III-R memory impairment is a prerequisite for the diagnosis of dementia; in the ICD-10 classification predominance of memory impairment is required for the diagnosis of 'Dementia in Alzheimer disease, senile onset' (Type I) in addition to age over 65 years at onset.

The sharper definitions and classifications of dementia, and the consensus recommendations for team investigation of patients exhibiting symptoms of a dementia syndrome, including neuropsychological assessment, extensive laboratory investigations and modern imaging, have already led to a reduction in

the overdiagnosis of Alzheimer type dementia. Because of the application of these standardized assessment procedures, the ability to diagnose Alzheimer type dementia clinically has improved greatly, from a 10 to 50 percent error rate to at least a 90 percent assurance of accuracy (Katzman 1986). However, the study by Homer et al (1988) is disquieting, and she and her coworkers correctly point at the need to confirm the clinical diagnosis by a post-mortem investigation of the brain. In the neuropathologist's laboratory, there is the need for (internationally agreed) standardization of the neuropathological procedures in order to improve diagnostic accuracy and concordance on Alzheimer type brain changes in relation to the severity of dementia; this is especially true for mildly affected cases (Duyckaerts et al 1990).

Those of us working with older people could all make a significant contribution by assessing our demented patients during life, and by helping relatives to understand the relevance of research. Researchers working on basic science investigation of dementia, and in the laboratory field in general, rely heavily on their clinical colleagues for material. Such collaborative ventures are mandatory if we are to enhance our understanding of the mechanisms underlying the disorder.

Lastly, it might well be that newer imaging techniques such as nuclear magnetic resonance (NMR) will enhance diagnostic accuracy, especially with regard to the diagnosis of multi-infarct dementia.

I.2 Current concepts of dementia, definitions, diagnostic criteria and differential diagnosis.

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I.3 THE SIZE OF THE PROBLEM: EPIDEMIOLOGY OF DEMENTIA.

Prevalence of dementia all types.

Dementia is a common disorder in modern societies because of the size of their elderly populations. The prevalence of dementia (i.e., the percentage of the population afflicted at a given time) rises with age, and depends on the ages of those in a population over 65.

As the average age of the population over 65 increases - and the age group that is older than 80 is the fastest growing segment of the older population in the western world (US Bureau of the Census 1977, 1983; Torrey et al 1987) - the prevalence of dementia among those older than 65 is expected to become higher than that estimated from earlier studies (Mortimer 1983; Katzman 1986).

Hofman et al (1991) have undertaken a meta-analysis of European prevalence studies of dementia (all types). They pooled and reanalyzed original data of prevalence studies carried out in Europe between 1980 and 1990. The study followed these steps: census of existing data-sets, collection of data in a standardized format, selection of data-sets suitable for comparison, comparison of age and gender patterns. From 23 data-sets of European surveys conducted or published between 1980 and 1990, 12 were selected for comparison (see Table I.3.1; Hofman et al 1991). Only population-based studies in which dementia was defined by DSM-III (American Psychiatric Association 1980) or equivalent criteria and in which all subjects were examined personally were included. Although prevalence estimates differed across studies, the general age- and gender-distribution was similar for all studies. Table I.3.2 shows the age-specific prevalences in percentages of dementia (all types) for both sexes, and for men and women separately (Table I.3.2; adapted from Hofman et al 1991). As can be seen from Table I.3.2, the meta-analysis confirms the steep rise in prevalence of dementia (all types) with age; the prevalence figures nearly double with every 5 years of increase in age. No major differences in prevalence between men and women were observed; however, the overall estimates were somewhat larger for men than for women until the age of 75, and somewhat larger for women after the age of 75 (see Table I.3.2; adapted from Hofman et al 1991). A comparison of the estimates across the 12 studies which were analyzed suggested a similar general pattern of prevalence by age and gender. However, there appeared to be evidence for a somewhat larger variation between populations in men than in women. It is as yet unclear whether this is a result of differing competing risks of other diseases, particularly cardiovascular disease.

Table I.3.1: Characteristics of Study Population.

POPULATION	Investigators	Geographic Location	Urban or Rural	Population Size or Sample Size	Age or Lower Age Limit (Yrs)	Type of Sample	Years of Survey	Prevalence Time Reference
FEDERAL REPUBLIC OF GERMANY Mannheim	Cooper & Bickel (1989)	City of Mannheim	Urban	519	65+	Random sample: 5% community 50% nursing homes 100% psychiatric long-stay	1978 - 1986	Area specific point prevalences
FINLAND* Total Country	Sulkava et al (1985)	40 areas representing the whole country	Approx. 50% rural 50% urban	8,000	30+	Two-stage stratified cluster sample	1977 - 1980	Area specific point prevalences
ITALY* Appignano	Rocca et al (1990)	Commune of Appignano, Macerata province	Rural	778	60+	Complete enumeration from the Registry Office list	1987 - 1988	January 1, 1987
THE NETHERLANDS Amsterdam/ Rotterdam	Breteler/ Jonker Breteler et al (in press)	General practices, Amsterdam; Ommoord, Rotterdam	Urban	621	65+	Complete enumeration	1989 - current	July 1, 1989
THE NETHERLANDS Leiden	Heeren et al (1988)	Community of Leiden	Urban	1,258	85+	Complete enumeration	1986 - 1989	Period prevalence
NORWAY Oslo	Engedal et al (1988)	City of Oslo	Urban	1,027	75+	Random sample: 1,334 from City Registration Office (community sample)	1984 - 1985	Period prevalence

Table I.3.1 (continued)

POPULATION	Investigators	Geographic Location	Urban or Rural	Population Size or Sample Size	Age or Lower Age Limit (Yrs)	Type of Sample	Years of Survey	Prevalence Time Reference
SPAIN* Zaragoza	Lobo et al (in press)	Urban area of Zaragoza	Urban	334	65+	Stratified random sample	1988 - current	January 31, 1989
SWEDEN* Lund	Hagnell et al (1981), Rorsman et al (1986)	Two parishes, Dalby and Bonderup = "Lundby"	Urban and rural	1,617	30+	All survivors of the original 1967 cohort (complete enumeration)	1971 - current	July 1, 1972
UNITED* KINGDOM Cambridge	O'Connor et al (1989)	Six general practices, Cambridge urban area	Urban	2,311	75+	Complete enumeration (plus small systematic sample)	1986 - 1987	12 month+ prevalence
UNITED* KINGDOM Cambridgeshire	Brayne & Calloway (1989)	Rural town and villages, Cambridgeshire	Rural	365	70-79	Complete enumeration	1985 - 1986	12 month+ prevalence
UNITED KINGDOM Liverpool	Copeland et al (1987)	Metropolitan Liverpool	Urban	1,070	65+	Simple random sample from practitioners	1982 - current	12 month+ prevalence
UNITED KINGDOM London	Livingston et al (1990)	Urban London Inner city, Gospel Oak electoral ward	Urban	813	60+ (women) 65+ (men)	Complete enumeration	1986 - 1987	12 month+ prevalence

Hofman et al 1991; Rocca et al 1991 (six asterisked populations).

(continued....)

Table I.3.1 (continued)

[+] Data collection covered a 12-month period; however, each subject in the sample was screened and/or examined only at one point in time. This approach is approximately equivalent to that used for point prevalence.

References:

Hofman A, Rocca WA, Brayne C et al (1991) The prevalence of dementia in Europe: A collaborative study of 1980-1990 findings. Internat J of Epidemiology {in press}.
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Rocca WA, Hofman A, Brayne C et al (1991) Frequency and distribution of Alzheimer's disease in Europe. A collaborative study of 1980-1990 prevalence findings. Annals of Neurology {in press}.
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Table I.3.2: Age- and sex-specific prevalence (%) of dementia (all types) in Europe.

POPULATION	Age Class								
	30-39	60-64	65-69	70-74	75-79	80-84	85-89	90-94	95-99
Average Men	0.2 (5/3,164)	1.6 (8/506)	2.2 (16/739)	4.6 (29/629)	5.0 (40/793)	12.1 (63/520)	18.5 (62/336)	32.1 (26/81)	31.6 (6/19)
Average Women	0.1 (3/3,273)	0.5 (3/638)	1.1 (11/1,001)	3.9 (43/1,115)	6.7 (106/1,589)	13.5 (126/933)	22.8 (196/861)	32.2 (89/276)	36.0 (18/50)
Average Both sexes	0.1 (8/6,437)	1.0 (11/1,144)	1.4 (25/1,740)	4.1 (64/1,559)	5.7 (125/2,203)	13.0 (189/1,453)	21.6 (258/1,197)	32.2 (115/357)	34.7 (24/69)

Numbers in brackets indicate the actual numerator and denominator figures.

Adapted from Hofman A, Rocca WA, Brayne C et al (1991) The prevalence of dementia in Europe: A collaborative study of 1980-1990 findings. Internat J of Epidemiology {in press}.
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The authors conclude that it seems unlikely that geographical comparison of prevalences within the European countries will yield major aetiological clues for dementia (all types), which may be due to the restriction in geographical variation within the European countries included in their meta-analysis. However, they point at the need for further research in order to clarify this issue (Hofman et al 1991).

Incidence of dementia all types.

Determination of the incidence (frequency of occurrence of new cases) of dementia (all types) requires that a population be followed over time and that occurrence of new cases of the disorder be carefully monitored. Few studies ofthis type have been performed. Kay's 4-year study of the Newcastle population indicated an incidence rate of 1.4 per 100 person-years for a combination of senile and vascular dementia among persons over age 65 (Kay 1972). Jarvik, Ruth, and Matsuyama reported a somewhat higher incidence (2.7 per 100 person-years) for dementia (all types) for a small sample of 22 persons who averaged 83 years of age at the beginning of the 6-year study period (Jarvik et al 1980). Computations performed by Mortimer, Schuman, and French (1981) on the Baltimore Longitudinal Study data (Sluss et al 1981) yielded an average incidence of slightly more than 1 per 100 person-years for persons aged 65 and over in that study.

At present, it is generally agreed that approximately 1% of those over age 65 develop dementia (all types) each year (Mortimer 1983).

A rough estimate of the incidence of dementia (all types) calculated for the various age groups from age 55 onwards is as follows:

55 - 64 years old	1 per 10.000 person-years
65 - 74 years old	1 per 1.000 person-years
75 and over	1 per 100 person-years

These figures should be regarded as a rule of thumb (Hofman 1988).

The cumulative incidence, i.e., the risk of developing dementia (all types) at a certain age (%) up to age 90, has been estimated as follows:

at age 55 years	: 16.6%	
65 years	: 16.5%	
75 years	: 15.4%	
85 years	: 8.4%	(Hofman & Duyn van 1989, p 245).

However, if there is a positive family history of dementia, the cumulative incidence up to age 90 increases roughly four-fold:

at age 55 years : 54.3%
65 years : 54.0%
75 years : 51.2%
85 years : 31.4% (Hofman & Duyn van 1989, p 247).

Prevalence of Alzheimer type dementia.

A further meta-analysis was carried out by Hofman and coworkers (Rocca et al 1991) in order to determine the frequency and distribution of Alzheimer type dementia in Europe. The study included: census of existing surveys; collection of disaggregated data in a standardized format; selection of comparable data-sets; and study of prevalence patterns by time, place, and personal variables. Only studies in which Alzheimer type dementia had been diagnosed by NINCDS-ADRDA (McKhann et al 1984) or equivalent criteria, all subjects were examined personally, sample size was appropriate, and institutionalized cases were included, qualified for comparison. Of the 23 European surveys of dementia conducted or published between 1980 and 1990, six qualified for comparison of prevalence of Alzheimer type dementia (see Table I.3.1; the six asterisked studies were included in the analysis of the prevalence of Alzheimer type dementia by Rocca et al {1991}). Taking into account the possible effect of age and sex, Rocca et al (1991) failed to show major geographic differences in prevalence of Alzheimer type dementia across Europe. Overall European prevalences (per 100 population) for the age groups 30-59, 60-69, 70-79, 80-89 years were 0.02, 0.3, 3.1, and 10.8 respectively (see Table I.3.3; adapted from Rocca et al 1991). The exponential increase in prevalence with age was the most consistent finding of the study.

The sex-specific patterns were less homogeneous; in two studies - total Finland (Sulkava et al 1985) and Appignano, Italy (Rocca et al 1990) - and in the overall European estimates, the prevalence was higher in women for all age groups. In three other studies, the sex pattern was inconsistent. These findings suggest that, overall, women have higher prevalences than men in the same age category; the inconsistent findings might be due to differential survival of men and women affected by Alzheimer type dementia in various populations. Rocca et al (1991) hypothesize that the consistently higher prevalence in women which is found in

ERRATUM: In table I.3.3, chapter I.3, page 60, the age class distribution should be as follows:

Table I.3.3: Age- and Sex-specific Prevalence (%) of Alzheimer's Disease in Europe.

POPULATION	Age Class							
	30-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94
Average++ Men	0.0 (0/3,164)	0.3 (3/947)		2.5 (15/608)		10.0 (58/581)		
Average++ Women	0.03 (1/3,273)	0.4 (4/1,127)		3.6 (48/1,349)		11.2 (119/1,059)		
Agerage++ Both sexes	0.02 (1/6,437)	0.3 (7/2,074)		3.1 (49/1,592)		10.8 (177/1,640)		

Numbers in brackets indicate the actual numerator and denominator figures.

++ Weighted average restricted to those studies for which the prevalence estimate covers the entire age class.

Adapted from Rocca WA, Hofman A, Brayne C et al (1991) Frequency and distribution of Alzheimer's disease in Europe. A collaborative study of 1980-1990 prevalence findings. Annals of Neurology {in press}.

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	30-59	60-64	65-69	70-74	75-79	80-84	85-89
Average++ Men	0.0 (0/3,164)		0.3 (3/947)		2.5 (15/608)		10.0 (58/581)
Average++ Women	0.03 (1/3,273)		0.4 (4/1,127)		3.6 (48/1,349)		11.2 (119/1,059)
Agerage++ Both sexes	0.02 (1/6,437)		0.3 (7/2,074)		3.1 (49/1,592)		10.8 (177/1,640)

Numbers in brackets indicate the actual numerator and denominator figures.
++ Weighted average restricted to those studies for which the prevalence estimate covers the entire age class.

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some studies may be due to a higher risk of Alzheimer type dementia (incidence rate) or, alternatively, by longer survival of women compared to men among patients with Alzheimer type dementia of the same age. Available data on the incidence (i.e., frequency of occurrence of new cases) of Alzheimer type dementia suggest that women have higher age-specific incidence rates than men (Mölsä et al 1982; Rorsman et al 1986; Treves et al 1986; Kokmen et al 1988, 1989; Rocca et al 1991). On the other hand, Nilsson, in Sweden, found incidence rates constantly higher in men (Nilsson 1984), and Schoenberg et al, in the United States, found an inconsistent age pattern (Schoenberg et al 1987). As Rocca et al (1991) state, it is unclear whether these contrasting findings regarding sex-specific incidence rates are due to methodological differences or to true geographical differences (Rocca et al 1991; Rocca & Amaducci 1990). Rocca et al (1991) finally point at the fact that comparison of incidence and prevalence of Alzheimer type dementia in men versus women might be confounded by the

effect of education or other unknown intervening variables.

A comparison of prevalences of Alzheimer type dementia from Europe with those from other continents reinforced the impression of small international differences. Rocca et al (1991) compared the European prevalences with two studies from the United States (Folstein et al 1985; Kokmen et al 1988, 1989) and one from Japan (Hasegawa et al 1986), and found age-specific prevalences of the same magnitude and slope as in the European studies, despite important methodological differences. Findings from the study in Rochester, Minnesota (Kokmen et al 1988, 1989), based on the Mayo clinic records-linkage system, almost overlap the average European estimates. On the other hand, a recent United States study carried out in East Boston (Evans et al 1989) yielded prevalences of dementia (all types) and of Alzheimer type dementia higher than previously reported in the United States (Folstein et al 1985; Kokmen et al 1988, 1989), and higher than those found in Europe (Hofman et al 1991; Rocca et al 1991). The unusually high prevalence values found in the East Boston study have been ascribed to methodological differences; although the authors (Evans et al 1989) defined Alzheimer type dementia by the NINCDS-ADRDA criteria (McKhann et al 1984), their criteria for dementia were broader than those required by DSM-III (American Psychiatric Association 1980). Therefore, Rocca et al (1991) considered the East Boston study not comparable with their European meta-analysis.

As Rocca et al (1991) point out, the small international variations in the prevalence and incidence of Alzheimer type dementia are in striking contrast with the wide international variation of both genetic and environmental factors which could influence risk of Alzheimer type dementia; the authors explain this paradox by stating that age may well be the most important risk factor for Alzheimer type dementia, and that age may conceal the effect of other, weaker, risk factors in population studies.

Only the Lund data set (Rorsman et al 1986) was considered suitable for studying time trends of prevalence of Alzheimer type dementia. Rocca et al (1991) conclude that, overall, the prevalence of Alzheimer type dementia has remained stable over 15 years; this stability in prevalence is consistent with the absence of significant time trends for incidence of Alzheimer type dementia found in the same Lund Longitudinal Study (Rorsman et al 1986) and in one United States

population (Schoenberg et al 1987; Kokmen et al 1988, 1989).

The East Boston study.

In the East Boston study (Evans et al 1989), clinically diagnosed Alzheimer type dementia and other dementing illnesses were assessed in a geographically defined US community. Of 3623 persons (80.8% of all community residents over 65 years of age) who had brief memory testing in their homes, a stratified sample of 467 persons underwent neurological, neuropsychological, and laboratory examination. Prevalence values of Alzheimer type dementia were calculated for the community population from the sample undergoing clinical evaluation. Of those over the age of 65 years, an estimated 10.3% (95% confidence limits, 8.1% and 12.5%) had probable Alzheimer type dementia. This prevalence was strongly associated with age. Of those 65 to 74 years old, 3.0% (95% confidence limits, 0.8% and 5.2%) had probable Alzheimer type dementia, compared with 18.7% (95% confidence limits, 13.2% and 24.2%) of those 75 to 84 years old and 47.2% (95% confidence limits, 37.0% and 63.2%) of those over 85 years. Other dementing conditions were uncommon. Of community residents with moderate or severe cognitive impairment, 84.1% had clinically diagnosed Alzheimer type dementia as the only probable diagnosis. Evans et al (1989) conclude that clinically diagnosed Alzheimer type dementia is a common condition and that its public health impact will continue to increase with increasing longevity of the population.

These data from East Boston are notable not only for their high prevalence values of dementia (all types), but also for the unusually high proportion of cases attributed to Alzheimer type dementia.

In the Editorial accompanying the article, Larson (1989) states that the high prevalence values may reflect methodological differences. Most importantly, the investigators could not apply the DSM-III criterion that there 'be a loss of intellectual abilities sufficient to interfere with social or occupational functioning' in a 'uniform, meaningful way' when cases were identified by active screening. Thus, diagnoses were based on performance on objective tests to assess cognition. Functional impairment in everyday life was not a factor in diagnosis, but was inferred based on the magnitude of cognitive impairment. Thus, the East Boston study does not tell us what sort of 'dis-ease' clinically diagnosed Alzheimer type

dementia was causing in this population (Larson 1989). As Larson (1989) correctly points out, we need to know this in order to judge the nature of the disease in practical terms. Also, there is the lack of histological confirmation, which, in the NINCDS-ADRDA criteria, is considered the sine qua non for the diagnosis of Alzheimer type dementia (McKhann et al 1984). But a cross-sectional, point-prevalence study cannot be expected to diagnose Alzheimer type dementia pathologically. Nonetheless, we are left wondering if the nearly 50% of patients over 85 years of age diagnosed as having clinical Alzheimer type dementia had plaques and neurofibrillary tangles (Larson 1989).

The East Boston study (Evans et al 1989) excluded institutionalized patients. Surveys conducted in communities that have relatively higher rates of out-migration to nursing homes will have spuriously low rates of Alzheimer type dementia, whereas surveys in communities like East Boston, which have lower out-migration owing to strong family-support systems, active home-care programs, lack of access to long-term care places, and perhaps certain cultural patterns will measure higher rates. In addition, educational achievement levels are relatively low in East Boston, especially in persons over 65 years of age, and English is a second language for some (the questionnaire was given in Italian for nearly 10% of the sample) (Evans et al 1989). Is a low level of education a risk factor for cognitive impairment alone or for cognitive impairment due to Alzheimer type dementia? Without more information on the course of illness and brain pathology, a point-prevalence study simply cannot answer these important questions (Evans et al 1989; Larson 1989). However, for practising physicians, the message of the East Boston study is clear but complicated; cognitive impairment is extremely common in persons in the over-85-year age group (Larson 1989).

Discussion of the East Boston study.

This study demonstrates how important it is for investigators to adhere to diagnostic criteria in the most accurate manner in order to reduce diagnostic error to a minimum. In addition, the low educational achievement levels in East Boston may well have contributed to the unusually high prevalence values found. It has been demonstrated before, that misclassification of patients occurs especially in those of low socioeconomic class and education, both in epidemiological studies (Kay et al 1964a, 1964b, 1968; Bergmann et al 1971; Kay 1972; Kay & Bergmann 1980; Gurland 1981) and in the individual patient (Van der Cammen et al 1987).

Although the East Boston study excluded institutionalized patients, prevalence values for dementia (all types) and for Alzheimer type dementia were unusually high; this may be due in part to the fact that many demented elderly in the area are sustained in their own homes because of lack of access to long-term care places.

Dutch prevalence figures for dementia all types and Alzheimer type dementia. Like most industrialized countries, the Netherlands have an ageing population (see Figure I.3.1; CBS 1990).

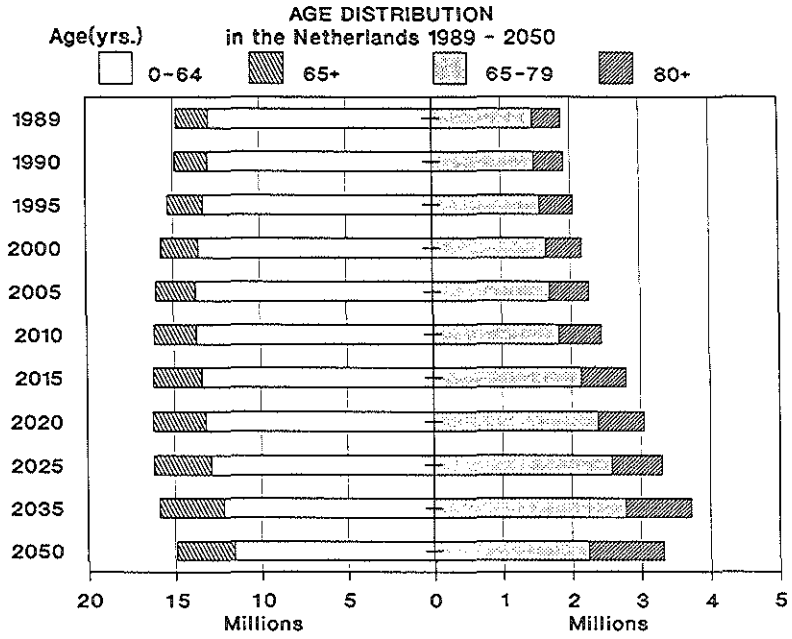

Figure I.3.1. Age distribution in The Netherlands 1989 - 2050.
Adapted from: CBS, Statistisch Jaarboek 1990.

As can be seen from Table I.3.4 (adapted from Hofman et al 1991), age-specific prevalence of dementia (all types) in both sexes has been studied in the Amsterdam/Rotterdam study (Breteler et al {in press}) and in the Leiden study

Table I.3.4: Age- and sex-specific prevalence (%) of dementia (all types) in two studies in The Netherlands.

POPULATION	Age Class								
	30-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94	95-99
Men Amsterdam/Rotterdam			2.4 (1/42)	1.7 (1/60)	3.0 (1/33)	4.5 (1/22)	30.0 (3/10)	25.0 (1/4)	
Men Leiden							17.7 (23/130)	33.2 (12/36)	26.6 (4/15)
Women Amsterdam/Rotterdam			0.0 (0/68)	1.3 (1/75)	4.2 (3/71)	6.6 (4/61)	21.3 (10/47)	64.3 (9/14)	
Women Leiden							24.2 (97/400)	35.9 (46/128)	52.6 (10/19)
Both sexes Amsterdam/Rotterdam			0.9 (1/110)	1.5 (2/135)	3.8 (4/104)	6.0 (5/83)	22.8 (13/57)	55.6 (10/18)	
Both sexes Leiden							22.6 (120/530)	35.4 (58/164)	41.2 (14/34)

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(Heeren & Lagaay 1988). Prevalence values for both sexes in the first study range from 0.9% in the 65-69 age group to 55.6% in the 90-94 age group; in the second study, only persons aged 85 and over participated, and prevalence values range from 22.6% in the 85-89 age group to 41.2% in the 95-99 age group. At present, in the Netherlands, an estimated 80.000 to 100.000 elderly (aged ≥ 65) are suffering from severe dementia (all types), based on prevalence values of 5% in those aged 65 and over, and of 20% in those aged 80 and over. If these prevalence values are extrapolated to the year 2000, an estimated 120.000 to 130.000 elderly (aged ≥ 65) in the Netherlands will be suffering from severe dementia (all types) by that time (Tanja & Hofman 1985).

In a secondary analysis of detection of Alzheimer type dementia and depression in a general practice, Wevers (1987) has examined the possibilities for the general practitioner to distinguish between psychological complaints in general and symptoms possibly caused by dementia and depression. The percentage of elderly in this practice possibly suffering from Alzheimer type dementia was found to be about the same as mentioned in two earlier Dutch registrations of morbidity in general practice, i.e., 1.2-1.6% of people aged 65 and over (Lamberts 1982; Nijmeegs Universitair Huisartsen Instituut 1985). However, these figures are considerably lower than the prevalence figures mentioned in epidemiological studies from other countries, most likely due to the fact that only patients who had initiated the consultation with their general practitioner were included in Wevers' analysis (Wevers 1987; see also chapter IV).

De Leeuw and Hofman (1987) have analyzed the incidence of long-term care placement for dementia (all types) from 1981 to 1985 in Rotterdam; they discuss sex- and age-specific incidence rates of long-term care placement for dementia (all types) in the city of Rotterdam in the period from 1 January 1981 to 31 December 1985. Data were based on the moment that the diagnosis of dementia (all types) was established and patients' names were registered on the waiting list for psychogeriatric day treatment or admission to a long-term care place in a psychogeriatric nursing home. The incidence of long-term care placement for dementia (all types) rose sharply with age from age 55 onwards, for men from 0.1 to 18.8 per 1000 person-years and for women from 0.1 to 25.2 per 1000 person-years (see Figure I.3.2; De Leeuw & Hofman 1987). These observations probably give an underestimate of the incidence of dementia (all types), as data were

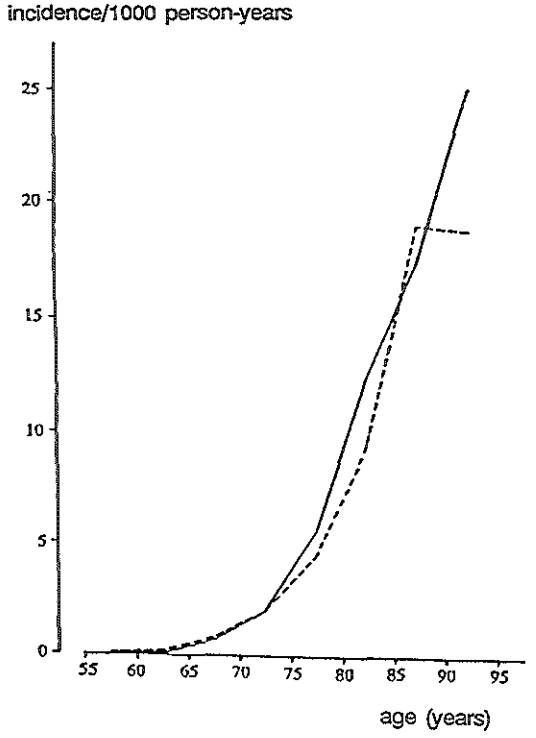

Figure I.3.2. Mean incidence (per 1000 person-years) of long-term care placement for dementia (all types) in Rotterdam 1981-1985.
(——— = men; ——— = women).
From De Leeuw CJ & Hofman A (1987) De incidentie van opname wegens dementie in Rotterdam van 1981-1985. Ned Tijdschr Geneeskd 131; 37: 1616-1618.
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based on the number of patients who had been registered on the waiting list for psychogeriatric care. Extrapolation of these figures to the whole of the Netherlands indicates that over 8300 new patients with dementia (all types) were admitted in 1985, and that this figure might rise to over 12.000 in the year 2000 (De Leeuw & Hofman 1987).

Table I.3.5: Prevalence of moderate or severe dementia (%).

Age	[1]Kaneko (1969) N=531	Nielson (1963) 978	[2]Syracuse Study (1961) 1503	[1]Kay et al (1970) 758	[3]Essen-Möller (1956) 443
65-	1.9	2.1	3.7	2.4	0.9
70-	2.7	4.0	5.4	2.9	5.1
75-	11.3	7.8	9.3	5.6	
80-	9.9	12.6	8.8	22.0	21.8
85-	33.3	21.4	23.7		
All Ages	7.1	5.9	6.8	6.2	5.0

[1] Persons living at home only.
[2] Includes some functional psychoses?
[3] Age groups 60-69, 70-79, 80+.

Report of the Royal College of Physicians on Organic Mental Impairment in the Elderly (1981) Journal of the Royal College of Physicians 15: 4-29.
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Table I.3.6: Prevalence of 'mild dementia' (%).

Age	[1]Kaneko (1969)	Nielson (1963)	[2]Essen-Möller (1956)
65-	44.3	4.2	
70-	62.6	12.1	16.6
75-	55.7	23.8	
80+	48.7	37.1	25.5
All Ages	52.7	15.4	10.8

[1] Persons living at home only.
[2] Age groups 60-69, 70-79, 80+.

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Epidemiology of severe versus mild dementia.

Prevalence estimates from earlier community surveys have indicated that an average of 4.6% of persons over 65 suffer from 'severe' dementia - that is, they are so incapacitated that they need either institutional care or full-time care in their own homes; just over 10% have a 'mild to moderate' degree of cognitive dysfunction and are still able to live semi-independently (Katzman 1976, 1986; Mortimer et al 1981). Other studies have demonstrated that 'severe' dementia is present in less than 1% of persons aged 65, but in more than 15% of those who are over 85 (Gruenberg 1961; Nielson 1963; Terry & Katzman 1983).

The Royal College of Physicians' report on 'Organic Mental Impairment in the Elderly' (1981) includes an analysis of prevalence values of 'moderate or severe' and 'mild' dementia (all types) as found in previous field surveys of elderly populations (age $\geq$ 65 years); in the five studies included in the analysis, the prevalence of 'moderate or severe' dementia (all types) was found to be remarkably consistent at about 6% (see Table I.3.5, from the Report of the Royal College of Physicians on Organic Mental Impairment in the Elderly 1981; Essen-Möller et al 1956; Syracuse-New York State Department of Mental Hygiene 1961; Nielson 1963; Kaneko 1969; Kay et al 1970); in the three studies which reported prevalences of 'mild' dementia (all types), values varied from 10.8% in the study by Essen-Möller et al (1956) to 52.7% in the study by Kaneko (1969) (see Table I.3.6, from the Report of the Royal College of Physicians on Organic Mental Impairment in the Elderly 1981; Essen-Möller et al 1956; Nielson 1963; Kaneko 1969). In Britain, prevalences of 'mild' dementia (all types) in elderly populations have varied from 2.6% in the study by Bergmann et al (1971) to 21.9% in the study by Parsons (1965). These figures demonstrate that the consistency in the prevalence of dementia (all types) in elderly populations disappears when one looks at the prevalence of 'mild' dementia. In all of these surveys, only a general indication was provided on how cases of mild dementia had been recognized.

While the apparent variation in overall prevalence values of mild dementia might be partly due to different proportions of the very old in the populations sampled, this explanation is unlikely (Henderson & Huppert 1984). As Henderson and Huppert (1984) point out, there seems no reason for this to apply only to mild dementia, but not to the moderate or severe categories, where prevalence values are much more consistent. The main source of variation is likely to be due to

differences first in the criteria and secondly in the methods/instruments used to identify cases of mild dementia.
As we have seen in chapter I.2, both DSM-III-R (American Psychiatric Association 1987) and the research criteria of ICD-10 (WHO 1988; Sartorius et al 1988; Jablensky 1989) include mild dementia as a special entity, but they fail to specify the diagnostic criteria for these conditions. Without an operational definition of dementia severity, terms such as 'mild', 'moderate', or 'severe' might be incorrectly used and thereby induce diagnostic variance in dementia severity.
The diagnosis of mild dementia in epidemiological studies has been designated a special research entity. As can be seen from Table I.3.7 (from Rocca et al 1991), some of the Eurodem centres are addressing this issue (Appignano, Italy, Rocca et al 1990; Cambridge, UK, O'Connor et al 1989; Lund, Sweden,. Hagnell 1966 and Rorsman et al 1986; from: Rocca et al 1991).

Case ascertainment in epidemiological studies.
Table I.3.7 (from Rocca et al 1991) shows the case finding procedures used in the six European prevalence studies of Alzheimer type dementia. As Rocca et al (1991) state, the sensitivity of the screening instruments used in the various studies is an important methodological issue. Five of the six studies were based on a two-phase design; unfortunately, the studies used different screening instruments. Two studies (O'Connor et al 1989; Lobo et al, in press) applied the Mini-Mental State Examination (Folstein et al 1975), but in different languages and with some adaptations to the local culture (Lobo et al 1979). The use of different instruments, or of different translations of a common test, might introduce unknown variations in the observed prevalences. On the other hand, in three studies (Finland, total country, Sulkava et al 1985; Italy, Appignano, Rocca et al 1990; Spain, Zaragoza, Lobo et al, in press) the sensitivity of the screening instrument was compared to the clinical diagnosis (standard) and found to be high. Differences in prevalence may also occur due to different interpretation and application of common diagnostic criteria such as DSM-III and DSM-III-R (American Psychiatric Association 1980, 1987) or NINCDS-ADRDA (McKhann et al 1984).
In epidemiological studies, the assessments used for case ascertainment vary considerably (see Table I.3.8; from Rocca et al 1991).

Table I.3.7 and Table I.3.8 show the steps used in the six European studies which were included in the meta-analysis of Alzheimer type dementia. As Rocca et al (1991) explain, the major area of uncertainty is that between Alzheimer type dementia, vascular (including mixed) dementia, and dementia due to other causes. Of the six European studies, only two used imaging tests (computerized tomography and nuclear magnetic resonance) (Finland, total country, Sulkava et al 1985; Italy, Appignano, Rocca et al 1990); priority was given to clinical criteria versus imaging findings in all studies (see Table I.3.8; from Rocca et al 1991). In most epidemiological studies, imaging tests cannot be performed on each prevalent case of dementia; in addition, findings at any given time represent the sum of all previous changes in the brain, without specifying the chronological sequence of degenerative and vascular lesions. The exclusion of dementia due to other disorders depends on the intensity and completeness of the search for specific causes. In the six European studies which were included in the meta-analysis of Alzheimer type dementia, a specified list of blood tests was performed only in one study (Cambridgeshire, UK, Brayne & Calloway 1989); in another three, blood or urine tests were performed only when required on the basis of medical history or physical examination (Finland, total country, Sulkava et al 1985; Italy, Appignano, Rocca et al 1990; Spain, Zaragoza, Lobo et al, in press); in two studies, laboratory tests were not carried out (Sweden, Hagnell 1966 and Rorsman et al 1986; Cambridge, UK, O'Connor et al 1989; see also Table I.3.8, from Rocca et al 1991). These facts demonstrate the problems of case ascertainment in epidemiological studies.

The future.

Longitudinal (intra-individual) studies of large populations using standardized screening instruments are now being carried out in order to determine prevalences of dementia (all types) and of the various specific dementias (Hofman 1987; Copeland 1990; Hofman et al 1991; Rocca et al 1991). Epidemiological studies also aim to identify those with early dementia, and to search for identifying factors for the diagnosis of early dementia. They may reveal a variety of significantly different clinical pictures corresponding to different clinical entities. In addition, they may identify the sensitive test(s) for the diagnosis of the various dementias.

Table I.3.7: Case-finding procedures used for the diagnosis of dementia.

POPULATION*	PHASE 1				PHASE 2			
	Screening Procedure (Personnel)	Degree of Case-Finding	Validity	Reliability	Diagnostic Protocol (Personnel)	Psychometric Instruments	Exclusion of Depression	Validity or Reliability
Finland Total Country	G-factor & verbal memory tests (non medical)	Excluded mild dementia	Sens. Probably high Spec. Low (not measured)	--	Review of existing medical documentation; Interview of caregivers (neurologists)	--	History and clinical evaluation	Only 2 neurologists together
Italy Appignano	AMT <= 7 (non medical)	Should detect mild dementia	Sens.=100% Spec.= 71%	--	Specifically designed (psychiatrist and neurologist)	MMSE B-R Test B-R Scale	Hamilton rating scale and history	Joint evaluation by a psychiatrist and a neurologist
Spain Zaragoza	GMS MMSE (non medical)	--	Sens.= 91% Spec.= 69%	Interobserver (lay) K=0.93 Interviewers vs. psychiatrists	GMS MMSE HAS (psychiatrist)	MMSE B-R Test B-R Scale etc.	GMS HAS	GMS and MMSE Interobserver psychiatrists Kw=1.0;k=0.81
Sweden Lund	Semi-structured Interview plus review of medical documentation (psychiatrists)	All degrees of dementia	--	Frequent exchanges among observers	Specifically designed protocol plus review of existing medical documentation (psychiatrists)	None	Clinical evaluation	Doubtful cases evaluated jointly

Table I.3.7 (continued)

POPULATION*	PHASE 1				PHASE 2			
	Screening Procedure (Personnel)	Degree of Case-Finding	Validity	Reliability	Diagnostic Protocol (Personnel)	Psychometric Instruments	Exclusion of Depression	Validity or Reliability
United Kingdom Cambridge	MMSE <= 23 of 30 (1/3 scores of 24 or 25) (non medical)	Should detect mild dementia	Sens.= 86% Spec.= 92%	Interobserver K=0.97	CAMDEX (psychiatrist)	CAMDEX tests	CAMDEX depression scale	--
United Kingdom Cambridge-shire	----------	[one-phase only]	----------		Interview at home using CAMDEX; informant interviewed for all subjects (physician)	CAMDEX tests	Direct clinical (CAMDEX criteria)	Only one investigator

* Populations are listed in alphabetical order by country and within country.

G-factor test = Cattell's G-factor test;[1] verbal memory test;[2] Sens. = Sensitivity: true positives/(true positives + false negatives);[3] Spec. = Specificity: true negatives/(true negatives + false positives);[3] AMT = Abbreviated mental test;[4] MMSE = Mini mental state examination;[5] B-R Test = Blessed-Roth information-memory-concentration test;[6] B-R Scale = Blessed-Roth dementia scale;[6] Hamilton rating scale;[7] GMS = Geriatric mental state;[8] K = Kappa statistic: the proportion of agreement beyond chance;[3] HAS = History & aetiology schedule;[9] CAMDEX = The Cambridge examination for mental disorders of the elderly.[10]

[1] = Cattell (1960)
[2] = Tuunainen (1972)
[3] = Last (1988)
[4] = Hodkinson (1972)
[5] = Folstein et al (1975)
[6] = Blessed et al (1968)
[7] = Hamilton (1967)
[8] = Copeland et al (1976)
[9] = Saunders & Glover (1990)
[10] = Roth et al (1986, 1988)

From: Rocca et al (1991).

Table I.3.8: Diagnostic Criteria for Dementia and Specific Dementing Disorders.

POPULATION*	Dementia (All Types)	Alzheimer's Disease	Vascular Dementia	Mixed Dementia	Secondary Dementias
FINLAND Total Country	DSM-III but excluding mild dementia	Equivalent to NINCDS-ADRDA probable AD	Clinical criteria only (CT considered but not required)	Merged with VD	Medical history and/or laboratory findings required
ITALY Appignano	DSM-III	NINCDS-ADRDA probable and possible AD	Clinical criteria and HIS >= 7 (CT-MRI considered but not required)	HIS = 5 or 6 (CT-MRI considered but not required)	Specific clinical findings laboratory tests as suggested by history and clinical evaluation
SPAIN Zaragoza	Equivalent to DSM-III; ICD-10R also used	NINCDS-ADRDA	Clinical criteria and HIS >= 4 of 6 items	Clinical criteria and HIS >= 3 of 5 items	Medical history, physical examination, and/or laboratory tests
SWEDEN Lund	'Age psychosis' Lundby criteria (comparable to DSM-III-R)	'Senile dementia' Lundby criteria (comparable to DSM-III-R)	Lundby criteria only patients with focal signs	Merged with VD	Not specified
UNITED KINGDOM Cambridge	CAMDEX (=DSM-III)	CAMDEX (equivalent to NINCDS-ADRDA)	CAMDEX (= HIS) No CT or imaging tests	Both AD and VD criteria satisfied	Medical history, medical records, and brief physical examination; no laboratory tests
UNITED KINGDOM Cambridgeshire	CAMDEX (=DSM-III)	CAMDEX (equivalent to NINCDS-ADRDA)	Clinical criteria CAMDEX (= HIS) No CT or imaging tests	Clinical criteria CAMDEX	Clinical evaluation plus blood tests: urea, glucose, electrolytes, thyroid tests

Table I.3.8: (continued)

*Populations are listed in alphabetical order by country and within country.

DSM-III (-R)= Diagnostic and statistical manual of mental disorders - 3rd edition[1] (-Revised);[2] NINCDS-ADRDA = Diagnostic criteria of the National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association Work Group;[3] AD = Alzheimer's Disease; VD = Vascular Dementia; CT = computerized tomography; HIS = Hachinski ischemic score;[4] MRI = Magnetc resonance imaging; ICD-10R = International classification of diseases-10th revision (unpublished draft, 1989); CAMDEX = The Cambridge examination for mental disorders of the elderly.[5]

[1] = American Psychiatric Association (1980)
[2] = American Psychiatric Association (1987)
[3] = McKhann et al (1984)
[4] = Hachinski et al 1975
[5] = Roth et al 1986, 1988

Tables I.3.7 and I.3.8 are from Rocca WA, Hofman A, Brayne C et al (1991) Frequency and distribution of Alzheimer's disease in Europe. A collaborative study of 1980-1990 prevalence findings. Annals of Neurology {in press}.

International comparison with studies carried out in the United States and Japan is ongoing, but data from third world countries have not yet been included in meta-analyses. The meta-analyses by Hofman et al (1991) and Rocca et al (1991) have shown remarkable consistency in prevalence figures for dementia (all types) and for Alzheimer type dementia within populations with similar ethnic background. Multi-site studies now being mounted by the Medical Research Council in the UK, by Eurodem in the EEC, and by the Pan American Health Organization and the World Health Organization using standardized measures will, for the first time, allow extensive comparisons to be made between different geographical areas (Copeland 1990). Moreover, epidemiological researchers are in an excellent position to test specific aetiological hypotheses.

Discussion.

In summary, chapter I.3 demonstrates that both dementia (all types) and Alzheimer type dementia are age-related disorders; the life-time risk is estimated at 15 to 20%. The risk factors for Alzheimer type dementia which are known so far, are advancing age, a positive family history, and a history of head trauma associated with loss of consciousness which has occurred within the last 15 years (Amaducci et al 1986; Rocca et al 1986; Brayne & Calloway 1988).

The meta-analysis by Rocca et al (1991) demonstrates that the prevalence of Alzheimer type dementia is similar throughout Europe, increases exponentially with increasing age, is consistently higher in women than in men, and has remained stable over time.

Comparison of the European data with data from the United States and Japan indicates that international variations in the prevalence and incidence of Alzheimer type dementia are small, which again points towards the possibility of age being the most important risk factor for the condition. This has implications not only for the specialties of geriatric medicine, neurology and psychiatry, but for all branches of the medical profession caring for elderly people. Already, in the western world, elderly patients have more hospital admissions and longer hospital stays than members of younger age groups (National Health Interview Survey US 1986; Hoogendoorn 1990). Demented elderly patients are known to have much longer hospital stays than non-demented elderly patients (Kay et al 1970; Fields et al 1986; Johnston et al 1987; Maguire et al 1987; Binder & Robins 1990).

I.3 The size of the problem: epidemiology of dementia.

Correct diagnosis and the development of models of care for elderly patients with dementia become increasingly important as more people in western populations survive into very old age.

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I.4 THE CHALLENGE OF EARLY DIAGNOSIS.

The diagnosis of mild dementia in epidemiological studies.

Case definition has been a problem in epidemiological research. This is especially true for dementia, where diagnosis is based on clinical rather than on aetiological grounds. Epidemiological studies of dementia are now more and more concerned with early identification, and the development of better criteria of prediction, by using more stringent criteria for diagnosis. Thus, mild dementia has become an area of particular research interest. Although this term is already in common usage in the clinical and epidemiological literatures, there are certain difficulties about the concept: there are no specific criteria by which its presence can be asserted; it is not itself a diagnosis, but rather a rubric for the early stages of several neuropathologically distinct disorders; and little is known about its natural history (Henderson & Huppert 1984). It is uncertain whether all cases of mild dementia proceed to a moderate or severe dementia (Kay 1962; Bergmann et al 1971; Bergmann 1977; Gurland 1981). As Henderson and Huppert (1984) have pointed out, little is known about features which, at ascertainment, might differentiate a benign course from a more rapid deterioration. Lastly, a reliable and valid method of ascertainment is important if there is success in developing a specific pharmacological remedy to enhance memory. For these reasons, clinical and epidemiological studies of mild dementia are needed. But the results of any systematic study of the prevalence, natural history or treatment of mild dementia will depend on the material included as cases. Insofar as possible, therefore, homogeneity between samples is desirable if findings are to be compared. Such homogeneity can be achieved only by adherence to standard criteria and casefinding methods.

Characteristics of mild dementia.

Henderson and Huppert (1984) have reviewed the problems of diagnosing mild dementia. They observed that the single common feature in mild dementia is the presence of mild cognitive impairment, presumed to be a decline from a formerly higher level of functioning. The principal characteristic of mild dementia, a modest impairment of memory and other aspects of cognition, is shared with several other states.

The first of these is clouding of consciousness from medical disorders or medication. Such delirious states may be common in an age group with a high prevalence of cardiovascular and respiratory disease, while in developing

countries parasitic disease and malnutrition probably lead to impaired cognition in the elderly (Henderson & Huppert 1984). Iatrogenic clouding may be induced by pharmacological agents such as sedatives, psychotropic drugs, certain antihypertensives, and any preparation with anticholinergic properties (Anonymous, Lancet 1982; Solomon et al 1983; Vecht-van den Bergh 1983; Anonymous, Lancet 1984; Laan van der & Slangen 1988). Drugs which have been associated with delirious states are shown in Table I.4.1 (Van der Cammen et al 1991, p 212).

Table I.4.1: Drugs associated with delirious states.

Amantidine
Anticholinergic drugs
Anticonvulsants
Antidepressants
Antihistamines
Antiparkinsonian drugs
Atropine
Centrally acting analgesics
Centrally acting antihypertensives
Corticosteroids
Digoxin
Hypoglycaemics
Isoniazid
Opiates
Sedatives
Tranquillizers

Adapted from: Van der Cammen TJM, Rai GS, Exton-Smith AN (1991) Acute Confusional States. In: Manual of Geriatric Medicine. Edinburgh: Churchill Livingstone, ch 22, p 207-219.

However, delirium can usually be distinguished from dementia by a history of acute mental impairment of short duration in a patient with a previously normal mental state; in addition, the patient is often seriously ill.

Secondly, there is the problem of distinguishing early dementia from depression in old age; there is ample evidence that depressive illness can be accompanied by cognitive impairment, at times mimicking dementia ('pseudodementia')*. There are many well-documented cases of cognitive improvement after treatment of depression. For example, Rabins (1985) reported on 16 patients who presented with symptoms of dementia accompanying major depression. Thirteen patients (81%) had a full recovery of cognition after treatment for their depression. Most maintained this improvement after two years of follow-up, but not all patients do so. Some patients who at first seem to show improved cognition when depression is treated, ultimately manifest the presence of an underlying irreversible dementia that shows up only on follow-up, as was demonstrated by Reding et al (1984). Questioning the patient about memory problems is more likely to result in positive replies in patients who are depressed than in those who are demented. In their study of the reliability of a standardized psychiatric interview on 47 day-patients, Henderson et al (1983) found that the item 'Have you had any difficulty with your memory?' correlated 0.55 ($p < 0.001$) with the depression score (Spearman coefficient), but only 0.21 (NS) with the score for cognitive impairment. In a recent study, O'Connor et al (1990) asked normal, depressed and demented elderly persons to assess their memories and to complete a battery of memory tests. Memory complaints and memory performance were found to correlate poorly in the normal and depressed groups. Conversely, it is important to bear in mind that depressive symptoms may be a prominent feature in cases of mild dementia, particularly where the individual is aware of his impairment.

Thirdly, there is the important problem of distinguishing mild dementia from what may be normal ageing.

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* Kiloh 1961; Wells 1979; Caine 1981; McAllister & Price 1982; McAllister 1983; Reifler et al 1982; Cooper & Bickel 1984; Heeren 1988; O'Connor et al 1988.

Kral (1962) described a state he called benign senescent forgetfulness, characterized by occasional dysnomia and difficulty in recalling parts of past episodes, with no such difficulty at other times. This state is said not to carry the downward course and increased mortality of dementia (Kral 1978). Insufficient information is at present available for the validation of this category of cognitive impairment (Henderson & Huppert 1984). Yet the possibility that it exists is clearly of great importance in detecting cases of mild dementia, from which it is said to be distinct. Lastly, several authors have found that persons who were first classified as cases of mild dementia were later found to have limited intelligence or education (Bergmann et al 1971).

Bergmann and his colleagues (1971) found that, of those who were suspected of dementia, only 32% progressed to unequivocal dementia over a three-year follow-up period, 37% turned out to be psychiatrically normal subjects of low IQ and social class leading a marginal and deprived existence, the remainder continued to be mildly impaired and of uncertain diagnostic status. Conversely, the largest number of subjects developing dementia came from the previously 'normal' and 'functional' groups in whom dementia had not been suspected (for definitions see chapter I.2; Kay et al 1964a, 1964b, 1968; Bergmann et al 1971). Gurland (1981) cites a number of studies in which less well educated persons were diagnosed as mildly demented more often than those who were better educated. A recent study by Fillenbaum et al (1988) also demonstrated that the score obtained on a mental status questionnaire was related to education, age and race. This study is discussed extensively later in this chapter.

The task for epidemiology, then, is to develop a method for identifying cases of mild dementia free of contamination with other diagnoses and independent of previous levels of intelligence or education (Henderson & Huppert 1984). We shall consider first the criteria being used, and then the methods/instruments currently available.

The criteria for the diagnosis of mild dementia.

Here, a dilemma arises. A reliable and sensitive test for diagnosing early dementia has not yet been invented. The condition can be studied only if there is a method for identifying it reliably and validly. However, until longitudinal studies have been conducted, we do not know which features will turn out to be the distinctive ones.

Therefore, if progress is to be made, criteria will have to be chosen in the full knowledge that they are only tentative at this stage. This will improve reliability, but the validity of the method can be assessed only later (Henderson & Huppert 1984).

Some attempts have been made to set up working criteria in the course of developing standardized interviews or clinical assessments with reference to the diagnosis of early and mild dementia.

We shall now discuss the methods and instruments currently available for the diagnosis of dementia and their ability to distinguish between early and late stages of the disease.

Methods and instruments for the diagnosis of dementia.

Henderson (1989) has recently reviewed the diagnostic procedures currently used for the diagnosis of Alzheimer type dementia.

He points out that, in epidemiological work, screening is a two-phase procedure. The 'phase I' screening instrument is necessarily brief; at the same time it must tap a broad spectrum of cognitive functions. Furthermore, it should tap several levels on the continuum of global impairment, which is universally acknowledged to be a necessary, though not sufficient characteristic of the dementia syndrome. Screening instruments should also, under ideal conditions, tap deterioration from some previously higher levels of functioning. This latter property is particularly hard to achieve (Henderson & Huppert 1984; Henderson 1989). The 'phase I' screening instrument can be used to yield either a dichotomy of likely cases and likely non-cases, or a continuum of scores. The second phase is a clinical assessment, which usually includes taking of the history, a physical and mental state examination and sometimes special investigations. It is desirable that a proportion of persons who were negative in the screening phase should go on to have the second phase assessment. Without such representation of likely cases and non-cases, values for sensitivity and specificity of the screening instrument cannot be computed. It is important to recognize that no screening instrument can purport to provide a diagnosis of dementia. Indeed, all that can reasonably be expected is that it detects probable cognitive impairment. Dementia is only one of several conditions where cognitive impairment is present, others being e.g. amnesia, depression, delirium, institutionalization and sensory deprivation. To this

list, some would add normal ageing. Dementia is not a categorical state, such as e.g. pregnancy. But like anaemia, it is dimensional and it has diverse types and aetiologies, in the case of dementia all with the common core of global impairment of higher brain functions. A screening test should be assessed for that level of cognitive impairment where it is most discriminating. Some screening tests function well at differentiating moderate or severe impairment from normal cognitive performance. Unfortunately, most are seriously deficient in discriminating between normals and those who are only mildly impaired (Henderson 1989). We shall now discuss the methods to diagnose dementia (unspecified).

Screening for the presence of dementia.

PHASE 1 SCREENING INSTRUMENTS.

The mental status examination is a clinical interview technique for identifying the possible presence of a dementing process. Several mental status questionnaires have been published by different investigators who recognize the advantages of standardizing and quantifying mental status screening. The resulting instruments differ in length and in the number of items relevant to Alzheimer type dementia, and in some cases they include performance tasks in addition to verbal questioning. Most of the brief screening instruments tend to emphasize memory impairment over other manifestations of dementia. Most of the mental status questionnaires will not detect features of early dementia (Henderson 1989; Applegate et al 1990).

I will now discuss some of the 'phase I' screening instruments which are at present commonly used to detect cognitive impairment.

SPMSQ:

The Short Portable Mental Status Questionnaire (SPMSQ) (Pfeiffer 1975) consists of 10 questions assessing orientation, recent and remote memory, plus serial subtraction of 3's to evaluate attention and concentration. Each item is scored 'pass or fail' to yield a total error score ranging from 0-10. The SPMSQ is among the briefest of the standardized dementia screening instruments, and it is easy to incorporate into clinical settings because the content is consistent with the depth of questioning that is ordinarily included in a clinical 'history and mental status examination'.

MSQ:

The earlier Mental Status Questionnaire (MSQ) (Kahn et al 1960) is highly similar in content to the SPMSQ, and Fillenbaum (1980) concluded that the two instruments are equivalent in reliability and discriminant validity.

MIT:

The Memory and Information Test (MIT) (Kay 1977) consists of 13 items taken from the cognitive portion of the longer Blessed Dementia Rating Scale, and will be discussed more extensively later in this chapter (see Blessed Dementia Rating Scale).

The MIT, MSQ and SPMSQ are equally effective as brief screening instruments. The only real difference in content of the three schedules is the serial subtraction task in the SPMSQ.

Royal College of Physicians' Mental Test Score:

This questionnaire consists of 28 questions which test for short- and long-term memory, orientation, awareness of events, and ability to count backwards and forwards (Roth & Hopkins 1953). The advantage of this questionnaire is the inclusion of a fictitious name and address for recall by the patient after 5 minutes. This type of test has been described by Priest and Woolfson (1986), whose list details the administration procedure with one exception. Prior to presentation of the target material, the patient should be warned that it will be necessary to recall it after 5 minutes (Van der Cammen et al 1987). If this warning is omitted, the nature of the task is altered and it becomes more difficult.

Hodkinson's Abbreviated Mental Test Score:

Hodkinson (1972) developed an abbreviated version of the Royal College of Physicians' Mental Test Score. It has been found an effective screening instrument.

Mini-Mental State Examination (MMSE):

The instrument on which most experience has been obtained is the Mini-Mental State Examination (MMSE) (Folstein et al 1975). It evaluates several distinct cognitive functions that have been frequently reported to be affected in Alzheimer

type dementia. These include orientation, instantaneous and delayed recall, attention, language facility, constructional and volitional acts (praxis). Those are indeed among the primary manifestations of cognitive impairment that have been noted in neuropathologically confirmed Alzheimer type dementia. The representation of multiple facets of dementia in the MMSE is considered by many to be a major advantage over the MSQ and the MIT, which concentrate primarily on impairments in memory and orientation.

The MMSE consists of 10 questions for orientation to time, person, and place; 3 object names administered orally for immediate and delayed recall testing; serial subtraction of 7's (so-called serial 7's) as a measure of attention and concentration; 5 items of language fluency and understanding, and 1 figure copying exercise for constructional praxis. Correct responses are given differential weights to define a total score that ranges 0-30. Test-retest reliability of r=.89 or greater has been reported for both neurological and psychiatric samples (Folstein et al 1975). Folstein and McHugh (1979) have reported a high correlation between MMSE scores and Wechsler I.Q. test scores in evaluating individuals with varying degrees of dementia. Correlations with CT-scan indications of cortical atrophy have been reported by Tsai and Tsuang (1979).

Non-demented elderly individuals seldom score fewer than 24 out of the possible 30 points on the MMSE, whereas 87% of a sample of clinically demented patients scored below 23 points in a study reported by Anthony et al (1982). In a general medical ward at Johns Hopkins Hospital, Baltimore, they pitted the Mini-Mental State against a psychiatrist's standardized clinical diagnosis (based upon DSM-III criteria), and found a sensitivity of 87% and a specificity of 82% in the detection of dementia or delirium, or both, using a cutting point of 23/24. False positives were found particularly amongst blacks with limited education (Anthony et al 1982). This level of discrimination was repeated for the MMSE in a recent study in the UK (Roth et al 1986), in Norway (Nissen et al 1989) and in The Netherlands (Van der Cammen et al, submitted - see chapter III).

Thus, the Folstein instrument examines several cognitive impairments that are generally associated with Alzheimer type dementia; it has adequate reliability; and it appears to discriminate well between clinically demented and non-demented individuals. For these reasons, the MMSE was selected over other brief mental status inventories for use in community survey research sponsored by the

National Institute of Mental Health in the U.S.A. (Eaton et al 1981).
In a general population sample in Hobart, Tasmania, Kay et al (1985) examined the properties of the MMSE against a criterion diagnosis of DSM-III dementia. They found that the instrument performed very satisfactorily, taking no more than five minutes to administer, and being usable by a lay interviewer after brief training. Importantly, they found that a cutting point of 23/24 gave 100% sensitivity and 86% specificity for the diagnosis of moderate and severe cases of dementia, but these values changed to 59% and 93% respectively in the detection of mild dementia. These findings suggest that the MMSE is performing efficiently further up the continuum of cognitive impairment or dementia, with a high ability to discriminate between cases and non-cases. But lower down on the continuum, this discriminating power becomes much weaker; the MMSE will not detect mild cognitive disability (Kay et al 1985).

MMSE score and education.

A recent study by Fillenbaum et al (1988) assessing an elderly community sample (n = 1681, age 60+, randomly selected) demonstrated that the score on the Mini-Mental State Examination (MMSE) is related to demographic characteristics such as education, age and race (but not sex) and to functional status (performance of instrumental Activities of Daily Living), but not to selected aspects of physical or mental health. The authors recommend that if the MMSE is to be used to assess the prevalence of cognitive impairment among community resident elderly, adjustment for demographic characteristics, particularly education, should be considered, lest cognitive impairment be overestimated (Fillenbaum et al 1988).
Methodological adjustments for education which maintain the age effect have been proposed (Kittner et al 1986), the assumption being that education is not related to dementia, but that age may be. Berkman (1986) has pointed out that 'educational level and socioeconomic status are associated with virtually every cause of morbidity and mortality'. With reference to tasks more immediately similar to the MMSE, Fozard (1981) reports that while age may explain up to 25% of the variance in scores on some 93 psychological assessments, the addition of information on socioeconomic status nearly doubles the amount of variance in score which can be explained.
Berkman (1986) objects to the use of a correction for education or socioeconomic

status on the grounds that doing so prejudges consideration of the possibility of a common aetiology underlying education, socioeconomic status and aspects of poor health. However, where MMSE score is concerned, data published by Filley et al (1985) indicating that education is not protective for the course of Alzheimer type dementia, suggest that while further investigation into the relationship of education and socioeconomic status to MMSE score may be desirable, we will probably find that correction for such factors is justified.

The data obtained in the study by Fillenbaum et al (1988) both support and refute the position that the MMSE may be useful as a screen for dementia. They refute this position by indicating the minor importance of age in explaining MMSE score. The 2% of variance explained by age seems very little when compared to the accepted findings that the prevalence of 'severe' dementia is less than 1% at ages 65, and around 15% by age 85 (Gruenberg 1961; Nielson 1963; Terry & Katzman 1983). On the other hand, the data reported by Fillenbaum et al (1988) indicate that instrumental activities of daily living (ADL) is the most important of the variables examined in explaining MMSE score, and that it remains important even after demographic characteristics have been taken into account. Previous studies have shown that activities of daily living (as measured by the Blessed Dementia Rating Scale, which measures both ADL and instrumental ADL) correlated well with the severity of the neuropathological components of Alzheimer type dementia (Blessed et al 1968).

Fillenbaum et al (1988) conclude that MMSE score is most closely related to amount of education and to performance of instrumental ADL tasks. They hypothesize that these associations probably occur for different reasons:

- the relationship between education and MMSE score probably reflects the close similarity of many MMSE items to those tasks and the behaviour (obedience) stressed in schooling; it is possible that sufficient schooling may mask mild deterioration in cognitive functioning
- on the other hand, the relationship between MMSE and instrumental ADL performance may reflect a different process, i.e., that manifested by changes indicative of dementia or delirium. If that is indeed the case, and the work of Blessed et al (1968) suggests this to be so, a community relevant assesment of cognitive impairment indicative of dementia could be enhanced if the information from the MMSE was combined with standardized information on

instrumental ADL performance (Fillenbaum et al 1988).

The item characteristic curve analysis of the MMSE in relation to the severity of Alzheimer type dementia.

Ashford et al (1989), in their study of 86 patients (mean age 74 years; SD = 8; age range 53-91) who met DSM-III criteria for primary degenerative dementia - possible or probable Alzheimer type dementia-used an item characteristic curve analysis (ICC) to examine items from the MMSE in order to detect their relationship to the overall progression of the dementia. Their data indicate a systematic progression of the development of symptoms in Alzheimer type dementia related to the decline of memory function. Temporal orientation was lost before spatial and object orientation, and recollection of words was lost before ability to repeat them. The authors conclude that ICC of MMSE items can help to delineate the loss of mental functions during the course of Alzheimer type dementia. ADL scores and MMSE scores were highly correlated ($r = 0.76$, $n = 81$, $p = < 0.0001$), both for males and females. In addition, both ADL scores and MMSE scores were negatively correlated with age, possibly reflecting a greater tolerance for social and cognitive dysfunction in more elderly individuals; older patients thus seem to be brought to clinical attention for the first time at a more advanced stage of the dementing process.

The authors also demonstrate that the items of the MMSE with the highest severity at loss index (MMSE score above 20), indicating earliest loss, are recent memory items: the three detail memory items (ball, flag, and tree), recall of the date, and the serial 7 calculations beyond the first subtraction. The latter are difficult because they require a functional recent memory - the patient must recall what he or she is supposed to do next after being distracted by performing the first subtraction.

Items that became impaired in the middle category of severity level (MMSE greater than 10 and less than 20) were time and place orientation items that utilize longer term memory functions and involve many more cues for developing acquisition. The item requiring the perception and reproduction of intersecting pentagons was affected quite variably, perhaps because it involves many different cerebral systems.

The items lost late in the progression of Alzheimer type dementia (severity at loss

index of 10 or less on the MMSE) are those requiring use of the most solidly stored memories: early-learned verbal mimicking (the repetition of simple words), over-learned associations (the naming of simple objects), and frontal lobe procedural functions (the following of simple commands). Naming objects, writing, and reading are lost even later in Alzheimer type dementia progression than the repetition and command items (Ashford et al 1989). Expressive language deficits were considered late disease stage (Ashford et al 1989), as was also found by Kaszniak et al (1978), Folstein & Whitehouse (1983) and Heyman (1984). Ashford et al (1989) conclude that the pattern of loss of performance on MMSE items is consistent with the observed clinical course of Alzheimer type dementia.

A striking difference was found between the ability to repeat the names of three objects (ball, flag, tree) and to recall them later. Most of the patients in the study group, particularly those with mild and moderate impairment, clearly perceived these items and could repeat them easily (87%, 84%, and 86% correct, respectively). Yet only a few of the patients were able to recollect them after distraction (24%, 9%, and 16% correct, respectively). Ashford et al (1989) conclude that this clear example and the overall pattern of deficit development support the notion that the single underlying factor in Alzheimer type dementia is a disorder of memory. They state that the most recent, volatile memory storage is the first to be disrupted by Alzheimer type dementia, followed by longer term memories, with the pathological process affecting over-learned associations and highly practised motor skills late in the disease.

They suggest that the analysis of their study supports an alternative clinical impression, i.e., that aphasia, agnosia, and apraxia, which are frequently diagnosed in Alzheimer type dementia, are really difficulty in remembering words, what things are for, and how to do things, which leads them to the hypothesis that Alzheimer type dementia is quintessentially a disease of memory (Ashford et al 1989).

Main conclusions about the MMSE.

The MMSE has two weaknesses. First, the MMSE is not an adequate test to distinguish patients with very early or mild dementia from normal elderly persons. Problems in making this distinction include variation in educational and socioeconomic status (Cavanaugh 1983). There may be too much variability early

in the course of dementia to rely on any simple scale to reliably identify demented patients, and this task should be left to clinical judgement. Thus, there is a need to expand early patient evaluation with more difficult but still sharply discriminating test items that lack external bias, to assist the clinician in improving the early detection of dementia.

The second difficulty with the MMSE is that the score reaches zero at a stage in the disease after which a patient may continue to deteriorate for several years. Ashford et al (1989) conclude that at this phase, there is little left to evaluate in the way of cognitive functions, and the more relevant measures are ADL scales (Katz et al 1963; Lawton 1983; Linn & Linn 1983), which follow a parallel sequence of functional loss but are more sensitive to severe impairment (Ashford et al 1986).

THE DIAGNOSIS OF DEMENTIA (UNSPECIFIED): THE SECOND PHASE OF SCREENING.

The second phase of screening is a clinical assessment which usually includes taking of the history, a physical and mental state examination, and sometimes special investigations.

No questionnaire, psychometric test or rating scale is sufficient to make a diagnosis of dementia. The justification for this assertion lies in the diagnostic criteria to be fulfilled. At present, the most widely used diagnostic criteria are those from DSM-III-R (American Psychiatric Association 1987).

Tests and scales can be used to screen for cognitive impairment, to provide objective criteria for the diagnosis of dementia, to measure its severity, stage its clinical course, contribute to differential diagnosis, and measure change. Even though the diagnosis is at present one of exclusion, confirmation of the presence of dementia is a necessary first step, the documentation for which can best be provided by psychometric assessment.

I shall now discuss the second phase of screening.

Instruments in use for clinical diagnosis and validation of dementia (unspecified).

At present, three instruments are available for the clinical diagnosis and validation of dementia: The Comprehensive Assessment and Referral Evaluation (CARE), the

Geriatric Mental State Examination (GMS) and its algorithm AGECAT, and the CAMDEX. These instruments are still in different stages of development.

CARE interview:

The CARE interview has a wide coverage of psychopathology and impaired performance (Gurland et al 1977). The CARE interview was developed from the Geriatric Mental State (GMS) (Copeland et al 1976; Gurland et al 1976) and was used in the US/UK Cross-National (Diagnostic) Study of the elderly in the cities of New York and London by Gurland et al (Gurland et al 1983).

For the CARE interview, Gurland et al (1982) have proposed the following five features to make a diagnosis of 'Limited Cognitive Disturbance', which is the state less severe than 'pervasive dementia' and which can therefore be considered as synonymous with, or at least to include, mild dementia (Henderson & Huppert 1984). The respondent (1) reports a decline in memory; (2) has increased reliance on notes as reminders; (3) occasionally (less than once a week) forgets names of aquaintances, forgets appointments or misplaces objects; (4) occasionally (less than once a month) has destructive or dangerous memory lapses such as burning cooking or leaving on gas taps; and (5) has one or two errors on cognitive testing: forgets current or past President, exact date, phone number, post code, dates of marriage or moving to present location, or cannot remember interviewer's name even on third challenge. It is not specified how many of these features have to be present for a rating of Limited Cognitive Disturbance to be made. The Guide Notes for the CARE make it clear that such a person may still perform adequately in daily living, requiring little or no supervision. It is a weakness of the CARE interview that self-reports of a decline in memory contribute to the diagnosis of 'Limited Cognitive Disturbance', which may well lead to a diagnosis of mild dementia in patients who are depressed rather than demented (Kahn et al 1975; Henderson & Huppert 1984; O'Connor et al 1990).

As Henderson & Huppert (1984) have pointed out, the difficulty with the CARE interview is the inclusion of quite a number of objective items which may well vary between respondents and over time: some respondents will have moved to a new address more recently than others; interviewers do not all have a standard surname; and the social salience of Prime Ministers is greater near elections or at times of national crisis. Further work will therefore be necessary to develop criteria

and interviews free from such flaws (Henderson & Huppert 1984). The reliability reported for the CARE interview in community samples refers only to 'pervasive dementia' and not to limited cognitive disturbance (Gurland et al 1982; Henderson et al 1983).

GMS-AGECAT Package:

Evidence has begun to accumulate on the validity of the GMS-AGECAT Package against outcome (Copeland et al 1986), and neuropathological studies are underway. Its strength appears to reside in separating out depression ('pseudo-dementia'), not in discriminating among different aetiologies for primary degenerative dementias.

A recent study in persons aged over 65 (n = 1070, mean age 74 years) living in the Liverpool community (Copeland et al 1987a) found a level of 5.2 percent for organic disorder, probably mostly dementia, compared with 4.3 percent for London and 8.3 percent for New York. The prevalence figures for London and New York were derived from the application of a computerised diagnostic system (AGECAT = The Automated Geriatric Examination Computer Assisted Taxonomy, Copeland et al 1987b) to the CARE data (Comprehensive Assessment and Referral Evaluation, Gurland et al 1977-78) of the London and New York community study of the elderly (Copeland et al 1987b).

In the Liverpool study, Copeland et al (1987a) interviewed a sample of 1070 elderly persons aged over 65 living in the Liverpool community using the community version of the Geriatric Mental State (GMS); the findings were processed to provide a computerised diagnosis by AGECAT (Copeland et al 1986a, 1986b).

AGECAT (Copeland et al 1986a, 1986b, 1988; Dewey & Copeland 1986) consists of a computer program derived from a theoretical model which was subsequently tested against psychiatric diagnosis. It groups the items of the GMS and related interviews into 157 symptom components. These components are gathered under eight diagnostic 'clusters' and allocated to groups according to their importance for establishing the certainty of diagnosis for that diagnostic cluster. For example, in the organic cluster the groups concern 'mild memory disturbance'; 'moderate memory disturbance and time disorientation'; and 'place/person disorientation and organic thought disorder'. Each subject is awarded a level from 0-5 for most

diagnostic clusters according to the certainty of 'diagnosis' on that cluster. All levels on each cluster are then compared across clusters, one with another, according to a hierarchy of illness starting with organic and proceeding to schizophrenic, manic, depressive (psychosis and neurosis), obsessional, hypochondriacal, phobic and anxiety. The subject emerges with a main diagnosis and a subsidiary or alternative diagnosis if appropriate, the levels on all eight diagnostic clusters, the routes by which these levels are achieved, a symptom profile, a decision on whether or not the condition reaches the 'syndrome case' stage, organic and depressive scale scores and an Organic/Depression Index (Copeland et al 1986b, 1987a).

The 'diagnosis syndrome case' is reached when a psychiatrist recognises that a subject's symptoms have formed a recognisable diagnostic pattern. In practice, this usually implies the need for professional intervention. AGECAT diagnostic confidence levels of 03 or above were used to define 'syndrome case'.

In general, for the diagnosis of organic disorder, to achieve level 01 there must be a score of at least 2 on symptoms of mild memory disturbance, such as failing to remember the interviewer's name, miscalculating the length of time at the present address, the rater's opinion that the memory defect is a problem for the subject, etc, while for level 02 a higher proportion of such symptoms is required or others of moderate memory disturbance, such as inability to calculate age, failing to recall the interviewer's name on the second occasion or misidentifying objects. Case level 03 is reached when a substantial number of such symptoms is recorded often accompanied by time disorientation. Higher levels, 04 and 05 (the community version of the GMS did not provide for these levels at the time of the Liverpool study) require the presence of severe disorientation in place and person as well as organic thought disorder.

Prevalence for diagnostic syndrome cases of organic disorder, probably dementia (AGECAT diagnostic confidence level 03) reached 5.2% of the total sample, which is intermediate between levels reached in London and New York (Gurland et al 1983; Copeland et al 1987b). The combined proportions of subcases and cases of organic disorder, probably dementia, reached 10.1%.

These figures are remarkably similar to the findings of the original Newcastle studies of approximately 10% for both mild and severe organic brain syndromes and 4.9% for severe alone (see also chapter I.2; Kay et al 1964a, 1964b, 1968;

Bergmann et al 1971; Kay 1972; Kay & Bergmann 1980).
The rise in the prevalence of dementia with age was further confirmed.
However, the proportion aged over 80 with organic disorder, probably dementia, reached only 12.1%, rather below the often quoted figure of 20%. This may be due to the fact that the Liverpool study excluded those elderly resident in institutions.
So, the GMS-AGECAT Package (Copeland et al 1986b, 1987a) provides a method for standardising both the collection of data and the diagnostic process for comparative epidemiological studies and other research.
In a recent lecture, Copeland (1990a) reported that the GMS-AGECAT Package for use with older subjects in both institutional and community settings has now been tested in reliability studies in a number of centres in the UK and abroad, and that validity studies have been completed against psychiatrists' diagnosis and long-term outcome. Preliminary results from the UK and other centres using the measures show remarkable consistency in prevalence figures for dementia within populations with similar ethnic background. Multi-site studies now being mounted by the Medical Research Council in the UK, by Eurodem in the EEC, and by the Pan American Health Organization and the World Health Organization using these measures will, for the first time, allow extensive comparisons to be made between different geographical areas (Copeland 1990a, 1990b).

Discussion of the Liverpool study.
The Liverpool study by Copeland et al (1987a) was undertaken as part of a pilot longitudinal study aimed at examining the early detection of dementia in the community elderly. The sample therefore excluded those elderly resident in institutions. This may be the reason for the rather low prevalence of organic disorder, probably dementia, of 12.1% in those aged over 80, since this very age group is most likely to be institutionalized.
The point to note is that subcase levels 01 and 02 may well represent early stages of dementia, so follow-up over time using the GMS-AGECAT Package may lead to the identification of predictive features.

CAMDEX:
The CAMDEX (Roth et al 1986) is the most recent and comprehensive instrument

for the diagnosis of dementia and has been found useful for the differential diagnosis of Alzheimer type dementia, which, in the CAMDEX, is referred to as senile dementia of the Alzheimer type (SDAT). The CAMDEX attempts to standardize the gathering and recording of all information that would ordinarily be considered in the diagnostic evaluation of a patient suffering from dementia.
The CAMDEX consists of:

1) a structured interview with the patient to obtain information about current physical and mental state, personal and family history;
2) a cognitive test component that assesses each of the domains of cognitive functioning identified as criteria for diagnosis of dementia by DSM-III, including orientation, language, memory, praxis, attention, abstract thinking, perception, and calculation;
3) a structured interview with a relative or caregiver, including items pertaining to activities of daily living and manifest psychopathology.

The Hachinsky Ischemia Score (HIS) (Hachinsky et al 1975), the Blessed Dementia Rating Scale (BDRS) (Blessed et al 1968), and the Mini-Mental State Examination (MMSE) (Folstein et al 1975) are incorporated verbatim in the CAMDEX and can be scored separately (the HIS, the short version of the BDRS, and the MMSE are shown in the addendum of this thesis). The data form also contains sections for recording laboratory test results, skull X-ray, CT scan, current medications, and relevant results from physical and neurological examinations. The CAMDEX interview and cognitive test administration is said to require about 60 minutes for the patient's interview, plus 20 minutes for the informant's interview. Inter-rater reliabilities are reported as an amazing $r = 0.99$ for the patient interview, $r = 0.97$ for the cognitive examination, and $r = 0.90$ for the informant interview, based on a sample of 40 subjects with varying diagnoses. Sensitivity and specificity of the cognitive examination section of the CAMDEX has been investigated in a sample of 92 subjects, including 17 normals, 49 demented, 14 clouded (delirious), and 12 depressed. The composite cognitive score was 92% sensitive and 96% specific in discriminating organic brain disorder, dementia plus clouded (delirious) states from normal and depressed. These figures compare with sensitivity of 94% and specificity of 85% for the briefer Mini-Mental State Examination (MMSE) for this same discrimination in the same group of subjects. A primary aim of the CAMDEX is differential diagnosis. The cognitive

section alone discriminates well between dementia and non-dementia, but not between dementia and clouding of consciousness, i.e., delirium. Subscales for SDAT, MID, and depression were developed by identifying items from the CAMDEX that differed most in frequency of occurrence in different clinically defined diagnostic groups. Although the authors (Roth et al 1986) recognize some contamination due to common information being used for both the clinical diagnosis and the scale scores, the three subtests are reported to correlate substantially with clinical diagnoses. One would have liked to see the same type of sensitivity and specificity analysis reported for the SDAT and MID diagnostic discrimination which were reported for the dementia versus non-dementia discrimination. Nevertheless, the CAMDEX appears to be the most highly developed and comprehensive instrument for differential diagnosis of Alzheimer type dementia that is currently available (Overall 1989). The standardized use of the structured informant interview may appear valid for the early detection of dementia (O'Connor et al 1991).

RATING SCALES.

It is important to see the diagnosis of Alzheimer type dementia as quite separate from assessment of its severity or any attempt to grade cases according to the stage of deterioration reached. To this special aim, rating scales have been designed.

Measuring the severity of dementia.

Blessed Dementia Rating Scale (BDRS):

The Blessed Dementia Rating Scale (BDRS) (Blessed et al 1968) is one of the best known and most widely used research instruments for diagnosing the presence, and assessing the severity of dementia. It also has the most extensive validation against neuropathological confirmation of Alzheimer type dementia and its neurochemical markers, suggesting but not confirming that it may be somewhat specific to Alzheimer type dementia. The BDRS consists of 50 items, some of which are questions evaluating orientation and memory, others being ratings of performance on tasks that appear face valid with respect to requirements of everyday living. Administration requires about 30 minutes. Therefore, it is more involved than a simple screening instrument for general

survey or clinical applications, although it is often described as a standardized mental status examination for research use. The BDRS yields a single total score that measures severity of dementia, although it can be divided into cognitive and behavioral subtests that can then be scored separately. The cognitive items comprise the Memory and Information Test (MIT), and the behavioral items comprise the Dementia Rating Scale (DRS) (Kay 1977).
Blessed, Tomlinson, and Roth (1968) reported high correlation between BDRS scores obtained prior to death and the number of senile plaques found at autopsy. Perry et al (1978) reported a correlation between BDRS scores prior to death and brain choline acetyltransferase (ChAT) deficiency, which is the neurochemical marker for degeneration of cholinergic neurones. The specificity of the cognitive impairment assessed by the Blessed Dementia Rating Scale with regard to Alzheimer type dementia is, however, yet to be demonstrated for discrimination of Alzheimer type dementia from multi-infarct dementia (MID).

Alzheimer Disease Assessment Scale (ADAS):
The ADAS aims at assessing each of the primary cognitive and non-cognitive impairments that have been reported to be most frequently present in neuropathologically confirmed Alzheimer type dementia (Mohs et al 1983a; Rosen et al 1984). Based on reports from two previous studies in which brain biopsy confirmed the diagnosis (Sim & Sussman 1962; Coblentz et al 1973), the ADAS includes brief subtests for memory, disorientation, dysphasia, and dyspraxia in the cognitive domain and rating scales for depression, agitation, psychosis, and vegetative symptoms in the psychopathology domain. It is thus more comprehensive in representation of different primary deficits than are the mental status inventories, as well as most other scales that aim primarily at assessing severity of dementia. Administration of the ADAS usually takes about 45 minutes. Some test materials are required, but they can be constructed to ADAS specification by the user. The subtest scores can be combined to obtain a composite score that has been reported to have inter-rater and test-retest reliabilities exceeding 0.95 for assessment of overall severity of dementia (Mohs et al 1983b). Used in combination with a scale that is specific for multi-infarct dementia (MID), a high-probability diagnosis of Alzheimer type dementia can result (Mohs et al 1985).

Clinical stage of the disease.

Global Deterioration Scale (GDS):

Reisberg et al (1982) have developed a global deterioration scale for primary degenerative dementia, which requires a clinician to assemble all relevant information about the cognitive functioning of a patient and to relate it to descriptions provided for seven stages of 'cognitive decline' ranging from normal to late dementia. Each stage of cognitive decline is illustrated by several typical findings for that phase of the disease. The GDS has been included in the addendum of this thesis.

In the GDS, the clinical characteristics and 'psychometric concomitants' of very mild and mild cognitive decline have been set out. In 'very mild cognitive decline' (stage 2) there are subjective complaints of memory deficit, together with below-average performance for age on the Wechsler Adult Intelligence Scale (Wechsler 1958), but there is no objective evidence of memory deficit. In 'mild cognitive decline' (stage 3) objective evidence of memory deficit is required, characterized by more than one of the following: becoming lost in an unfamiliar situation; co-workers being aware of impaired performance; intimates notice difficulty in word and name finding; poor recall of material recently read; inability to remember names on being introduced; losing or misplacing possessions; and defective concentration in clinical tests. Stage 3 is considered to be the mildest level of impairment that is consistent with the probable development of Alzheimer type dementia, given that depression and alternative organic aetiologies have been ruled out. The impairments which are used in the GDS to illustrate the different stages of deterioration are clearly relevant for everyday living, although memory functioning is the primary focus.

The criteria used in the GDS can be criticized for placing too much weight on memory, which is only one aspect of cognitive function. Indeed, a reasonable hypothesis is that memory difficulty is common in both normal and mildly demented elderly persons, but that it is only the latter who have additional deficits in language, reasoning and spatial ability (Henderson & Huppert 1984). Another problem is that some patients may exhibit symptoms of more than one stage, so, in these cases, the use of figures, i.e., 'Reisberg 4', creates an illusory exactitude. On the other hand, there is now widespread familiarity with the Reisberg stage-of-illness categories which has resulted in their frequent use to describe the level

of cognitive impairment of patients in both research and clinical practice. It is not uncommon to hear a patient being described as functioning at 'Reisberg 4' or 'Reisberg 5'. Another advantage of the GDS is that it has already been used in describing the range of mild to moderate cognitive dysfunction required for entry of patients into treatment intervention studies.

Clinical Dementia Rating Scale (CDRS):

Hughes et al (1982) have proposed characteristics of 'questionable' and of mild dementia in the course of their prospective study of the latter. These features are: mild to moderate impairment in the spheres of memory, orientation, problem-solving, community engagement, performance at home and in recreation and personal care. A guide to the rating of these has been set out. These authors emphasize that validation of both the instrument and its component ratings can come only from a longitudinal study. Their criteria have the merit of carrying high face validity and of being based on a wide sample of cognitive performance in daily life. The CDRS differentiates between the different areas of cognitive functioning, but there are a number of problems with the scale: some of its wording is rather vague, and it is difficult to use. However, the scale deserves further attention from clinicians and researchers.

Discussion.

From the above, it is clear that several sets of criteria for the diagnosis of mild dementia are already in use. There is no certainty that these are leading to the identification of a homogeneous group of equivalent severity. It may not be sufficiently appreciated that the proposed diagnostic features of mild dementia have little empirical basis. They can be regarded only as working hypotheses.

OTHER ASPECTS OF SCREENING FOR DEMENTIA (UNSPECIFIED).

Assessment of premorbid level of cognitive function.

In screening, the central issue is to demonstrate deterioration from a previously higher level of performance. Therefore, estimates of previous levels of cognitive functioning should be included. The information on decline has to be based on a retrospective comparison. To date, only global measures are available, such as the Wechsler Deterioration Index (Wechsler 1958), the New Adult Reading Test

(NART) developed by Nelson and O'Connell (1978) and the vocabulary sub-test of the WAIS (Wechsler 1944) the latter two of which we will discuss now.

NART:

This test relies on the fact that, in adults, reading ability is highly correlated with intellectual level. Subjects are asked to read aloud a list of words whose pronounciation can be correct only if the reader is familiar with them. Persons with dementia have been shown to be able to pronounce those words with which they were once familiar, though they may not now be able to give their meaning. In this way it becomes possible to distinguish between those with mild dementia and higher levels of previous functioning and those with no dementia but limited premorbid levels of intelligence or education.

The vocabulary sub-test of the WAIS:

This sub-test belongs to the 'Hold' category of tests (i.e., tests which do not show a decline with ageing) and is often said to be a quick estimate of premorbid ability. This is generally true if cognitive status is not seriously impaired but may not be applicable to cases of dementia where more serious forms of cognitive impairment are expected.

Alternative approaches.

Informant interview.

The relevance of informant data as part of the assessment of an elderly person with cognitive impairment has been pointed out by various authors (Henderson & Huppert 1984; Van der Cammen et al 1987; Homer et al 1988; Henderson 1989). In this respect, Jorm and Korten (1988) have developed a brief questionnaire which is administered verbally to a close relative or other appropriate informant, rather than persisting in the search for an efficient psychometric instrument to be administered to the elderly respondent. The individual items of the questionnaire provide systematic coverage of several areas of cognitive performance. They require the respondent to compare the elderly person's current state with performance in the past. In a mixed sample of community and nursing home residents, the resulting score correlated 0.74 with the elderly persons' Mini-Mental State. It has yet to be determined how efficient this screening instrument is in detecting mild levels of impairment (Jorm & Korten 1988).

O'Connor et al (1991) have shown that the information gathered in the CAMDEX

informant history is in close accord with cognitive test scores and with observations made by psychiatrists. They believe that the accuracy of diagnoses made in community surveys of dementia would be greatly enhanced by asking family members, rather than the elderly people themselves, about changes in memory and other aspects of cognitive function (O'Connor et al 1990, 1991).

Automated testing.

There is a need for vigorous effort to develop a brief screening instrument that will efficiently detect mild dementia and exclude false positives. As mentioned earlier, the latter are commonly persons with limited intelligence or education. At present, as we have already seen, there is no efficient screening instrument for the detection of early or mild dementia in general populations. Test instruments on which the patient easily achieves near-perfect scores risk being insensitive to any future change.

In this respect, the usefulness of automated testing as a means of detecting cases of early dementia in the elderly has been considered.

Several studies (Watts et al 1982; Simpson & Linney 1985) have shown that automated testing is acceptable to the elderly. They found that refusal rate was lower and subjects reported finding the video displays more interesting than the conventional paper-and-pencil methods.

Jorm (1986) has reviewed controlled and automatic information processing in the assessment of senile dementia. The former requires intellectual effort and is likely to decline early in Alzheimer type dementia. Considerable advances have recently been made by some groups in the development of automated tests, using portable visual display units.

However, automated tests may prove unsuitable for general population screening, particularly in the very elderly, in whom motor and visual impairment is common.

Studies undertaken so far with the aim to diagnose mild dementia.

With regard to the diagnosis of early and mild dementia, both the instruments for clinical diagnosis and validation of dementia and the dementia rating scales attempt to specify and further identify features of these stages of the disease. Some prospective studies of mild dementia have been carried out:

A study with a combination of CARE interview and GMS:

Henderson et al (1983) have combined parts of the CARE interview and the GMS

interview in an attempt to produce an interview for community surveys or general practice research, where case finding of mild dementia is most likely to be pursued. In a reliability study on 47 geriatric day-patients in Canberra, they obtained a phi coefficient of 0.90 for two psychiatrists rating the cognitive items of the same interview, which was audiotaped; and 0.60 for cognitive items between two interviews averaging 12 days apart. Patients with mild to moderate cognitive impairment comprised over two-thirds of this sample.

Measuring specific deficits: the use of psychometric tests.

Psychometric tests have been documented exhaustively in a comprehensive publication by Israel et al (1984). Israel et al (1986) have now gone on to provide a selective review of the literature on the clinical assessment and psychometric measurement of dementia.

In contrast to clinical tests which are essentially qualitative, psychometric tests can yield information about quantitative aspects of task performance, including the subject's level of ability and speed of responding. Psychometry is important in three areas: a) in quantifying and establishing a baseline for intellectual, memory and other cognitive functions; b) in testing and measuring areas of specific dysfunction in the patient's behaviour so as to assist in a differential diagnosis; c) in helping plan management.

Many psychometric tests are sensitive to cognitive change and can therefore provide evidence for a decline in performance more readily than a clinical interview. However, psychometric tests can only be interpreted in conjunction with all other clinical information. There is no one psychometric test valid for all cases showing brain damage, and misleading information may be obtained in patients whose dysfunction is less than clear-cut.

The problem facing investigators in this area is that there is no agreed rationale to guide them in the choice either of cognitive functions or of the tests which assess these. Henderson and Huppert, in their article 'The problem of mild dementia' (Henderson & Huppert 1984), offer two guiding principles. First, an assessment should be made of those functions which are likely to be impaired early in the dementia process and also of those which may contribute to a differential diagnosis and therefore to prognosis. Secondly, the psychometric properties of the test instrument should be satisfactory in terms of sensitivity to change,

reliability, validity and, of particular importance in this age group, acceptability. Many cognitive test are threatening or demeaning to the elderly (Comfort 1978) or have little relevance to daily living (Henderson & Huppert 1984).
Beyond these general principles the initial choice of psychometric tests must be largely arbitrary.

Studies of suitability of tests for the diagnosis of mild dementia.
Some studies have been carried out with the specific aim to 'test a test' for its capacity to identify patients with early or mild dementia. In this respect, most experience has been gained with a few tests:
NART:
We have already discussed the use of the New Adult Reading Test (NART) (Nelson & O'Connel 1978) to distinguish between those with mild dementia and higher levels of previous functioning and those with no dementia but limited premorbid levels of intelligence or education (see p 108).
The Colour-Word Test (Stroop 1935):
The Colour-Word Test (Stroop 1935) consists of a list of words printed in different colours. The task is to name the colour of each word. The words are the colour names such as red, green and blue, but they are printed in ink of a conflicting colour. The task can be performed successfully only if the subject pays attention to the colour of the word and avoids being distracted by its meaning. Persons with mild dementia find this difficult.
Semantic categories:
Weingartner et al (1981a, 1981b) have developed word lists where the words are either in semantic categories (e.g. animals or plants) or they are unrelated. Patients with even mild dementia have difficulty in using their knowledge structures, so that, unlike depressed patients, their performance in recalling the words does not benefit from the use of related lists.
Selective Reminding Test (SRT) (Buschke 1973):
The SRT (Buschke 1973) has been used most in clinical research in SDAT. This is a verbal memory task that involves presentation of a list of 12 words to elicit immediate and delayed recall. It provides a total score for prompted and for unprompted recall, plus several derived scores that aim at identifying whether the primary problem exists in encoding, storage or retrieval from primary or

secondary memory.

Category Retrieval:

Category Retrieval (Battig & Montague 1969) requires flexibility in scanning cognition for random members of a specified class or category of objects, geographic regions, or events. For example, list as many girls' names that begin with the letter W as you can think of in a brief period of time. This task, which provides no structure nor association for retrieval, has been shown to be sensitive to early Alzheimer type dementia (Overall 1989).

Tests relevant to everyday life.

It is relevant to note that some investigators question the everyday practical implications of small changes in the ability to recognize or recall words from a repeatedly presented word list.

Face validity of memory tests with regard to requirements of daily living has been stressed, especially by Crook, Ferris and their collaborators. Facial recognition and name-face association using photographs (Ferris et al 1980), the telephone number task (Crook et al 1980), shopping list (McCarthy et al 1981), and misplaced objects task (Crook et al 1979) are examples of memory tests that have obvious reference to the real world.

The Rivermead Behavioural Memory Test (RBMT) has been developed specifically to provide an objective measure of everyday memory (Wilson et al 1985). The test contains items such as remembering names, recognizing faces, following a route and recalling a short passage of prose. It also measures prospective memory - remembering to do something at a particular time or place - which is an important aspect of successful everyday living. Cockburn and Collin (1988) investigated 40 community dwelling elderly people, 20 living independently in or near Oxford (age range 70-90 years, mean age 78.8), and 20 Geriatric Day Hospital attenders who were partially dependent (age range 69-89 years, mean age 80.6). All subjects completed the RBMT and the MMSE. The RBMT as a whole correlated well with the MMSE. In addition, it was found to provide a more sensitive measure of memory function when general cognitive decline was minimal (Cockburn & Collin 1988). A validation study of the Dutch translation of the RBMT has been carried out in 40 stroke patients who were attending a rehabilitation centre (mean age 62.2 years, s.d. 2.2) several months after their stroke (mean time interval between

the stroke and the application of the RBMT was 3.6 months, s.d. 2.8) (Feen van der et al 1990). Observations of everyday memory problems reported by the patient, the partner and the rehabilitation staff were used as validity criterion. Significant correlations were found between the scores on the RBMT and the observation results. Moreover, it was found that the RBMT provided information which cannot be acquired with other psychometric tests. The RBMT was found a useful tool for assessing memory problems in everyday life (Feen van der et al 1990).

With regard to everyday functioning, instrumental ADL score has been found to correlate with MMSE score in the study by Fillenbaum et al (1988) (see earlier in this chapter).

It is too early to tell how important these types of instruments will become in specific relation to the early diagnosis of Alzheimer type dementia, but it is clear that they should be included in future studies of Alzheimer type dementia, especially since the relevance of laboratory memory tests for the actual adjustment and functioning of elderly patients is likely to be increasingly questioned as drug companies seek to establish claims for new 'memory enhancing drugs'.

The most recent study: testing the tests: CAPE versus other tests.

In a recent study by Black et al (1990) the performance of the Clifton Assessment Procedures for the elderly (CAPE) (Pattie & Gilleard 1976) was examined in an elderly general practice sample with a higher than usual risk of dementia (based on advanced age of the participants, i.e., 75 years and over). The study diagnosis was based on a combination of the diagnosis made by the computer program AGECAT and a clinical diagnosis made by the interviewing psychiatrist. Forty-five per cent of patients with definite or probable dementia, as defined, and 100% of those with possible dementia had scores above the cut-off-point on the CAPE. The sensitivity of the CAPE was low compared with that of other rating scales. The authors conclude that the low reported rate with the CAPE is probably due to only the more severe cases being identified, and that for comparative purposes it is important to know the level of dementia that the instruments used are detecting (Black et al 1990).

In his commentary on this study, Copeland (1990b) concludes that it would be

neither sensible nor desirable for any one interview system to gain a monopoly and thus to exclude others, as this would hinder the scientific development of new techniques. However, the greater the variety of instruments used the more difficult it will be to make sensible comparisons between studies. Before new interviews are introduced, it should be incumbent on the originators to show that they have substantial advantages over existing methods and have been thoroughly tested in the range of applications for which they have been designed (Copeland 1990b).

Studies of prognosis.

As far as prognosis is concerned, some tests for cognitive impairment have been shown to be of particular interest. McDonald (1969) claimed that tests of spatial function, attributed to the parietal lobes, discriminate between a relatively benign cognitive impairment and true senile dementia. The group who performed poorly on his tests were significantly younger and had a much higher mortality rate over 6 months.

This was also found by Naguib and Levy (1982) and Berg et al (1984), who demonstrated that patients with aphasia, apraxia and agnosia had a higher mortality rate than patients without these signs.

Kaszniak et al (1978) found that in patients with senile dementia of the Alzheimer type, 'functional brain impairment' (e.g. aphasia, EEG abnormalities) was a better predictor of mortality than the degree of cerebral atrophy on the CT-scan.

In the recent study by Ashford et al (1989) it was found that the systematic progression of the development of symptoms in Alzheimer type dementia related to the decline of memory function. Temporal orientation was lost before spatial and object orientation, and recollection of words was lost before ability to repeat them.

Expressive language deficits were considered late disease stage (Ashford et al 1989), as was also found by Kaszniak et al (1978), Folstein & Whitehouse (1983) and Heyman (1984).

Discussion.

It is clear that there are now sufficient methods and instruments available for the diagnosis of dementia and for the assessment of its severity. Their ability to detect early diagnostic features remains a field open to further research.

Early diagnosis of dementia is hindered by the variety of symptoms with which the condition may present and by the lack of valid tests to identify early stages. Early dementia is still a vague, not well defined entity which may resemble cognitive changes occurring during normal ageing and which can only be ascertained by future decline found during intra-individual follow-up over time. In addition, there is the problem of distinguishing early dementia from depression.
The item characteristic curve analysis of the MMSE in relation to the severity of Alzheimer type dementia by Ashford et al (1989) produced the striking data that both ADL scores and MMSE scores were negatively correlated with age, possibly reflecting a greater tolerance for social and cognitive dysfunction in more elderly individuals; older patients thus seem to be brought to clinical attention for the first time at a more advanced stage of their dementing process. This has important implications for intervention and management approaches, and for the development of models of care (see also chapter IV).
In the assessment of an elderly patient with cognitive impairment, informant data should be obtained whenever possible.
Tests relevant to everyday life, such as the telephone number task, shopping list, misplaced objects task, the Rivermead Behavioural Memory Test and instrumental ADL score, should be included in future studies of early dementia as they may well be sensitive to the earliest changes in memory function, and thus be a better predictor of memory impairment than laboratory memory tests.
Rather than continuing the search for the identifying test for early and mild dementia, it seems wise that researchers worldwide should now make use of the existing diagnostic criteria in combination with well-tested screening instruments and rating scales in an attempt to achieve consistency in prevalences of early and mild dementia across nations.

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CHAPTER II: AIM OF THE STUDY.

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My interest in memory impairment in old age and in Alzheimer type dementia dates from the moment I started my training in geriatric medicine at University College Hospital London in 1982. While working on the wards of the Department of Geriatric Medicine, I became aware of the impact of dementia on the lives of patients and their relatives. At the same time, I heard histories of memory problems reported by patients and their relatives during outpatient clinic assessments. The question arose whether the memory problems reported in the geriatric outpatient clinic represented the earliest stages of dementia, especially of the Alzheimer type.
On the wards, I had discovered that some patients who were severely demented had not yet been diagnosed as such, either because their relatives had not discussed the problem with the general practitioner, or because they were living alone so their dementia was not detected until some disastrous event precipitated admission to hospital. In addition, there were the patients for whose relatives the burden of care had become so high that once they required hospital admission, their relatives decided that they could no longer care for them at home. In such cases, no offer of help and support could change the relatives' mind.
I became interested in the differential diagnosis of memory impairment in old age and in the early stages of Alzheimer type dementia in particular. At the same time, there was a worldwide interest in Alzheimer type dementia, so, together with several members of staff at the Geriatric Research Unit, University College London, it was decided to try and contribute to the knowledge of the early stages of the disorder. This led to the opening of a Memory Clinic at the Geriatric Research Unit, University College London, in 1983.

This thesis has been written with the aim to identify the problems surrounding the early diagnosis of dementia, especially of the Alzheimer type, and to recommend diagnostic approaches and management aspects, with particular reference to the role which a Memory Clinic can play within this context.

The early diagnosis of Alzheimer type dementia.

Alzheimer type dementia is an age-related disorder which affects thousands of elderly people each year. In the western world, the increasing number of elderly people has led to an increasing number of patients with Alzheimer type dementia, in need of care.

Although the last decade has seen an explosion of research into the disorder, its aetiology and the nature of its progression are still unclear. Alzheimer type dementia is a clinical diagnosis; the clinician attributes dementia to Alzheimer type dementia following an assessment of probabilities and the exclusion of other causes of dementia.

Early diagnosis of Alzheimer type dementia is hindered by the variety of symptoms with which the condition may present and by the lack of valid tests to identify early stages. At present, one has to await the scala of symptoms required in order to diagnose dementia as defined within one of the definitions currently available. By the time definitions and criteria are fulfilled, the patient's dementia may be anything but early and a clear decline from previous intellectual functioning may have taken place.

Memory impairment is generally acknowledged to be an early feature of Alzheimer type dementia and has gained predominance over other diagnostic criteria within the current definitions and classifications. However, the list of differential diagnoses of memory impairment is extensive and covers medical, neurological and psychiatric disorders. To this list, some would add normal ageing.

Hence, the early diagnosis of Alzheimer type dementia is hindered by many difficulties:

- the lack of knowledge about its very earliest stages
- the lack of valid tests to identify early stages
- the extensive differential diagnosis applicable to memory impairment in old age

A second problem hindering the early detection of Alzheimer type dementia is the fact that the health care system in the western world is demand-based, i.e., the patient has to initiate the consultation with his general practitioner. Such a system is severely handicapped in terms of the early detection of disease, and this applies especially to the detection of psychiatric disorders and memory problems in old age. Most elderly people do not contact their general practitioner about their intellectual decline, and their relatives commonly present only when the burden of care becomes too high. Moreover, not all elderly people have a relative or key helper available to them, so that their dementia may not be detected until the mental deterioration has reached an advanced stage. Especially the very old may be at risk of late detection, since society at large seems to accept a degree

of social and cognitive dysfunction in more elderly individuals.
Hence, the early detection of Alzheimer type dementia is hindered by various problems:

- the lack of self-reporting of memory impairment to the general practitioner, especially in the very old
- the fact that relatives tend to contact the general practitioner only when the patient's dementia becomes a problem to them
- the fact that not all elderly people have relatives or a key helper available to them, so that their general practitioner may not be aware of their dementia until some disastrous event occurs
- the extensive list of differential diagnoses with which the general practitioner is confronted once the patient's memory impairment is reported to him.

As a result of my interest in memory impairment in old age and in the management of patients suffering from dementia, the following questions arose:

1) Does memory impairment in old age represent early dementia, especially of the Alzheimer type?
2) Are there causes of memory impairment in old age which are potentially curable?
3) Is there a risk of missing early cases of Alzheimer type dementia by attaching too much value to the criterion of memory impairment, and if so, are there options for improving early diagnosis?
4) What is the value of the early detection of Alzheimer type dementia, a disorder for which no treatment exists?
5) Is it possible to offer guidelines to general practitioners in order to enhance their awareness of possiblities of early diagnosis within the primary care setting?
6) Can a Memory Clinic play a role in reducing the under-reporting of memory impairment to the medical profession, and in improving the management of early cases of dementia?
7) Can a Memory Clinic contribute to the search for the identifying test for early cases of Alzheimer type dementia?

To find the answers to these questions, I reviewed the literature and studied the

effect of the opening of a Memory Clinic.
This thesis is based on the results of my investigations and discusses diagnostic approaches and management aspects of memory impairment in old age and of early dementia, especially of the Alzheimer type.

CHAPTER III: THE VALUE OF THE MINI-MENTAL STATE EXAMINATION IN A GERIATRIC OUTPATIENT POPULATION IN THE NETHERLANDS*.

Van der Cammen TJM, Harskamp van F, Stronks DL, Passchier J, Schudel WJ.

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* Submitted for publication.

CHAPTER III: THE VALUE OF THE MINI-MENTAL STATE EXAMINATION IN A GERIATRIC OUTPATIENT POPULATION IN THE NETHERLANDS.*

Summary.

The dutch version of the Mini-Mental State Examination (MMSE) was administered to 138 elderly patients, who were referred to a geriatric outpatient clinic for a variety of reasons. It was found a valid screening instrument for the detection of cognitive impairment in this patient population. An optimal cutting point of 23/24 out of a total score of 30 was found. Using this cutting point, the sensitivity and specificity reached approximately equal values (79 and 84% respectively). These data indicate that the MMSE score is representative for the cognitive status of elderly patients referred to a geriatric outpatient clinic.

The discriminative validity of the MMSE was not influenced by level of education. However, we found a significantly higher percentage of patients with a psychiatric disorder other than dementia among the false positives in comparison to the sample as a whole. Therefore, the MMSE should not be used as a sole criterion for diagnosing dementia.

We also found that suffering from dementia or amnestic syndrome is associated with the presence of complaining informants.

Introduction.

The Mini-Mental State Examination (MMSE) has been widely advocated as a screening instrument for cognitive impairment in the elderly. In their original article, Folstein et al (1975) reported a test-retest reliability of $r = .89$ or greater for both normal and psychiatric samples. Folstein and McHugh (1979) have reported a high correlation between MMSE scores and Wechsler I.Q. test scores in evaluating individuals with varying degrees of dementia. Correlations with CT-scan indications of cortical atrophy have been reported by Tsai and Tsuang (1979). In a general medical ward at Johns Hopkins Hospital, Baltimore, Anthony et al (1982) pitted the MMSE against a psychiatrist's standardized clinical diagnosis - based upon DSM-III criteria (American Psychiatric Association 1980) - and found a sensitivity of 87% and a specificity of 82% in the detection of dementia or delirium,

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* Submitted for publication.

or both, using a cutting point of 23/24 out of a total score of 30. False positives were found particularly amongst blacks with limited education (Anthony et al 1982). Nissen et al (1989) used a cutting point of 24/25 when they administered the MMSE to a sample of neurological patients with various disorders; they found the test useful for detecting cognitive impairment, but not for differentiating between different causes of cognitive impairment. In a sample of elderly patients who were referred to a general medical outpatient clinic (n=183, age range 70-95 years), Miller et al (1990) found the MMSE useful to detect those with cognitive impairment using a cutting point of 23/24.

A very large body of data is also available on the performance of this screening instrument in general population samples in the United States, Europe and Australia*, where it was found a useful although rough method to detect cognitive impairment. In a general population sample in Hobart, Tasmania, Kay et al (1985) examined the properties of the MMSE against a criterion diagnosis of DSM-III dementia. They found that a cutting point of 23/24 gave 100% sensitivity and 86% specificity for the diagnosis of moderate and severe cases of dementia, but these values changed to 59% and 93% respectively in the detection of mild dementia. These findings suggest that the MMSE is performing efficiently further up the continuum of cognitive impairment or dementia, with a high ability to discriminate between cases and non-cases, but lower down on the continuum this discriminating power becomes much weaker; the MMSE will not detect mild cognitive disability (Kay et al 1985).

These studies demonstrate a remarkable consistency, i.e., a cutting point of 23/24 distinguishes well between those with cognitive impairment and those without, both in the general population and in patient samples. It is generally accepted that memory impairment is one of the hallmarks of dementia. Therefore, we were particularly interested whether memory complaints were present, and if so, whether they correlated with the patient's MMSE score.

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* Kramer et al 1985; Weissman et al 1985; Kay et al 1985; Roth et al 1986; Fillenbaum et al 1988; Brayne & Calloway 1989.

III The value of the Mini-Mental State Examination in a geriatric outpatient population in The Netherlands.

Aim of the study.

Until now there have been no reports on the validity of the MMSE as a screening instrument for cognitive impairment in elderly patients referred to geriatric outpatient clinics. Therefore, we analysed the value of the MMSE for the detection of cognitive impairment in such a patient population. Our first aim was to establish the optimal cutting point for distinguishing between those with cognitive impairment and those without, and to determine the sensitivity, specificity and misclassification ratios for this cutting point. The second aim of our study was to investigate whether a relationship could be found between the MMSE score and the presence of memory complaints, as formulated by the patient and/or the informant(s) accompanying the patient to the outpatient clinic.

Materials and methods.

One hundred and thirty-eight patients who were referred to the geriatric outpatient clinic at the University Hospital Rotterdam Dijkzigt for a variety of reasons, were enrolled as participants in our study. They were initially seen by a geriatrician with an interest in memory function in old age. The assessment consisted of a medical history obtained from the patient and from an informant (usually a close relative), a full medical examination including a neurological examination, and the dutch version of the MMSE (Rooymans 1984). Level of schooling and previous professional status were recorded, according to a standardized classification by the Dutch Ministry of Social Affairs (Directoraat-Generaal voor de Arbeidsvoorziening 1985). Laboratory investigations included ESR, full blood count, serum glucose, urea and electrolytes, creatinine, rapid plasma reagin test and treponema pallidum haemagglutination assay (TPHA) test, liver function and thyroid function tests, serum vitamin B12 and folate concentrations. All patients had a chest X-ray and electrocardiogram (ECG) done. For patients in whom suspicion of either a neurological or psychiatric disorder arose, the opinion of a neurologist or psychiatrist was sought, regardless of the patient's score on the MMSE. Extensive neuropsychological testing and/or CT-scanning of the brain was carried out when indicated and after consultation with the neurologist. A consensus diagnosis of dementia or amnestic syndrome was reached based on this assessment using DSM-III-R criteria (American Psychiatric Association 1987).

In addition to the assessment described above, the geriatrician asked the patients whether they had any memory complaints. The informants were asked whether they had observed memory problems or behavioural evidence of memory dysfunction in the patient. Special attention was paid to depressive symptomatology and indications of social withdrawal which are sometimes associated with an early dementia.

Results.

Table III.1 shows the characteristics of the study sample.

The sample had a mean age of 78.2 years with an age range of 57 to 92 years. Two patients were below 60 years of age (2 Females, 57 and 58 years old, each with an MMSE score of 16 points and with a diagnosis of Alzheimer type dementia). The sample was predominantly female with a male to female ratio of 29.7 to 70.3 %, which is compatible with the demographic characteristics of the elderly in the Netherlands.

We defined seven diagnostic categories (see Table III.2).

Patients with a dementia were divided into three groups: Alzheimer type dementia (ATD), multi-infarct dementia (MID) or a combination of ATD and MID. Fourteen patients had a diagnosis of amnestic syndrome for which no underlying cause other than a possible early Alzheimer type dementia could be detected. A further category of patients had either a physical disorder, or a psychiatric disorder other than dementia or amnestic syndrome, or a neurological disorder. The low number of MID patients may well be due to 'referral filter', i.e., these patients are usually referred to the department of Neurology in our hospital.

There were no patients with a diagnosis of delirium in our sample; delirium in an elderly patient is a medical emergency and is more likely to be found in acutely ill hospital inpatients rather than among patients referred to a geriatric outpatient clinic.

In order to calculate the sensitivity, specificity, and misclassification ratios, using each score as a cutoff-score, we divided the subjects into two groups to serve as the validity-criterion, i.e., those with dementia or amnestic syndrome (diagnostic categories 1-4; n=89) and those without (diagnostic categories 5-7; n=49) (see Table III.2).

Table III.1 Frequencies and percentages of the characteristics of the sample

Characteristics	Frequency	Percentage
Sex		
Male	41	29.7
Female	97	70.3
Age		
50–59	2	1.4
60–69	13	9.4
70–79	61	44.2
80–89	57	41.3
90–99	5	3.6
Schooling		
unknown	7	5.1
< 6 classes pr school	2	1.4
6 classes pr school	81	58.7
> 6 classes pr school	11	8.0
technical school	4	2.9
secondary school	15	10.9
grammar school	16	11.6
University	2	1.4
Profession		
unknown	7	5.1
very simple	11	8.0
simple	7	5.1
somewhat complicated	30	21.7
rather complicated	5	3.6
complicated	9	6.5
very complicated	15	10.9
academic	2	1.4
housewife/unemployed	52	37.7

Table III.2: Distribution of subjects across diagnostic categories

Category	Diagnosis	Frequency	Percentage
1	Senile Alzheimer type (SDAT)	61	44.2
2	Possible SDAT/amnesia syndrome	14	10.1
3	Multi-infarct dementia (MID)	3	2.2
4	Combination of SDAT and MID	11	7.9
5	Physical disorder	21	15.2
6	Psychiatric disturbance other than dementia	16	11.5
7	Purely neurological disorder	12	8.7

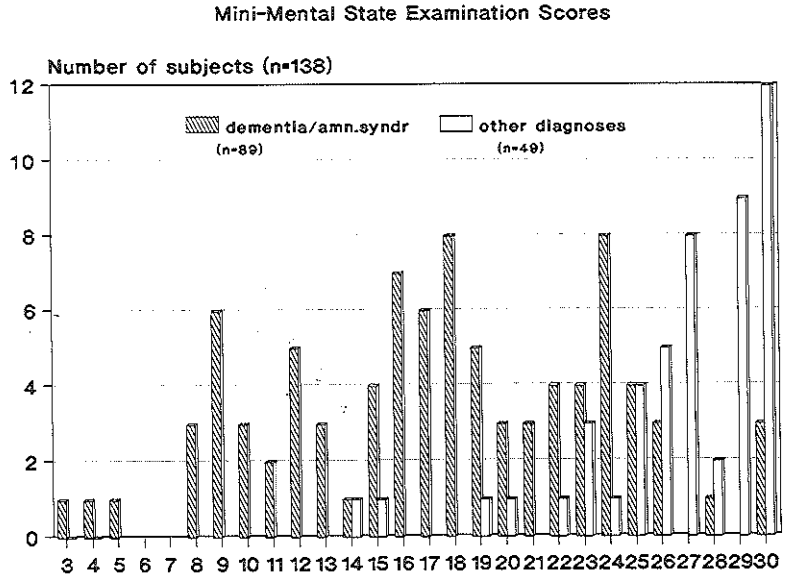

Fig III.1: Distribution of MMSE-scores in 138 geriatric outpatients

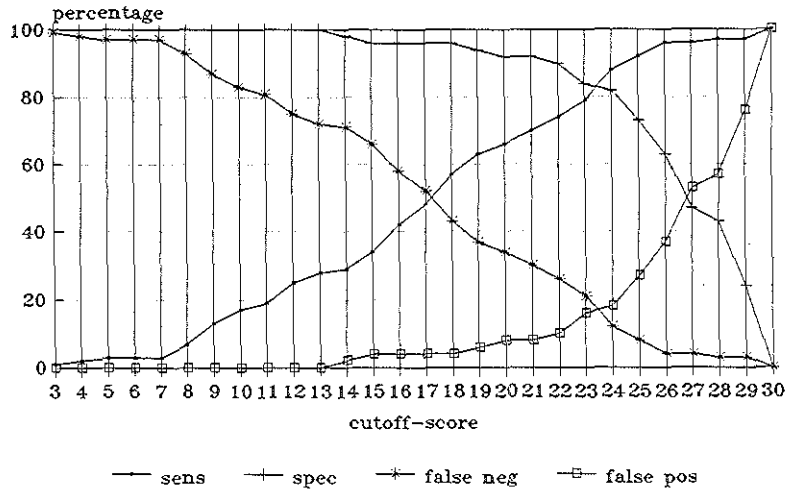

Figure III.2: Sensitivity, specificity and misclassification ratios by cutoff-score (n=138)

Table III.3: MMSE-score compared with clinical judgement on the presence of dementia/amnesia.

Clinical Judgement Dementia/amnesia	MMSE-score < 24	>=24	Row total
present	a 70	b 19	89
absent	c 8	d 41	49
Column total	78	60	138

Sensitivity = a/(a+b)=70/89=78.7%
Specificity = d/(c+d)=41/49=83.7%
False negative ratio = b/(a+b)=19/89=21.3%
False positive ratio = c/(c+d)= 8/49=16.3%

Figure III.1 shows the distribution of the MMSE scores for the two groups, i.e., those with dementia/amnestic syndrome (arched columns, n=89) and those with other diagnoses (open columns, n=49). Both groups did not differ significantly in age (78.7 vs 77.2 years respectively; $p > .10$).

Figure III.2 shows the sensitivity, the specificity and the misclassification ratios (the false negatives and the false positives) for the MMSE, using each score as the cutoff-score. It appears that in this sample a cutting point of 23/24 yields the best discrimination of the MMSE (see also Table III.3).

Using this cutting point, we found eight false positives. Among the eight false positives, there were five patients with a psychiatric disorder other than dementia or amnestic syndrome; this proportion was significantly higher than that for the total patient sample ($p < 0.001$).

Contrary to the findings by Anthony et al (1982), the percentage of false positives with a low level of education (6 years of primary school or less) was not larger than in the sample as a whole ($p = .78$). We also found no difference in level of education between the group of false negatives (n=19) and the total sample ($p = .59$).

With regard to the presence of memory complaints we distinguished four groups: 1) no memory complaints (n=38); 2) only the patient complained (n=5); 3) only the informants complained (n=27); 4) both the patient and the informants complained (n=68) (see Table III.4).

An ANOVA revealed a significant difference in mean MMSE-score between the four groups ($F(3,134) = 23.14$; $p < .001$).

Table III.4: Frequency, percentage and mean MMSE-score in relation to memory complaints

Memory complaint	Frequency	Percentage	Mean Score
No complaints	38	27.7	26.4
Patient complaining	5	3.6	29.2
Informants complaining	27	19.6	17.7
Patient and informants complaining	68	49.2	18.1

Using a test for multiple comparisons (Modified LSD) we found that groups in which the informants complained (i.e., group 3 and group 4) had significantly lower MMSE scores than the groups in which only the patient complained (group 2) or no complaints of amnesia were presented (group 1) ($p < .05$). A chi-square test showed that suffering from dementia or amnestic syndrome is associated with the presence of complaining informants ($X^2(1) = 47.4$; $p < .01$).

Discussion.

As can be seen from Figure III.2, we found an optimal cutting point of 23/24 for the detection of cognitive impairment in our sample of geriatric outpatients. This corresponds with the cutting point found by Anthony et al (1982) in their psychiatric sample and by Nissen et al (1989) in their neurological sample. Moreover, we found a similar sensitivity and specificity at this cutting point as Anthony et al (1982) did, although, contrary to our patient sample, their sample included patients with delirium.

The group of false positives (n=8) included a high proportion of patients with psychiatric disorder other than dementia (depression, n=4; personality disorder, n=1). This finding indicates that a psychiatric diagnosis such as depression or personality disorder in elderly subjects may well hamper performance on cognitive testing.

In the group of false negatives (n=19), there were seven patients with amnestic syndrome. The remaining 12 false negatives were patients who presented with behavioural disorders rather than memory problems as the first manifestation of their dementia (nine patients with Alzheimer type dementia, one patient with MID, two patients with 'mixed dementia').

With regard to the presence of memory complaints, we found that if the informants complained (see Table III.4, group 3 and group 4), the chance that the patient actually suffers from dementia or amnestic syndrome is about 0.9.

Conversely, if the informants do not complain (see Table III.4, group 1 and group 2), there is a similar chance that the patient is not suffering from dementia or amnestic syndrome. These data are in accordance with the findings by O'Connor et al (1990) that informant data improve the overall assessment of the patient with a dementia syndrome.

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CHAPTER IV: MEMORY FUNCTION AND EARLY DIAGNOSIS OF DEMENTIA IN GENERAL PRACTICE.

The pros and cons of case finding for dementia in general practice; guidelines for patient management in general practice.

CHAPTER IV: MEMORY FUNCTION AND EARLY DIAGNOSIS OF DEMENTIA IN GENERAL PRACTICE.

The pros and cons of case finding for dementia in general practice; guidelines for patient management in general practice.

Introduction.

The iceberg of unreported ill health in the elderly.

The health care system in the western world has been based on the self-reporting of symptoms by the patient. Doctors wait till patients take the initiative to consult them and then try to address the presenting problem in an efficient manner ('ad hoc management'). This demand-based model of care has particularly deleterious consequences for the elderly, and reports from both hospital and general practice have stressed that there is an iceberg of unreported ill health in the elderly*, a large proportion of which can be alleviated.

Ill health in old age is made up of many and varied, often interrelated problems. These may be symptomatic, but may be either unreported or undetected. The elderly person may not think the problem legitimate or remediable, or may ascribe his complaints to old age rather than to ill health. In addition, problems may remain hidden because of difficulties of communication due to factors such as hearing loss or loss of vision, impaired cognitive function, depression and social isolation. Problems can also be undetected by the doctor because he, like the patient, attributes the symptoms to ageing (for example, hypothyroidism), or is misled by an atypical presentation (for example, painless myocardial infarction or fracture), or assumes that a new pathology can be explained by a long-standing problem (for example, carcinoma of the colon in a patient with chronic constipation) (Freer 1987b).

With regard to cognitive impairment, it has been demonstrated that most elderly patients with cognitive decline do not consult their general practitioner and their families commonly present for help only when they have reached the limits of their endurance in caring for such an elderly person (Kay et al 1970; Isaacs 1971; Bergmann 1982; O'Connor et al 1988).

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* Williamson et al 1964; Townsend & Wedderburn 1965; Fuldauer 1967, 1972, 1973a, 1973b; Thomas 1968; Burns 1969; Tonino 1969; Lowther et al 1970; Hodes 1971; Demmenie 1972; Huygen 1972; Williams et al 1972; Currie et al 1974; Gruer 1975; Barber & Wallis 1976, 1978; Tulloch & Moore 1979; Barber et al 1980; Svanborg et al 1982; Barber 1983; Hendriksen et al 1984; Vetter et al 1984; Bakker 1985; Buyssen & Verhulst 1985; Buyssen & Wyterlinde 1985.

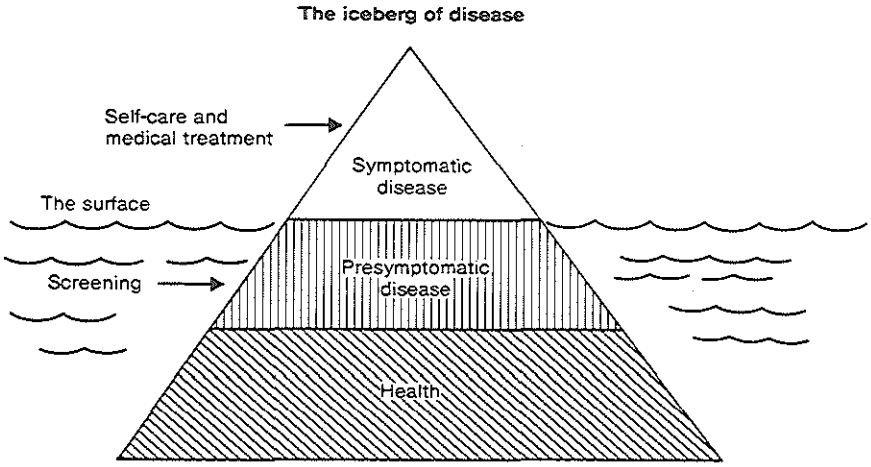
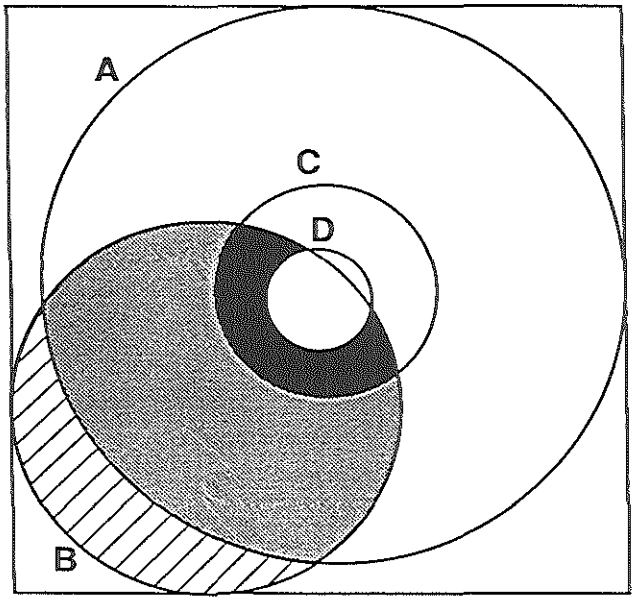


Figure IV.1. The iceberg of disease.
From Fowler G (1982) Practising prevention: What does it mean? Br Med J 284: 945-946.
Reproduced with kind permission of G. Fowler and the British Medical Journal.

The item characteristic curve analysis by Ashford et al (1989) demonstrated that both ADL scores and MMSE scores were negatively correlated with age, possibly reflecting a greater tolerance for social and cognitive dysfunction in more elderly individuals; older patients thus seem to be brought to clinical attention for the first time at a more advanced stage of their dementing process (see also chapter I.4).

The fact that much disease is 'below the surface' is illustrated by the diagram of the 'iceberg of disease' (Last 1963; Fowler 1982; see Figure IV.1).
With regard to the iceberg of psychiatric morbidity in primary care, it has been argued that there may be a lack of recognition of the psychiatric illness by the general practitioner, as has been extensively discussed by Goldberg and Huxley (1980) in their book 'Mental illness in the community'. They have constructed a Venn diagram of psychiatric disorders and primary care based on the concept that not all psychiatric morbidity is presented to the general practitioner, and if it is, it may not be recognized (see Figure IV.2; from Goldberg & Huxley 1991).

The Venn diagram is drawn to scale, so that the proportions represent the distribution of psychiatric disorders as they really occur at each level of care. The square round the circles represents the population at risk.



A = Consult their doctor during year
B = Episode of psychological distress during year (level 1)
C = Identified by their doctor as psychiatrically ill (level 3)
D = Referred to mental illness services (level 4)

Do not pass 1st filter (ill, but do not consult)
Do not pass 2nd filter (illness not recognised by Dr.)
Do not pass 3rd filter (not referred to mental illness services)

Figure IV.2. The Venn diagram.
From Goldberg DP & Huxley P (1991) Common Mental Disorders: A Biosocial Model. London: Routledge.
Reproduced with kind permission of D. Goldberg and Routledge, London, UK.

The largest circle, A, represents all those in the population who have consulted their general practitioner at least once during the survey year for any complaint, whether it be physical or psychological. Circle B defines those who experienced an episode of psychological distress during the survey year. Goldberg and Huxley (1980) have introduced the term level 1 morbidity to refer to that group. Note that circle B is not entirely within A: some people experience an episode of psychological distress but do not consult their general practitioner. This is what Goldberg and Huxley (1980) refer to as the 1st filter. Although the severity of a symptom is clearly one major factor impelling persons to go to their doctor, there are other significant determinants. This is the subject of illness behaviour, as developed by Mechanic (1962). It can be defined as the manner in which 'symptoms may be differentially perceived, evaluated, and acted (or not acted) upon by different kinds of persons' (Mechanic 1962). Level 2 morbidity refers to people who seek help during the survey year and are psychologically ill. That means that level 2 is represented by circle B minus the outer crescent (people who do not pass the first filter). However, their general practitioner may not detect their psychological illness. In Figure IV.2, this group is shown as the stippled area inside circle A. Goldberg and Huxley (1980) call the 2nd filter those factors which inhibit general practitioners (or other primary care staff) from recognizing that a psychiatric disorder is present. Circle C represents the psychiatric morbidity recognized by general practitioners (level 3). Note that some persons so recognized, would not be considered as cases of psychiatric disorder by the psychiatrist (i.e., the area of circle C outside circle B). They may have eccentricities of behaviour or difficulties in relationships, but they are not mentally ill. The more important area of circle C however, is the area shown in black in Figure IV.2, i.e., those identified by their doctor as psychiatrically ill, but not referred to mental illness services. Goldberg and Huxley (1980) call the 3rd filter those factors which inhibit such referrals. The patients referred to mental illness services are shown as circle D. The reason that this circle is not completely within B is that some patients are referred to psychiatrists with minor personality problems which fail to satisfy the research criteria for psychiatric illness.
Thus, the Venn diagram clearly illustrates those factors which contribute to the iceberg of psychiatric morbidity.

Prevention.

It has been argued that managing symptoms is no longer adequate and that there is scope for doctors - particularly general practitioners - to influence the health of their patients by preventive medicine (Fowler 1982). General practice provides a good framework for preventive medicine. In Britain, as in the Netherlands, virtually everyone is registered with a general practitioner and, more importantly for prevention, each general practitioner has a defined list of patients. Two-thirds of these patients consult him at least once a year and nearly all of them at least once every five years (Fowler 1982). In the Netherlands, 80.4% of the persons aged 65 or over consult their general practitioner at least once a year (CBS 1990). Therefore, general practice seems to be the ideal setting for preventive medicine.

Primary, secondary, and tertiary prevention.

The ideal form of prevention is removing the cause, so-called primary prevention. Much illness today is due not to external agents but to unhealthy human behaviour. Diseases related to smoking are an obvious example, and avoiding cigarette smoking is the most important form of primary prevention. It requires the doctor to add an educational role to his diagnostic and therapeutic ones. Secondary prevention is the early detection of disease before symptoms, or disordered function, appear and when action may stop, or even reverse, the disease process. Detecting hypertension is an example. In secondary prevention risk factors are acknowledged, and their presence is associated with an increased chance of developing a disease. Raised blood pressure and smoking are risk factors, both being associated with the development of cardiovascular disease and smoking with respiratory and other diseases. Risk factors may be asymptomatic - until the damage is done. Tertiary prevention is the management of established disease to avoid or limit the development of a disability or handicap. Supervision of diabetic patients is an example of tertiary prevention (Fowler 1982).

Screening.

Screening is the scrutiny of a population to find those who have risk factors for a disease or have the disease itself. Case finding is a form of screening in which

the initiative is limited to the opportunistic approach: the patient seeking advice from the doctor about symptoms is at the same time questioned, examined, or investigated for an unrelated condition. This contrasts with the more aggressive pursuit of the individual with no complaints to which a narrow definition of screening may sometimes be confined and which is a feature of population surveys. The term 'anticipatory care' has also been used to describe case finding (Fowler 1982).

Views about screening of the elderly: the pros and cons.

Two views prevail about screening. The evangelists argue that doctors should be more committed to screening procedures than they are. The cynics, on the other hand, maintain that few of the screening procedures that have been properly evaluated have been shown to be valid (Fowler 1982). The application of extensive medical screening, especially that using multiple laboratory tests and measurements ('multiphasic screening') (Knox 1974) has been shown by controlled trials not to reduce morbidity and mortality and not to improve use of services (Olsen et al 1976; South-East London Screening Study Group 1977). Enthusiasm for screening for precursors of disease in older people has been severely restricted by these negative results (Buckley & Williamson 1988).

Modern interest in geriatric screening dates from the Rutherglen experiment initiated in 1952 by Anderson and Cowan (1955). Since then, with a few exceptions (Evans et al 1970; Irwin 1971), studies have shown a high prevalence of unreported physical, social and psychological problems in screened elderly populations*. Williamson et al (1964), in their study of 200 people aged 65 and over, randomly selected from three Edinburgh general practices, found an average of three medical problems per person, many of them serious, of which only half were known to the doctor.

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* Williamson et al 1964; Townsend & Wedderburn 1965; Fuldauer 1967, 1972, 1973a, 1973b; Thomas 1968; Burns 1969; Tonino 1969; Lowther et al 1970; Hodes 1971; Demmenie 1972; Huygen 1972; Williams et al 1972; Currie et al 1974; Gruer 1975; Barber & Wallis 1976, 1978; Tulloch & Moore 1979; Barber et al 1980; Svanborg et al 1982; Barber 1983; Hendriksen et al 1984; Vetter et al 1984; Bakker 1985; Buyssen & Verhulst 1985; Buyssen & Wyterlinde 1985.

Since that study was published in 1964, the case for surveillance has been made virtually irrefutable - notably by Barber in Glasgow using an annual postal questionnaire sent to all patients over 75 years old (Barber & Wallis 1976, 1978; Barber et al 1980; Barber 1983), by three randomised trials of screening (Tulloch & Moore 1979; Hendriksen et al 1984; Vetter et al 1984), and by several other studies*. It has been argued that screening of the elderly should be comprehensive and include assessment of physical, mental and social problems. In the past few years it has become clear that the emphasis in prevention for this age group should be on assessing loss of function rather than on earlier detection of disease, and this functional assessment should encompass physical, mental and social function (Buckley & Williamson 1988). The two most recent randomized studies by Hendriksen et al (1984) and Vetter et al (1984) have shown the benefits of planned programmes of screening that concentrate on functional assessment; in the study by Hendriksen et al (1984), the screening programme led to an increased use of home helps and district nurses and to a reduction in mortality in the intervention group. The same was true for the urban intervention group in the study by Vetter et al (1984). In addition, in the study by Hendriksen et al (1984), there was a reduction in the number of hospital admissions in the intervention group, which was mainly due to a reduction in the number of readmissions; this suggests that the presence of a strong community support system results in a better after-care after hospital discharge and may prevent a number of hospital readmissions in this age group. In both studies, there was no difference in the number of general practitioner contacts between the intervention and control groups (Hendriksen et al 1984; Vetter et al 1984).

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* Fuldauer 1967, 1972, 1973a, 1973b; Thomas 1968; Burns 1969; Tonino 1969; Lowther et al 1970; Hodes 1971; Demmenie 1972; Huygen 1972; Williams et al 1972; Currie et al 1974; Gruer 1975; Bakker 1985; Buyssen & Verhulst 1985; Buyssen & Wyterlinde 1985.

In their conclusion, both Tulloch & Moore (1979) and Hendriksen et al (1984) draw attention to the opportunities which their studies created for improving communication between patients, their relatives and members of the primary health care team; they record their impression of improvement in patient morale and self-esteem, supporting earlier views that 'the quality of life in the elderly may be much enhanced by recognizing and treating disabilities which they do not present to their doctor' (Freedman et al 1978; Taylor 1982).

However, mass comprehensive screening of all people aged over 65 has been largely discredited because it has been found to be time-consuming, with a high cost to benefit ratio and a rather low yield (Freedman et al 1978; Tulloch & Moore 1979; Nuffield Provisional Hospitals Trust 1968; Holland 1974).

Instead, opportunistic case finding in high risk elderly patients has been advocated (Tulloch & Moore 1979; Freer 1987a; Buckley & Williamson 1988; Van der Cammen 1987, 1988), i.e., the detection of hidden problems during contacts initiated by patients for other reasons; the contact with the patient is used by the doctor to ask questions and make observations aimed at identifying those at high risk, who may then be offered further assessment (Freer 1987a, 1987b).

One approach to selecting those at high risk of disability is to identify the very old (85 years or older), those recently discharged from hospital, the recently bereaved and those taking multiple medication (Buckley & Williamson 1988). Taylor and Ford (1983) claimed that only the first two of these categories were likely to be valid indicators of high vulnerability. Another approach has been using postal questionnaires (Duke 1978; Barber et al 1980), and two recent initiatives have used volunteers to visit all older people; those identified to be in need are then followed up by general practitioners, health visitors, and district nurses (Beales 1987; Carpenter & Demopoulos 1987). However, a detailed study has concluded that, given current knowledge, defining high risk groups of the elderly cannot be done with sufficient accuracy for use in routine general practice (Taylor & Ford 1983; Taylor et al 1983). As Freer (1987b) has pointed out, one problem may be the validity and sensitivity of accepted risk factors; for example, though it is widely believed that living alone is a high risk factor, it may be that when people living alone begin to fail, the health or social services are involved quite quickly whereas the degree of support provided by relatives for old people living with families may

mean that their level of immobility and dependency is very much greater when they do present. Indeed, contrary to established teaching and belief, living alone might in some cases be a lower risk factor than living with a supportive family (Freer 1987b). Quite apart from the problem of identifying high risk groups of elderly individuals, opportunistic case finding in the elderly has its own problems. It would, for instance, mean a major change in the way that most general practitioners work. While the limitations of consultation time are probably somewhat overstated, it is unreasonable to expect general practitioners to add 5 or 10 minutes to each appointment with elderly patients. To plan for this in a routine appointment system would in itself be additional workload. In addition, the elderly patient may be so anxious about his presenting problem that he may not be willing to discuss other topics at the same time. Moreover, the doctor should not appear to be attaching more importance to his own agenda than to the agenda of the patient. It is accepted that patients should not be overloaded with information during consultations and older people may have particular difficulty in dealing with several topics (Freer 1987b). Another difficulty is that the 20 per cent of patients aged 65 or over not seen in any one year might be missed. This problem of non-attenders is inherent in most screening programmes, where there is often the danger of missing high risk patients. Although there is reassuring evidence that, in the main, elderly non-attenders are fit and well (Ebrahim et al 1984; Goldman 1984; Williams & Barley 1985), it seems likely that the elderly with cognitive impairment are the very ones who do not attend their general practitioner.

In view of the above, it appears that in the nearby future more attention must be paid to the development of opportunistic case finding programmes in the elderly, and the immediate need is for the development of protocols to demonstrate the feasibility of case finding in every day general practice (Freer 1987a, 1987b).

I will now discuss the 'iceberg of psychiatric illness' in the elderly and then continue with a discussion of Cooper and Bickel's review of the possibilities for screening and case finding for early dementia in general practice.

The iceberg of psychiatric illness in the elderly.

The famous study by Williamson et al (1964) clearly demonstrated the iceberg of

unreported ill health in the elderly. As mentioned before, they found a mean of 3 invalidating conditions per patient, 50% not being known to the general practitioner, the majority treatable c.q. ameniable to treatment. Depression was found in 10% of the elderly patients, but the condition had not previously been recognized in 75% of the cases; 28% of the elderly patients appeared to be demented, but the condition had not previously been recognized in over 80% of the cases.

Barber and Wallis (1976) investigated 100 elderly people aged 60+, living in the community, whom the health visitor considered in need of further assessment.

Table IV.1: Prevalence of known and unknown symptoms in 100 elderly people (aged 60+).

Symptoms identified	Number of symptoms	Percentage of symptoms not previously known, or requiring action
General health	47	34
Gastrointestinal tract	60	37
Skin	11	27
Genitourinary tract	57	28
Locomotor	75	10
Cardiac and respiratory	247	22
Neurological	157	27
Memory	37	68
Psychiatric	98	56

From Barber JH & Wallis JB (1976) Assessment of the elderly in general practice. Journal of the Royal College of General Practitioners 26: 106-114.
Reproduced with kind permission of J.H. Barber and the Journal of the Royal College of General Practitioners (now the British Journal of General Practice).

Seven hundred and eighty symptom complaints were identified (i.e., 7.8 per patient), of which 309 (39%) were not previously known to the doctor, but were sufficiently troublesome to make the health visitor conducting the symptom inquiry consider that further action should be taken. Table IV.1 (Barber & Wallis 1976) shows the prevalence of known and unknown symptoms identified in this study.
As can be seen from the table, the percentage of existing symptoms previously unknown ranged from 10% for locomotor conditions to 68% for memory loss. In addition, it was found that the number of unknown symptoms increased with age. These figures demonstrate that a patient is more likely to consult his doctor for physical problems (especially those hindering mobility) than for psychiatric and memory problems, and that more problems remain hidden in the very old.
In the study by Fuldauer (1973a) it was found that the elderly overestimated their health status and were not able to register decline reliably.
In a secondary analysis of detection of Alzheimer type dementia and depression in general practice, Wevers (1987) found an extremely low percentage of elderly suffering from Alzheimer type dementia; he examined the possibilities for the general practitioner to distinguish between psychological complaints in general and symptoms possibly caused by dementia and depression. The secondary analysis was carried out on material from previous research on primary care for the elderly. The data originated from two general practitioners and 282 of their patients. Twenty variables concerning dementia, depression and non-specific psychological complaints were selected and subsequently analyzed by a loglinear model of first order interactions between each pair of variables.
The results lead to the conclusion that the general practitioners in the practice were not very inclined or able to couch the various psychological complaints possibly caused by dementia or depression into well-defined diagnostic entities. Moreover, it appeared that the general practitioner and the patient often did not agree about the existence of depressive complaints.
The percentage of elderly in this practice possibly suffering from Alzheimer type dementia was found to be about the same as mentioned in two earlier Dutch registrations of morbidity in general practice, i.e. 1.2-1.6% of people of 65 and over (Lamberts 1982; Nijmeegs Universitair Huisartsen Instituut 1985). However, these figures are considerably lower than the prevalence figures mentioned in

epidemiological studies from other countries. This may well be due to the fact that only patients who had initiated the contact with their general practitioner were included in the analysis, suggesting that most patients with dementia did not do so, i.e., according to the Venn diagram they did not pass the first filter (ill, but do not consult). A second reason for the low prevalence figures of Alzheimer type dementia found in this study may well be that the general practitioner did not recognize the dementia in a number of cases, i.e., according to the Venn diagram some patients did not pass the second filter (illness unrecognized by the doctor).

Discussion.

These studies demonstrate that in the elderly, the iceberg phenomenon seems to occur especially with regard to psychiatric and memory problems. Thus, one may conclude that physical illness is identified more readily than psychiatric and memory problems. This may represent the fact that:

a) memory impairment may not be reported to health care professionals as readily as physical illness
b) memory loss may well be seen as a normal concomitant of old age both by the patient and the carers, especially in the very old
c) memory impairment may induce a fatalistic approach in the carers based on the idea that 'nothing can be done anyway', thereby preventing early consultation.

Screening and case finding for early dementia in general practice.

Criteria which diseases should fulfil if screening in a general population is to be attempted have been stipulated by Acheson (1963) and by Wilson and Jungner (1968). These criteria or so called 'principles of screening', were listed by Wilson and Jungner (1968) as follows:

1) The disease should constitute an important public health problem.
2) There should be an accepted form of treatment for those persons having the disease once recognized.
3) Facilities for diagnosis and treatment should be available to the population in question.
4) There should be general agreement among physicians with regard to the

indications for treatment.

5) The natural history of the condition - that is to say, its typical course and outcome, in the absence of effective methods of treatment - should be adequately understood.
6) There should be a recognizable latent or early symptomatic stage of the disease.
7) A suitable test or method of examination should be available, with whose help the disease is detectable in its early stages.
8) The screening method should be acceptable to the public.
9) The cost of case finding should not be excessive in relation to other existing health service priorities.
10) The screening programme should provide the basis for a continuing process of early detection, and should not be simply a 'one-off' exercise.

Recently, Cooper and Bickel (1984) have reviewed these criteria with respect to the early detection of dementing disorders in old age. They state that:

'These requirements now command broad acceptance in the field of preventive and social medicine. Since, however, their too-rigorous application would in effect rule out the possibility of prescriptive screening for all but a small handful of diseases, they should perhaps be regarded less as absolute criteria than as general guidelines, which can be helpful to clinicians and planners in weighing up the pros and cons of each individual situation. Certainly, a relative approach is essential, if the possibility of screening for psychiatric illness is to be seriously considered'.

In their article, Cooper and Bickel (1984) consider the scope and limitations of population screening for late-life dementia in relation to the criteria listed by Wilson and Jungner (1968).

1. Significance as a public health problem.

With regard to criterion (1) from Wilson and Jungner's list, Cooper and Bickel conclude that 'the importance of dementia as a public health problem is no longer a matter of dispute' and that there can thus be no question as to the desirability of methods of early detection, if these promise to lead to a reduction in chronic disability and dependence on institutional care.

2. Efficacy and availability of treatment.

With regard to the criteria (2) and (4) from Wilson and Jungner's list, Cooper and Bickel discuss the absence of treatment for senile dementia: 'The most powerful argument against systematic early detection of late-life dementia has been that it could be of no practical value, since this is an untreatable condition with a uniformly poor prognosis'. There are, however, two grounds for qualifying this judgement, quite apart from the need for experimental and evaluative research. To begin with, a number of clinical workers have reported that a significant minority of elderly patients admitted to hospital with the diagnosis of dementia were, in fact, found to be suffering from treatable and potentially reversible conditions (Marsden & Harrison 1972; Freemon 1976; Victoratos et al 1977; Hutton 1981; Smith & Kiloh 1981). The findings summarized in Table IV.2 (from: Cooper & Bickel 1984) indicate a wide range of variation, which may be explicable in terms of differing local referral and admission policies. Of more general interest is the rather high proportion of cases in each centre in which no organic brain pathology could be confirmed. This observation suggests that the principal benefits of early detection of dementia, at least in the shorter term, may reside less in the diagnosis of cerebral tumours, normal pressure hydrocephalus or other potentially reversible but uncommon causes of chronic brain syndrome in old age, than in the identification and treatment of cases of depression. Secondly, as Cooper and Bickel (1984) point out, the potential usefulness of early case detection is by no means restricted to treatable disease; indeed, this may prove not to be its most important consequence. The main objectives of medical care, in a situation where the natural course of the illness is one of progressive deterioration and no specific therapy exists, must be to mitigate distress and suffering, to avoid or postpone acute crises and to support independent functioning for as long as possible.

Bergmann (1982) has pointed out that the strain on the family tends to rise with the growing demands on their resources, until there is a phase of rapid, exponential increase, followed by a rapid decline in the support offered to the old person (see Figure IV.3; from Bergmann 1982).

Table IV.2: Clinical diagnostic assessment of patients investigated for reported dementing disorders.

Diagnostic assessment	Marsden & Harrison (1972): UK (N = 106)	Smith & Kiloh (1981): Australia (N = 200)	Hutton (1981): USA (N = 100)	Kohlmeyer* (1982): FRG (N = 240)
Diagnosis of dementia not confirmed	10.4	18.0	26.0	15.8
Potentially treatable/reversible disorder	4.7	6.5	19.0	2.5
Irreversible dementing disorder	84.9	75.5	55.0	81.7

* Investigation by CAT only.
The numbers are percentages.

From Cooper B & Bickel H (1984) Population screening and the early detection of dementing disorders in old age: A review. Psychological Medicine 14: 81-95.

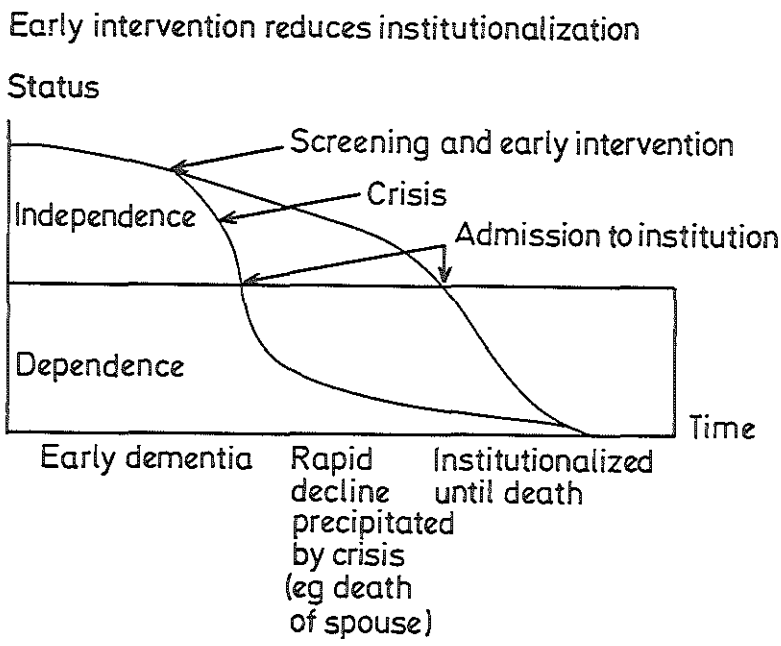

Figure IV.3. Early intervention reduces institutionalization.
Adapted from Bergmann K (1982) A community psychiatric approach to the care of the elderly. Are there opportunities for prevention? In: Magnussen G, Nielsen J, Buch J (eds). Epidemiology and Prevention of Mental Illness in Old Age, p 87-92. EGV: Hellerup, Denmark.
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An important aim of preventive care, therefore, must be to avoid the occurrence of this type of rejection by means of timely supportive measures. Early detection is then a preliminary, not to curative treatment, but rather to intervention aimed at reducing disability and postponing the need for institutional care.

3. Natural course and outcome of the condition.

With regard to the criteria (5) and (6) from Wilson and Jungner's list, Cooper and Bickel (1984) argue that remarkably little is known about the natural history of the dementias. The course and outcome of these disorders in patients who come under psychiatric care has been carefully studied from the point of first hospital

admission (Roth 1955; Blessed & Wilson 1982), so that for this group the clinical prognosis can now be assessed with some confidence. Much less is known about the development of the illness during the pre-admission period, to say nothing of its features and course in the great mass of affected persons who are never admitted to psychiatric units. Cooper and Bickel (1984) state that it is at present unknown what proportion of old persons who, labelled as 'mildly demented' on the strength of apparent memory and cognitive defects, in fact proceed to show the progressive mental deterioration required by the diagnosis. Nielson et al (1977) followed up 151 persons with a diagnosis of mild dementia, 15 years after they had been identified in a field study on the island of Samsö. For each age group over 70, the duration of life was found to be appreciably shorter than that of mentally intact persons, but longer than that of persons with undoubted clinical dementia. Bergmann et al (1971) made a similar observation in Newcastle, but noted that only 6 of the 20 cases of mild or questionable dementia found in their sample had gone on to develop definite dementia within a 3-year period. It thus appears that this diagnostic group is heterogeneous in nature.
Cooper and Bickel (1984) conclude that much more research must be undertaken into the natural history of chronic brain syndromes from their earliest stages, before programmes of prescriptive screening for these conditions could be justified.

4. Cost and acceptability of screening programmes.

With regard to the criteria (3), (8) and (9) from Wilson and Jungner's list, Cooper and Bickel (1984) agree with Eastwood and Corbin (1981) that the expense of providing diagnostic services in neuropsychiatric units for all suspected dementia cases would be prohibitive. Eastwood and Corbin (1981) have suggested that a rational alternative to admitting all patients with suspected dementia to specialist units for investigation would be the enhancement of diagnostic methods available to the physician of first contact. The development of diagnostic methods and tools for use by the general practitioner could, in their opinion, result in procedures both less costly and more effective than wholesale specialist referral (Eastwood & Corbin 1981).

5. Screening as a basis for continuing early detection.

With regard to criterion (10) from Wilson and Jungner's list, Cooper and Bickel

(1984) argue that there is some evidence from earlier studies that methods of early detection can, under favourable circumstances, become part of the day-to-day operation of existing primary care services, thus adding an important preventive component to the mainly 'curative' functions of such agencies (Lowther et al 1970; Hodes 1971; How 1973; Williams 1974; Barber & Wallis 1978; Freedman et al 1978). Lowther et al (1970), for example, reported on the experience of two 'early diagnosis' clinics for the elderly, which had been running successfully for a number of years in Edinburgh. The screening procedure they used included, in addition to a detailed physical examination, a short psychiatric assessment designed to detect early dementia and depressive states. A follow-up of 300 patients who had been screened consecutively showed that the recommendations made to the patients' general practitioners had been followed in 83% of instances and that over half this group showed some clinical improvement. After assessing each individual case, the authors concluded that early diagnosis had led to a significant improvement in 42% of treated cases: a conclusion which, however, must be regarded as tentative because of the absence of controls. They did not report specifically on the usefulness of the psychiatric screening component. The Edinburgh workers were hospital-based geriatricians, who placed great importance on close cooperation with the local family doctors (Lowther et al 1970). Since then, there has been a marked interest in the possibilities of preventive health care for the elderly, and a number of experimental projects have been reported, in which systematic geriatric assessment has been incorporated into the clinical routine of the general practitioner himself (Hodes 1971; How 1973; Williams 1974; Barber & Wallis 1978; Freedman et al 1978). Cooper and Bickel (1984) argue that, so far, too little attention has been paid in such projects to the identification of cognitive impairment or affective disorder, and to their possible diagnostic significance. Nevertheless, these small pioneering studies serve to indicate the potential scope for on-going programmes of early detection at the primary care level, within the framework of a preventively-oriented health service. They also stress the value of general practice as a vantage-point for identifying and making contact with those old people who are thought to be at particularly high risk for mental disorder: namely, those aged over 75; those who suffer from chronic physical ill-health and disability; those who have recently suffered

bereavement or have been discharged from hospital; and those requiring home-help or community services (Bergmann 1982).

6. Psychological screening instruments.

With regard to criterion (7) from Wilson and Jungner's list, Cooper and Bickel (1984) argue that simple economic biological tests for the diagnosis of dementing processes, or for the non-specific identification of progressive cerebral pathology in the elderly, do not yet exist. Diagnostic techniques which are available for certain rare but potentially treatable causes of dementia are unsuitable as population screening methods, in view of the very low prevalence of these conditions (Report of the Royal College of Physicians 1981). Detailed neurological, neurophysiological and neuroradiological investigation of unselected population groups must also be ruled out on general grounds of impracticability, and there are obvious objections to the use of any invasive techniques. Cooper and Bickel (1984) then continue to discuss suitable screening instruments and they conclude that the use of a short questionnaire approaches most closely the objective of population screening: namely, to identify probable cases of disease as quickly and economically as possible, without necessarily being able to allocate a precise diagnosis (see also chapter I.4). They draw attention to the importance of information from relatives and they point out that the extensive overlap in symptom-profiles between dementia and depression, especially in the earlier stages, suggests that, wherever possible, screening for cognitive and affective disturbances in the elderly should be conducted in tandem.

Lastly, they argue that once dementia scales are fully structured and standardized they might lend themselves to automation based on the use of microcomputers (Anonymous 1983; Carr et al 1982). They consider, however, that in practice the human skills required for this type of investigation are concerned less with administering the standard questions than with gaining the old person's cooperation and allaying his fears, to say nothing of adapting the techniques for use with those who are blind, deaf, tremulous, dysarthric, apathetic or otherwise indisposed. Since skills of this kind are not so readily transferred to computers, it may be doubted whether the development of automated methods will make more than a marginal contribution to the problems of psychogeriatric screening (Cooper & Bickel 1984) (see also chapter I.4).

Cooper and Bickel summarize their main conclusions as follows:

1) The extent of unmet need in elderly populations, as indicated by the findings of epidemiological research, suggests that a systematic approach to health surveillance and preventive care is required.
2) In view of the disappointing results of mass screening programmes directed at other sections of the population, it seems essential that any move towards the introduction of prescriptive screening for old people should be preceded or accompanied by careful assessment based on the principles outlined earlier in this chapter.
3) Quite apart from the economic considerations, prescriptive screening would be bound to raise difficult ethical problems. A physician or other health care professional who actively intervenes in the lives of his fellow-men, diagnosing previously unrecognized disease and proffering treatment which, in the event, proves ineffective or even harmful, is in a worse ethical position than those who administer such treatment in the course of normal clinical practice, based on patient-initiated consultations. Prescriptive screening should be postponed, therefore, until the outstanding methodological and practical issues have been resolved.
4) Screening for dementia and other late-life mental disorders is still at an experimental stage and is not yet ready for widespread application in the medical services or in 'ad hoc' screening programmes. Much more evaluative research will be required before this stage is reached.
5) In view of the growing importance of psychogeriatric disorders as a public health problem of worldwide dimensions, research into the feasibility and effectiveness of early detection measures as a first step towards preventive action should be given high priority in mental health programmes.
6) Such programmes of early detection are likely to prove succesful only if they can be incorporated into the work of the community-based primary medical and social services. In particular, the active cooperation of general practitioners, community nurses and other health-care professionals at this level will be essential if systematic screening and health surveillance is to have any significant impact on psychogeriatric morbidity (Cooper & Bickel 1984).

In summary, the evidence collected and discussed in this chapter so far, indicates that at present the advice must be against screening and case finding for dementia in routine general practice until further studies on its feasibility have been carried out. Even opportunistic case finding for dementia in high risk elderly individuals should at present only take place within the framework of research.
I will now discuss the most recent studies carried out in general practice.

The Cambridge study.

In a recent study in Cambridge (O'Connor et al 1988), general practitioners and community nurses were asked to rate the likelihood of dementia for each of their elderly patients. Cases of dementia were identified by research psychiatrists using the Cambridge mental disorders of the elderly examination (CAMDEX) (Roth et al 1986). General practitioners correctly identified dementia as at least a possibility in 121 of the 208 cases found. Nevertheless, they mistakenly rated as demented several patients suffering from functional psychiatric disorders, in particular depression. Community nurses correctly identified dementia as at least a possibility in 64 of the 74 demented patients known to them, but they incorrectly suspected dementia in a greater proportion of instances. Both general practitioners and families appeared to have low expectations of what general practice has to offer demented elderly people.

Subjects and methods used in the study were as follows: All patients aged 75 and over in six group practices in Cambridge city were asked through their doctors to take part in a screening interview which inquired into personal details, family contact, and health and concluded with the mini-mental state examination (MMSE) (Folstein et al 1975). Respondents who scored 23 or less on the MMSE out of a maximum score of 30, together with a one in three sample of those who scored 24 or 25, were assessed in more detail by using the CAMDEX (Roth et al 1986). As already discussed in chapter I.4, the CAMDEX is a lengthy diagnostic interview made up of a mental state examination, medical and psychiatric history, neuropsychological testing, and a brief physical examination. It includes an interview with an informant, usually a close relative, to establish whether there has been any change in cognition, personality, and behaviour.

In the Cambridge study, dementia was diagnosed only when operational criteria

appended to the examination protocol were satisfied. In addition to the CAMDEX, relatives were asked to complete rating scales of the elderly persons' need for help in activities of daily living (Lawton & Brody 1969) and of the strain they felt in providing care (Gilleard 1984). A proportion of relatives were interviewed in detail about their experiences. Two groups of patients were excluded from the analysis. Those in long stay hospitals were not included since it was thought unreasonable to ask doctors and nurses to assess people who were no longer their responsibility. Another group of patients were diagnosed as having minimal dementia. They were excluded from the analysis because this is a new, unvalidated category and it would be inappropriate to include these cases in a study of the rightness or wrongness of diagnosis.

Of the 657 patients chosen for further investigation on the basis of their MMSE scores, 532 were assessed by the CAMDEX. Eighty-eight patients were excluded from the analysis for a variety of reasons, leaving 444 patients. Of these, 208 satisfied the CAMDEX criteria for dementia; 96 cases were graded as mild, 85 as moderate, and 27 as severe. The overall prevalence of dementia in this particular age group was 10.7% after adjusting for sampling of those scoring 24 or 25 on the MMSE.

General practitioners were able to rate the likelihood of dementia in 370 of the 444 (83%) patients available for analysis. They considered that they were unable to make an informed judgement about the remaining 74 patients. These 74 patients were included in the analysis under the general practitioners' rating of 'not demented' - that is, if dementia was found to be present, the doctors were judged to have been unaware of it. Thirty nine of these 74 patients were diagnosed as cognitively intact, 15 as mildly demented, 16 as moderately demented, and four as severely demented.

General practitioners correctly identified (that is, they rated as possibly or definitely demented) 48 of the 96 patients found to be mildly demented, 52 of the 85 found to be moderately demented, and 21 of the 27 found to be severely demented. Thus, they correctly identified 58% of all cases (121/208) and 65% of patients with moderate or severe dementia (73/112). When only those patients rated by the general practitioners as definitely demented were considered, they correctly identified 21 (22%) patients with mild dementia, 31 (36%) with moderate

dementia, and 18 (67%) with severe dementia.

Patients whose dementia was recognised by the general practitioners were compared with those whose dementia was not recognised in terms of their ability to perform simple activities of daily living, the strain reported by the relatives caring for them, and the number of times they had been seen by their doctor in the previous 12 months. There were too few cases of unrecognised severe dementia for analysis, and this group was therefore excluded. Inability to perform simple activities contributed to recognition only in the mildly demented group, and the strain experienced by relatives contributed to recognition only in the moderately demented group. The one factor which contributed to recognition to a significant degree in both groups was frequency of consultation; general practitioners more commonly recognised dementia in the patients they had seen most often in the previous year.

Of the 236 low scorers on the MMSE who were subsequently shown to be cognitively intact, 51 were incorrectly rated by the doctors as possibly or definitely demented, giving a misclassification rate of 22% in this group. Seventeen patients were found to be suffering from functional psychiatric disorders. Misclassified diagnoses included nine cases of depressive illness, five of personality disorder, and one each of anxiety disorder, paranoid disorder, organic personality disorder, and chronic schizophrenia. Four of the nine depressed patients had a past history of mood disturbance. Seven patients who were not psychiatrically disturbed were described by the interviewers using the CAMDEX as 'odd' or 'difficult'; four were frail, deaf, or blind; and four were dysphasic or dysarthric. The rest showed no obvious abnormality.

Misclassification rates were much lower (5%) when only patients rated as definitely demented were considered. There were 11 such patients, two of whom were diagnosed as having depressive illnesses and two as having personality disorders. One had severe Parkinson's disease and a history of acute confusional states.

The principal carers of 73 demented patients living in the community were interviewed in detail. Only six of the 24 (25%) caring for mildly demented relatives had discussed memory failure and its attendant problems with their general practitioners compared with 18 of the 44 (40%) caring for moderately demented

relatives and four of the five (80%) caring for severely demented relatives.
Referral rates to the psychogeriatric services increased with the progression of dementia. Five of the 236 non-demented patients, three of the 96 mildly demented patients, 15 of the 85 moderately demented patients, and nine of the 27 severely demented patients had been seen at some time by the psychogeriatric service on domiciliary visits, as outpatients, or during admissions to hospital.
The Cambridge researchers (O'Connor et al 1988) conclude that general practitioners nowadays appear to recognise dementia more frequently than Williamson et al suggested in 1964. General practitioners' ability to recognise mild dementia as at least a possibility in half the cases identified by the analysis was surprising. Few general practitioners appeared to make even occasional use of formal tests of orientation and memory. Clearly, they were alerted in some instances by reports from relatives of failing memory and disturbed behaviour, but this accounted for only some of their successes. A large proportion of the elderly people who were interviewed had been under the care of the same doctor for many years. This continuity of care puts doctors in an excellent position to note deterioration in mental state. Were they regularly to apply brief cognitive tests, which take only a couple of minutes, and to question relatives about changes in memory, intellect, and behaviour, their diagnostic accuracy would improve considerably (O'Connor et al 1988). The authors then go on to say that general practitioners should take the initiative in diagnosing dementia in elderly patients who show signs of the condition. The elderly are not immune from dementia secondary to many correctable medical or surgical conditions (for example, chronic subdural haematomas). The important point is that cognitive impairment due to these causes is reversible only if detected and treated at an early stage. Such cases can be identified only if a brief history is taken together with an examination of mental state and physical condition whenever dementia is suspected. Nevertheless, because demented patients rarely complain of failing intellect - owing to lack of insight or fear of being 'sent away' - and because families commonly present for help only when they have reached the limits of their endurance, doctors will need to take the initiative.
Demented elderly patients are known to have much longer hospital stays than non-demented elderly patients (Kay et al 1970; Fields et al 1986; Johnston et al

1987; Maguire et al 1987; Binder & Robins 1990). They are also at increased risk of acute confusional states due to infection and treatment with drugs, including anaesthesia (Evans 1982). However, O'Connor et al (1988) note that very few letters of referral to clinics or admitting officers made any reference to dementia, even when general practitioners were aware of it. This information is essential. Demented elderly people, who may appear to be perfectly normal on brief contact, have difficulty in understanding questions, giving accurate replies, remembering instructions, and following the sort of complex procedures entailed in testing eyesight and hearing. Acute confusional states commonly arise against a background of mild to moderate dementia. If they were given some warning, hospital staff could take preventive action (O'Connor et al 1988).

Both general practitioners and nurses participating in the Cambridge study seemed to have difficulty in differentiating dementia from other psychiatric disorders. Physically frail or 'odd' elderly people who are mistakenly thought to be demented are unlikely to come to any harm, as doctors fail to act on their suspicions. Depressive illnesses, however, are potentially treatable. Early dementia is sometimes accompanied by depression, and a few seriously depressed elderly people are so confused and retarded that they may give the impression of being demented. O'Connor et al (1988) recommend an inquiry into mood, capacity for pleasure, feelings about the future, appetite, and sleep in order to settle the diagnosis. Psychological support and a trial of antidepressant agents cured a number of cases.

With regard to the burden of care, O'Connor et al (1988) found that sixty per cent of the demented patients (125/208) were cared for at home by their families. Most demented elderly people want to stay at home for as long as possible and most families contemplate admission to care only as a last resort. Nevertheless, only a quarter of those caring for mildly impaired relatives and two fifths of those caring for moderately impaired relatives had raised the subject of dementia with their general practitioners. Many of the carers who laboured under considerable difficulties adopted a fatalistic approach thinking that there was little that doctors (or anybody else) could do to help. However, O'Connor et al (1988) found that relatives benefitted from talking about their difficulties, and those who felt able to talk to their doctors valued this greatly. O'Connor et al (1988) state once again

that doctors will need to take the initiative in many cases. Understanding, support, and advice about accommodation and social services may be all that are required.

Last but not least, community nurses correctly recognised an impressive proportion of cases of dementia. Since they spend much of their time caring for the very old and frail, who are at risk not just of dementia but also of functional mental disorders, in particular depression (Cooper 1986), they may have an important part to play in identifying cases, in alerting doctors to patients likely to benefit from more detailed assessment and treatment, and in supporting families.

Discussion of the Cambridge study.

This outstanding study demonstrates that:

- general practitioners and community nurses are able to recognise dementia in a significant number of cases
- in a number of cases, general practitioners are able to recognise dementia without needing tests, especially when they have known the patient for a long time
- in a high percentage of cases of dementia, the general practitioner is not consulted by the patient but by the relatives; these family-initiated consultations with the general practitioner increase with progression of the dementia
- in the various stages of dementia, there were a number of misclassified patients who were found to suffer from treatable mental disorders, especially depression
- the fact that the general practitioner was aware of the dementia relieved the burden of care for the relatives.

The Mannheim study.

In a recent study in West-Germany on the possibility of early recognition of dementia by the general practitioner (Sandholzer 1989), all patients over 65 attending the general practitioner during four weeks in eight general practices (n=1513; mean age 76.3 years; 60.7% female; 39.3% male) were assessed for cognitive impairment by the general practitioner. The assessment by the general practitioner consisted of a 4-point scale of cognitive impairment and

documentation of social demographic and medical data. Random sampling (stratified) took place to identify patients from each degree of cognitive impairment per practice. The interview sample consisted of 145 patients from 8 practices. They were interviewed and tested by a group of trained doctors/psychologists. They were subjected to thorough investigation using a standardized interview and psychological tests and a clinical assesment of cognitive impairment by the members of the research team. Instruments used were the Disability and Impairment Scales (Sandholzer 1982), the Hierarchic Dementia Scale (Dastoor 1987) and the Wechsler Memory Scale - logical memory subtest (Wechsler 1945). Final assessment consisted of diagnosis and severity of dementia using the CAMDEX criteria (Roth et al 1986) and the Physical Independent Handicap Scale of the WHO (1980).

The results from this survey in general practice were as follows:

1) The practitioners rated 5.6% of the patients as moderately or severely demented, 16.9% as mildly demented and 39.8% were considered to have minimal cognitive deficits without psychiatric disability. Surprisingly, only 37.7% of the sample were rated as cognitively unimpaired by their doctors.
2) A correlation was found between the age of the patients and their cognitive status. The proportion of those with no mental impairment decreased steadily from 65% in the youngest age group (age range: 65-69 years) to only 4% in the eldest (age 90+). Minimal cognitive impairment without psychiatric disability was discovered in all age groups to a significant extent. The proportion of mild dementia rose from 3.7% in the youngest age group (age range: 65-69 years) to 45% in those aged 85-89 years. Moderate/severe dementia affected mainly patients aged 75 years or over, with 40% of those aged over 90 years belonging to this category.
3) Findings for the interviewed sample were extrapolated to all elderly patients in the 8 general practices participating in the study, leading to the suggestion that 64% of elderly patients have no detectable cognitive deficit, 20.8% of elderly patients have minimal cognitive deficit, 6.6% of elderly patients have mild dementia, and 8.6% of elderly patients are demented.
4) The majority (61.4%) of the moderate/severe cases of dementia in this sample were living in old peoples' homes. The mildy demented were more likely to live

in private housholds: only 24.7% of this sub-group were institutionalized, 45.6% lived in households of more than 1 person and 20.7% lived alone. In about half of these mild cases no key helper was known to the general practitioner.

5) Looking at physical and functional disabilities in the study group, it was found that only a quarter (23.6%) of the definitely demented patients had no physical impairments. Moreover, even in those with minimal cognitive deficits a significantly higher prevalence of blindness, deafness, locomotor or other severe disabilities was found. The mean number of severe impairments increased steadily from 0.1 in those patients with normal cognitive functioning to 1.0 in the demented elderly. The mean impairment score showed a sharp increase with rising severity of cognitive impairment, with this association being attributed mainly to a higher severity of impairments of hearing, vision and locomotor function, impairment of speech, the presence of tremor, incontinence; there was no significant association with cardiorespiratory disease, diabetes or disorders of balance.
6) When looking at the mean score for activities of daily living such as self-care and mobility, and for instrumental activities of daily living such as the ability to use public transport, it appeared that with increasing severity of dementia, the elderly became more disabled in all these aspects of life. A highly significant correlation (r_s = 0.82) was found to exist between the Independence Handicap Scale of the WHO (1980) and the degree of dementia. Even in minimal cognitive deficits, where no psychiatric diagnosis was indicated, a raised dependence score was found.
7) In the end, the assessment of cognitive status made by the research team on the basis of tests and interviews with key informants was compared with the doctor's ascertainment of cognitive disorder. The results indicate that the general practitioners were able to detect dementia with a sufficient efficiency. When compared with the results of the Cambridge study (O'Connor et al 1988), the general practitioners in Mannheim were able to recognize dementia with a remarkable sensitivity, but a somewhat lower specificity due to a tendency to overdiagnosis (see Table IV.3; from Cooper & Bickel 1990).

Table IV.3: Accuracy of general practitioners in assessing cognitive status of elderly patients in two research projects.

Research interview assessment (CAMDEX criteria	Mannheim GPs' ratings			Cambridge GPs' ratings*		
	Not demented (incl. minimal deficits)	Mild to severe dementia	Total	Not demented	Possibly or definitely demented	Total
Not demented	71	22	93	185	51	236
Mild to severe dementia	2	50	52	87	121	208
Total	73	72	145	272	172	444

* Source: O'Connor et al (1988).

Sensitivity	96.2%	58.2%
Specificity	76.3%	78.4%
Positive predictive value	69.4%	70.3%
Negative predictive value	97.3%	68.0%

From Cooper B & Bickel H (1990) Early detection of dementia in the primary care setting. In: Goldberg D & Tantam D (eds). The Public Health Impact of Mental Disorder. Basel, Göttingen: Hogrefe & Huber.

8) In the Mannheim study, an increase in general practitioner consultations occurred during the study; home visits by the general practitioner were found to almost double for each stage of cognitive impairment. In addition, the study resulted in a higher referral rate to neurologists and psychiatrists, so that case ascertainment appears to be associated to some extent with specialist referral and treatment.

In his summary, Sandholzer (1989) concludes:
- that general practitioners are able to distinguish mild and moderate degrees of dementia from normal ageing
- that provision of simple diagnostic guidelines can considerably improve the identification of mild dementia by the general practitioner
- that the degree of dementia is clearly associated with that of physical impairment and diminishing performance in activities of daily living and instrumental activities of daily living
- that there is a need for a careful assessment of physical as well as mental status to assess disability in the elderly and to evaluate the clinical prognosis
- that for both the early detection and the treatment of dementing disorders, general practice could, in future, become an important setting.

He recommends that geriatric research and action should become a key topic of primary health care. However, the author acknowledges that more research on the disabilities and handicaps of the elderly is required, before case finding can be recommended for routine use in general practice.

Discussion of the Mannheim study.

The following remarks can be made about this study:
- First of all, the study included only those patients aged 65 or over who had initiated the contact with their general practitioner
- The data were then extrapolated to all elderly patients in the 8 general practices which participated in the study. One must bear in mind that elderly people with early or mild dementia might not contact their general practitioner so that extrapolation of data based on patient-initiated consultations to all elderly patients in general practice might give false lower prevalence values.

The study by Ashford et al (1989) has also demonstrated that very old patients usually present to their doctor at a more advanced stage of their dementia, indicating that with increasing age, the dementia is allowed to progress quite far before contact with the medical profession is sought; this suggests that quite a few of the very old non-attenders may well be demented.

- The increase in number of contacts between the general practitioner and the demented patient occurring as a result of the Mannheim study possibly reflects sensitization of the general practitioners to the needs of the demented elderly.
- The fact that for about half of the cases of mild dementia no key helper was known to the general practitioner is alarming, especially because the relatives are usually the ones to contact the general practitioner when a suspicion of dementia arises. It suggests that general practitioners should routinely ask elderly patients whether a key helper is available to them. It may also show changing demographic trends, with a high number of elderly people living in big cities having no key helper available to them. On the other hand, a similar lack of key helpers may be found in rural areas, as was demonstrated by Kay (1977), who recorded that for 17% of old people included in a rural survey sample, no informant could be contacted.

Discussion of the Cambridge and the Mannheim studies.

Both the Cambridge and the Mannheim study suggest that general practitioners are able to detect dementia with a sufficient efficiency, although with a tendency to underdiagnosis. However, a considerable improvement in detection rates seems to have occurred since the study by Williamson et al (1964). The extraordinary high prevalence of dementia in the study by Williamson et al (1964) was possibly due to a lack of congruence in the diagnostic criteria rather than the doctors' unawareness of the disease. Moreover, the absolute number of patients and the number of examined practices were small.

One must bear in mind that both the Cambridge and the Mannheim study were carried out as research projects and were guided by academic units. For both studies, extra financial resources and extra research personnel had been made available. In addition, in the Mannheim study, clear guidelines and instruments were available to the general practitioners: they received instruction sheets, a 4-

point scale of cognitive impairment and record sheets to document sociodemographic and medical data. It becomes clear from both studies, that case ascertainment was largely in the hands of the research staff attached to the academic unit, in the Mannheim study assisted by neurologists and/or psychiatrists.

The London General Practice study.

In a recent study in London, the MMSE (Folstein et al 1975) was used by non-medical staff to detect cognitive impairment among the elderly in primary care (Iliffe et al 1990). Patients aged 75 years and over registered with nine general practices in north and north west London, were invited by their general practitioners to take part in the study, and 1170 patients agreed to participate, a response rate of 90%. All of those who agreed to participate were interviewed by trained non-medical field workers using a standard schedule. The general practice medical records of all participants were scrutinized by one research worker with a nursing background and all major diagnoses were recorded. All participants had a brief interview which included the MMSE and collection of demographic data. Data were analysed from a total of 1160 participants, 404 men (34.8%) and 756 women (65.2%). The data of 10 participants were excluded from the analysis; three were too ill to be interviewed, three refused to continue the interview before reaching the MMSE, one carer intervened to stop the interview, two were so deaf that their answers were highly suspect, and one participant had too poor an understanding of English to answer reliably. Scores on the MMSE were grouped into three bands: 0 - 18, cognitive impairment; 19 - 24, possible cognitive impairment; and 25 - 30, no cognitive impairment. The prevalence of cognitive impairment or possible cognitive impairment (score below 25 on the MMSE) was 12.8% (see Table IV.4; from Iliffe et al 1990). Six per cent of patients scored below 19, at which score a high probability of dementia exists, although less than a third of this group had a diagnosis of dementia in their medical records. There was no significant difference between men and women or by social class in the proportion of patients with low scores, but the proportion with dementia rose from 2.5% in those aged 75-79 years to 29.0% among those aged 90 years and over (see Table IV.4; from Iliffe et al 1990).

Table IV.4: Mini-mental state examination scores by age.

Mini-mental state examination score	Number (%) of patients					
	75-79 years (n=611)	80-84 years (n=333)	85-89 years (n=152)	90+ years (n=62)	Total (n=1160)	
Cognitive impairment 0-18	15 (2.5)	17 (5.1)	19 (12.5)	18 (29.0)	70 (6.0)	149 (12.8)
Possible cognitive impairment 19-24	25 (4.1)	27 (8.1)	20 (13.2)	7 (11.3)	79 (6.8)	
No cognitive impairment 25-30	571 (93.5)	289 (86.8)	113 (74.3)	37 (59.7)	1011 (87.2)	

x^2 = 108.561, degrees of freedom = 6, $P<0.001$, n = total number of patients; age of two subjects was not recorded.

From Iliffe S, Booroff A, Gallivan S, Goldenberg E, Morgan P, Haines A (1990) Screening for cognitive impairment in the elderly using the mini-mental state examination. British Journal of General Practice 40: 277-279.
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Medical records were available for 1133 patients. The researchers considered patients with MMSE scores of 19-24 as 'possibly demented' and patients with MMSE scores of 0-18 as 'probably demented'. Dementia was recorded in the medical records of 29.2% of those with MMSE scores of less than 19 and in 9.0% of those scoring between 19 and 24 (see Table IV.5; from Iliffe et al 1990). Thus, overall, 18% of those with possible and probable dementia were already known to be demented. Only seven patients (0.7%) who showed no cognitive impairment on the MMSE had a diagnosis of dementia recorded in the general practitioner's notes.

Table IV.5: Mini-mental state examination scores by recorded diagnosis of dementia.

	Number (%) of patients	
Mini-mental state examination score	'Dementia' not recorded in notes	'Dementia' recorded in notes
Cognitive impairment		
0-18 (n= 65)	46 (70.8)	19 (29.2)
Possible cognitive impairment		
19-24 (n= 78)	71 (91.0)	7 (9.0)
No cognitive impairment		
25-30 (n=990)	983 (99.3)	7 (0.7)
Total (n=1133)	1100 (97.1)	33 (2.9)

n = total number of patients whose records were examined; records not available for 27 cases.

From Iliffe S, Booroff A, Gallivan S, Goldenberg E, Morgan P, Haines A (1990) Screening for cognitive impairment in the elderly using the mini-mental state examination. British Journal of General Practice 40: 277-279.
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In the discussion, the authors (Iliffe et al 1990) conclude that much of the morbidity from dementia is concentrated in those aged over 80 years, with 50% of dementia cases being aged 85 years or over. They point at the value of the MMSE as a research instrument for use in community surveys. They suggest that it could also be used as a case finding instrument in general practice. They record O'Connor's personal communication that, using the CAMDEX as the 'gold standard', the Cambridge researchers have found that 100% of patients were demented below a MMSE score cut-off of 15/16, that 73% were demented below a cut-off of 18/19 and that only 1% of those scoring 25 and above were suffering from dementia (In: Iliffe et al 1990).

Patients who have low scores on the MMSE need further assessment, which Iliffe et al (1990) suggest could be undertaken by the general practitioner or by a specialist. In the London study, a maximum of 12.8% of the study population was considered in need of further assessment. The investigators recommend that interviewing relatives or other informants about changes in memory, judgement, personality, drive and self-care would be a simple, cost-effective way of ascertaining the presence of dementia in the majority of those with low MMSE scores, but that specialist referral may be necessary where the diagnosis is uncertain. They give guidelines for the general practitioner on the differential diagnosis of a low MMSE score and state that causes could include delirium, depression, psychosis and educational disadvantage. They state that delirium is more likely to be found in acutely ill hospital inpatients rather than among patients in general practice, but questioning informants about the duration of confusion, together with evidence of clouding of consciousness, evidence from physical examination and knowledge of previous physical health and medication, is likely to aid the general practitioner to reach this diagnosis in many cases. They suggest that depression may be detected by evidence from informants about lowered mood, diminished appetite and disturbed sleep. With regard to an association between level of education and MMSE score, the London study suggests that educational disadvantage, at least as reflected by social class, has only a small effect on the MMSE score.

The authors conclude that the London general practitioners participating in the study showed a tendency to underdiagnose dementia among those subjects

whose MMSE scores were in the 'possibly demented' (19-24) and 'probably demented' (0-18) ranges. However, they note that general practitioners may not always record a suspicion of dementia as a firm diagnosis in the patient's medical record. Only a small proportion of subjects (0.7%) were incorrectly diagnosed as suffering from dementia by their general practitioner, a similar proportion to that found by O'Connor et al (1988).
The authors then go on to calculate the extra workload of case finding or screening for cognitive impairment in general practice. They state that the MMSE takes on average 10 minutes to administer, and so, in an average general practice with around 130 patients over the age of 75 years, administering the MMSE would take a minimum of 22 hours per year, not including travelling time and time needed to further assess those with low MMSE scores. The administration of the MMSE plus basic questions about known major medical problems, household size and the extent of the individual's support network took an average of 25 minutes, which if applied to an average general practice, would require 54 hours face-to-face contact each year. In an average general practice population of 2000 with 130 people aged 75 plus, 17 individuals might need further assessment (Iliffe et al 1990).

Discussion of the London General Practice study.
The following remarks can be made about this study: The study suggests that the MMSE can be used by non-medical staff to detect cognitive impairment among the elderly in primary care. General practitioners still have a tendency to underdiagnose dementia, although this may be partly due to caution in recording such a diagnosis in the patient's medical record.

Discussion of chapter IV.
Early detection of dementia in general practice is hindered by the fact that most elderly people do not contact their general practitioner about their intellectual decline, and their relatives commonly present only when the burden of care becomes too high. Moreover, not all elderly people have a relative or key helper available to them, so that their dementia may not be detected until the mental deterioration has reached an advanced stage. Especially the very old may be at

risk of late detection, since society at large seems to accept a degree of social and cognitive dysfunction in more elderly individuals, as was recently demonstrated by Ashford et al (1989).

Despite these worrying facts, the evidence collected and discussed in chapter IV indicates that at present the advice must be against screening and case finding for dementia in routine general practice until further studies on its feasibility have been carried out.

Even opportunistic case finding for dementia in high risk elderly individuals should at present only take place within the framework of research, especially since further definition of high risk factors for dementia is still a matter of research.

Another reason to refrain from case finding in general practice is the extensive overlap in symptom-profiles between dementia and depression, especially in the earlier stages. For this reason, screening for cognitive and affective disturbances in the elderly should be conducted in tandem, wherever possible. Persistent subjective memory complaints in an elderly person are more likely to lead to the diagnosis of depression than of dementia. Early dementia is sometimes accompanied by depression, and a few seriously depressed elderly people are so confused and retarded that they may give the impression of being demented. An inquiry into mood, capacity for pleasure, feelings about the future, appetite, and sleep may help to settle the diagnosis. From these data it is clear that there is a problem for the general practitioner when he applies case finding to memory complaints in elderly people. In addition, there is the important problem of distinguishing mild dementia from what may be normal ageing.

However, general practitioners should take the initiative in diagnosing dementia in elderly patients who show signs of the condition. The elderly are not immune from dementia secondary to many correctable medical or surgical conditions (for example, chronic subdural haematomas). The important point is that cognitive impairment due to these causes is reversible only if detected and treated at an early stage.

The detection of correctable conditions is only a minor aspect of general practitioner's management of demented patients. The fact that the general practitioner is aware of the dementia has been shown to relieve the burden of care for the relatives (Bergmann 1982; Rabins et al 1982; O'Connor et al 1988).

Bergmann (1982) has pointed out that the strain on the family tends to rise with the growing demand on their resources, until there is a phase of rapid, exponential increase, followed by a rapid decline in the support offered to the old person. An important aim of preventive care, therefore, must be to avoid the occurrence of this type of rejection by means of timely supportive measures. Early detection is then a preliminary, not to curative treatment, but rather to intervention aimed at reducing disability and postponing the need for institutional care (Bergmann 1982).

In cases where suspicion of dementia arises, the mini-mental state examination (MMSE) (Folstein et al 1975) is a suitable test to establish a baseline of cognitive functioning in general practice. However, patients should be judged not only on the degree of cognitive impairment but also on the amount of behavioural evidence of dementia. In this respect, the informant interview is all-important, and the general practitioner could gain considerably from talking to relatives whenever he suspects dementia in an elderly person. In view of the fact that in the Mannheim study no key helper was known to the general practitioner for a large proportion of mild cases, I would advice that general practitioners record the name of a key helper for each elderly person registering with them.

The continuity of care puts general practitioners in an excellent position to note deterioration in mental state. Most general practitioners have known their elderly patients for a long time, which places them in an excellent position to note the first signs of decline from a previously higher level of functioning. In the study by O'Connor et al (1988), general practitioners were able to correctly rate the possibility of dementia in a significant number of patients without using formal tests. The fact that general practitioners rated few false positives is impressive and shows the tendency of general practitioners to be extremely careful before diagnosing a patient as demented.

At this moment, case ascertainment remains associated with specialist referral in the majority of cases. In addition, there is the need for follow-up in order to arrive at a correct diagnosis (Bergmann 1979; Kay et al 1968; Van der Cammen et al 1987).

In the next chapter, I will discuss the position of a Memory Clinic as a tool in the diagnosis and follow-up of cognitive disorders in the elderly (Van der Cammen et

al 1987; Exton-Smith et al 1987).

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CHAPTER V: THE MEMORY CLINIC.
A NEW APPROACH TO THE DETECTION OF DEMENTIA.*

T.J.M. Van der Cammen, J.M. Simpson, R.M. Fraser, A.S. Preker and A.N. Exton-Smith.

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* British Journal of Psychiatry 1987; 150: 359-364.

CHAPTER V: THE MEMORY CLINIC. A NEW APPROACH TO THE DETECTION OF DEMENTIA.*

Summary.

Memory impairment is a salient and early feature of developing dementia, but in practice is often not recognised until it has reached an advanced stage. The operation described is of a Memory Clinic opened on an experimental basis at the Geriatric Research Unit, University College London, in 1983, with the aim of identifying the causes of memory impairment in the elderly, with particular reference to the early detection of dementia. It proved possible to identify a group of people with early dementia who had previously been undiagnosed, and also to reveal deficiencies in the utilisation of existing services. Memory clinics would be a valuable addition to geriatric and psychogeriatric services.

Introduction.

Dementia is often not detected until the mental deterioration has reached an advanced stage. Family doctors may fail to recognise it and the general public tends to accept poor memory as a normal concomitant of ageing. Thus, in many patients the diagnosis of dementia is not made until some other condition precipitates admission to hospital.

Epidemiological studies in the elderly population have shown a remarkable consistency in the prevalence of dementia. The results have been summarised in the Report of the Royal College of Physicians on Organic Mental Impairment in the Elderly (1981); some reported on the incidence of early dementia. Although it can be assumed that patients exhibiting moderate to severe symptoms will have passed through a stage of mild dementia, the diagnosis of early deterioration in these cases has presented many problems which have not been resolved satisfactorily (Kay et al 1968; Bergmann et al 1971; Henderson & Huppert 1984).

The detection of organic mental impairment in epidemiological studies has usually been based on mental status questionnaires (Roth & Hopkins 1953; Hodkinson 1974), which test for short- and long-term memory, orientation, awareness of events and ability to count forwards and backwards.

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* British Journal of Psychiatry 1987; 150: 359-364.

V The Memory Clinic: A new approach to the detection of dementia.

Memory impairment is a salient and early feature of developing dementia, but simple tests such as these are in themselves of restricted value for diagnostic purposes (Hinton & Withers 1971; Hare 1978; Whitehead & Hunt 1982).
We outline the operation of a Memory Clinic which we opened on an experimental basis in April 1983 with the aim of identifying the causes of memory impairment in the elderly, with particular reference to the early detection of dementia. The clinic was established to provide a service for patients, their carers and general practitioners. We describe a more comprehensive approach to diagnosis than is usual, based on team investigation, and report on the first 50 patients.

Operation of the clinic.
General practitioners are encouraged to refer elderly people who complain about their memory or whose friends or relatives have noticed memory problems. The team in the clinic consists of a psychologist, a physician and a psychiatrist who see the patient independently, each using his own method of assessment.

The psychologist.
The psychologist usually sees the patient first to ascertain whether there is a true memory deficit. A memory problem is defined as a condition experienced by the patient which may or may not be accompanied by an objectively observed memory deficit. By means of an in-depth interview, the psychologist elicits the evidence, in terms of actual incidents of behaviour, that has led the patient to suspect that he has a memory problem, and records the earliest failures which led to this suspicion being aroused. An informant is interviewed to obtain an independent and detailed behavioural history; this is especially necessary when the patient himself cannot give an accurate account. Several factors affect the readiness with which memory problems are reported.
Two simple tests are administered initially:

A: **The Cerebral Function Test** (Silver 1972)
This is a brief screen of various mental abilities, including memory for recently learnt material, naming, vocabulary and spatial skill. It is a short test battery which was designed to be carried out by unskilled observers and to be easily

understood. To this end, the items have face validity; i.e. their meaning is obvious and the implications of failure are readily interpretable. The predictive validity of the total test score has been established by Silver (1972) and again by Ross & Horne (1977) with respect to an old person's ability to live independently. In the Memory Clinic we were not concerned with this aspect of the test but used it as a brief neuropsychological screen for indications of language and spatial deficit, low educational level and inability to learn and retain new material. The memory component, learning a fictitious name and address and recalling it after 5 minutes has been described elsewhere by Priest & Woolfson (1986), whose list details the administration procedure with one exception. Prior to presentation of the target material, the patient is warned that it will be necessary to recall it after 5 minutes. If this warning is omitted, the nature of the task is altered and it becomes more difficult. This test is similar to that included in many screening tests familiar to geriatricians and psychogeriatricians. Many of these mini-batteries are of limited use, as they focus on memory and orientation alone, omitting screens of language and spatial ability. In the Silver test, spatial ability is tested in several ways, including that first described by Isaacs (1963) using toys. We had the test materials specially made in wood so that they looked less like toys and our patients found them perfectly acceptable.

B: **The Kendrick Battery for the Detection of Dementia** (Gibson & Kendrick 1979; Kendrick et al 1979)

This consists of two easily administered tests, for which there are normative data. The first subtest taps memory by immediate recall, i.e. immediately after exposure of the test material, which is a card displaying a number of pictures of common objects. There are four cards, the number of objects to be recalled increasing over the series. The second part tests perceptuomotor speed and patients are required to copy lines of digits as fast as possible. The instructions for administering, timing and scoring these procedures are precise. The battery has been tested for criterion validity on groups of normal and memory-impaired old people. It yields evidence of a person's definite memory deficit but does not indicate if he is below average for a person of his age and educational level. These tests can therefore offer evidence to confirm that a person's memory

problem does indeed reflect an actual memory deficit, but a diagnosis of dementia should not be made on test scores alone, in the absence of other evidence and without excluding alternative causes for the memory deficit.

If the patient fails the memory component of test A and scores in the abnormal ranges of test B, more sophisticated memory assessment is redundant, but the procedures are repeated in 6 weeks to confirm the results of the first observations.

If the patient scores in the normal range on the screening tests, more demanding memory assessments are made with particular reference to dual performance tasks and delayed recall (Randt et al 1980). At this stage, it is essential to establish a baseline of memory ability with which to compare future performance, as stability or decline in this skill is critical to establishing a diagnosis. To this end, the limits of the efficiency of the patient's memory are sought. Test instruments on which the patient easily achieves near-perfect scores risk being insensitive to any future change. In this respect, the usefulness of some computer-controlled tests that we have designed is also being assessed (Simpson & Linney 1985).

The psychologist assigns each patient to one of three categories according to the amount of evidence that is found after several visits. This grouping parallels the process by which a clinical diagnosis of dementia is finally made, i.e. based on memory deficit in the absence of another explanation. Characteristics of the patients in the three categories are:

Category 1: Clear evidence of memory deficit.

a) Memory deficit on objective tests that have established cut-off points, e.g. Object Learning Test (OLT) of the Kendrick Battery.
b) Behavioural evidence of deficit from the reports of an informant and/or as observed during visits to the clinic.
c) Subjective complaints about memory problems may or may not be present according to the amount of insight retained.

Category 2: Equivocal evidence of memory deficit.

a) Normal scores on the OLT although other memory tests may yield scores

lower than expected for the person's age-group and IQ.

b) Behavioural evidence from an informant and/or from observations during visits to the clinic.

c) Subjective feelings of memory problems.

Category 3: No objective evidence of memory deficit.

a) No clear evidence of memory deficit on testing; normal scores on OLT, and performance on other tests in the expected range for a person of this age and IQ.

b) No clear behavioural evidence from any source.

c) Subjective feelings of memory problems.

The physician.

The physician attempts to identify any extra-cerebral causes of memory loss (Report of the Royal College of Physicians 1981; Wood 1984) and to distinguish between acute confusion, dementia and depression. He screens for focal cerebral lesions presenting as dementia, and tries to distinguish between dementia of Alzheimer's type and multi-infarct dementia, using the Hachinski score (Hachinski et al 1975). This is an 'ischaemic score' based on the different clinical features of multi-infarct dementia and Alzheimer-type dementia. Patients with a score of 7 or more are rated as probable multi-infarct dementia; those below 4 as Alzheimer-type dementia. Exceptions to this demarcation are to be found in clinical practice, and the number and clinical extent of strokes, the amount of infarcted tissue seen on CT and the presence of pseudobulbar palsy should be taken into account, and perhaps weighted more heavily (Miller et al 1984). In a study of elderly demented patients who came to autopsy, the score has been shown to identify accurately patients with multi-infarct dementia or with mixed pathology (Rosen et al 1980).

A careful medical history is obtained from the patient and relatives wherever possible, a full medical examination is carried out, and in the neurological examination particular attention is paid to evidence of dysphasia and parietal lobe signs.

The laboratory investigations include a full blood count, serum glucose, urea and

electrolytes, creatinine, rapid plasma reagin test and treponema pallidum haemagglutination assay (TPHA) test, and liver function and thyroid function tests. Serum vitamin B12 and folate concentrations are measured only when the mean cell volume is raised. It is recognised that the yield from these tests is low when applied as a routine in the investigation of dementia (Report of the Royal College of Physicians 1981). Other diagnostic procedures, including CT scanning, are carried out when indicated.

Special attention is paid to the drugs that the patient is taking, since it is known that several groups of drugs can impair memory and cognitive performance in the elderly. These include hypnotics and other psychotropic drugs, anticholinergic agents and certain centrally acting antihypertensive drugs (Solomon et al 1983).

The psychiatrist.

The psychiatrist takes a history and carries out a mental state examination. The objects are, first, to diagnose any affective disorder that may be responsible for or contributing to the memory impairment; secondly, to diagnose dementia on clinical evidence - the diagnostic criteria are those of Hare (1978), based on the Kew Cognitive Map (McDonald 1969). Thirdly, the psychiatrist assesses the overall severity of the dementia and the future provision that the patient will require; he will have the continuing clinical responsibility for the majority of the patients. In the absence of a simple rating scale of severity that takes account of all the cognitive impairments of dementia, the various degrees of severity are characterised as below. (The validity of these categories will be tested by the follow-up studies, and it is hoped that a simple and useful clinical rating scale can be provided.)

Absent	No evidence of cognitive impairment.
Equivocal	Slight memory impairment, definitely or possibly due to affective disorder.
Minimal	Definite memory impairment **or** dubious or minimal memory impairment, together with slight nominal dysphasia.
Mild	Definite memory impairment, together with definite nominal dysphasia.
Moderate	Definite impairment of both recent and remote memory, possibly with confabulation. Moderate dysphasia (including difficulty in

naming simple objects) and some failure of comprehension. Possibly some parietal features (e.g. dressing apraxia). Possibly some personality deterioration (e.g. emotional lability, paranoia).

Severe — As above, but all worse in degree and with definite personality deterioration.

Profound — As above, but all worse in degree; totally dependent on others for self-care. Little coherent communication.

Main diagnostic categories.

The team members meet regularly to discuss the patients they have investigated. A diagnosis is established or, if this is not possible, a hypothesis about the likely diagnosis is formulated. The diagnostic categories for the first 50 patient (32 female, 18 male; age-range 61-90 years; mean age 75.2 years) who have been fully assessed by all three members of the team are shown in Table V.1.

A firm clinical diagnosis was made in 66% of patients. Of the total series of patients, 50% were dementing to some degree, and all these patients had a memory deficit in category 1. A provisional diagnosis of dementia was made in 14% of patients, and these had memory deficits in categories 1 or 2. In 10%, a diagnosis of probable affective disorder was made, and these patients had memory deficits in categories 2 or 3; the other diagnoses in 8% of patients included potentially reversible organic disorders such as polypharmacy (two patients), hyperthyroidism (one patient) and Wernicke's encephalopathy (one patient). In 10% of patients, no clinical diagnosis could be established and neither could a memory deficit be demonstrated.

Of the 25 patients who had evidence of Alzheimer type dementia, the psychogeriatrician rated eight as moderately demented, 11 as mildly demented and six as minimally demented. Amongst the 16 in this group who had been referred by their family doctor, only five had already been put in touch with the psychogeriatric and community support services prior to being referred to the Memory Clinic. Neither these five nor the other clearly demented patients in this group had thus far received the level of support their condition required. These patients, with a firm clinical diagnosis of dementia, were referred to their local consultant in psychogeriatrics who provided the continuation of care.

Table V.1. Clinical consensus diagnosis.

	Memory deficit			
	Category 1	Category 2	Category 3	
Firm diagnosis				
Alzheimer type dementia	25 (9)			
Multi-infarct dementia	3 (1)		1	66%
Other diagnoses	2	1 (1)	1 (1)	
Provisional diagnosis				
Probable affective disorder		3 (1)	2	42%
Probable dementia	3	4 (1)		
No diagnosis			5 (2)	

Notes: The vertical axis describes the clinical diagnosis and the horizontal axis the degree of memory deficit.
Figures in brackets are numbers of patients for whom referral was initiated by the patient or carer. Patients with other diagnoses, provisional diagnosis or no diagnosis are being followed up (42%).

Since the Memory Clinic was established for the early detection of dementia, only those patients whose diagnosis remained in doubt were followed up in the clinic. The memory deficit was reversible in the two patients who suffered from the effects of polypharmacy. This is illustrated by the following case reports. Drugs which can impair memory are asterisked.

Case 1 (other diagnosis; memory deficit category 2).
Miss K.A., a 78-year-old woman, was referred to the Memory Clinic in December 1983. The referral had been initiated by her relatives, with whom she lived. In 1975 she had been firmly diagnosed elsewhere as suffering from cerebral atrophy

and her relatives had been attending the relatives' support group of The Alzheimer Disease Society for several years. She had equivocal evidence of memory deficit (category 2). On the Kendrick Battery for the Detection of Dementia, she scored in the normal range but close to the cut-off point in both of the subtests (memory/visuospatial speed). She had some impairment of recent memory, and her scores on the Raven's Matrices (Raven 1956a, 1956b) indicated that her intelligence was below average for her age.

Past medical history: hypertension; hysterectomy.

She was taking oxprenolol hydrochloride*, hydralazine hydrochloride, Lasikal (frusemide 20 mg plus potassiumchloride 750 mg (= 10 mmol K+) per tablet), allopurinol, flurazepam*, piroxicam and medroxyprogesterone. Her medication was gradually reduced until she took only medroxyprogesterone 100 mg b.d. and Navidrex-K (cyclopenthiazide 0.25 mg plus potassiumchloride 600 mg (= 8 mmol K+) per tablet), one three times per week. She was seen at regular intervals and, as the drugs were reduced, her memory tests improved. The psychogeriatrician did not consider her demented.

Diagnosis: memory deficit due to polypharmacy.

Case 2 (other diagnosis; memory deficit category 1)

Mrs M.S., a 66-year-old woman, was referred by her family doctor in August 1984 because of increasing forgetfulness. She had been diagnosed elsewhere as suffering from dementia and her CT scan had been reported as showing small diffused areas of low density.

Past medical history: in 1952 whe was overweight and treated with amphetamines which caused overexcitement and resulted in her being prescribed chlordiazepoxide which she had taken since. She had also been diagnosed as having Parkinson's disease and had been started on anti-parkinsonian drugs. In addition, she had a history of depression, hypertension and more recently of low back pain. Her medication consisted of Moduretic (amiloride hydrochloride 5 mg plus hydrochlorothiazide 50 mg per tablet), carbamazepine*, Diphenal* (diphenihydantoin 100 mg plus phenobarbital 25 mg per tablet), benzhexol*, buflomedil hydrochloride, flunitrazepam*, chlorpromazine*, phenobarbitone*, diazepam* and biperiden hydrochloride*. Chlordiazepoxide* had been

discontinued 2 days prior to her being seen in the Memory Clinic.
On examination she was fully orientated. She had scoliosis of the thoracic spine, but otherwise there were no significant physical abnormalities. She initially had clear evidence of memory deficit (category 1). Her performance was below normal on two memory tests and she became exceedingly upset and confused when required to learn a new task. She was diagnosed as having extensive osteoporosis of the thoracic and lumbar spine and was treated with physiotherapy and paracetamol. She was gradually weaned off all other drugs and improved both mentally and physically. The psychogeriatrician did not consider her to be demented.
Diagnosis: memory deficit due to polypharmacy.

Most of the other patients, 42% of the total series, are being followed up in order to confirm or refute the original diagnosis with particular reference to the diagnosis of early dementia.

Source of referral.
In the total series, 26 patients had been referred directly by their family doctors and eight from other hospital departments. The other 16 patients had referred themselves, or their carers had asked the doctor to refer them. Of those who came directly or indirectly via their family doctors, some had not sought medical advice until the disease was far advanced; in other cases the doctor did not seem to be aware of the community support available.
As Table V.1 indicates, there were larger numbers of self-referrals in those with memory deficit category 1 than in categories 2 and 3. Moreover, the 10 self-referred patients in this group had not received any support until they came to the clinic.

Discussion.
Several studies have shown that a medical care system that depends upon the self-reporting of illness is severely handicapped in terms of the early detection of disease (Williamson et al 1964; Gruer 1975). This has particularly deleterious consequences in the elderly. In a study in three general practices in Edinburgh,

V The Memory Clinic: A new approach to the detection of dementia.

Williamson et al (1964) found that 28% of the elderly patients were demented, but that the condition had not previously been recognised in over four-fifths of the cases.

In our study, it was disconcerting to find that many patients who were clearly demented had not been referred to the appropriate community support service; it was also instructive to learn how difficult it may be for a busy family doctor to recognise an early memory deficit. It is probably hard for a doctor to acknowledge such problems in a patient whom he has known for some years and who retains a good social facade, particularly if the patient is known to be of relatively high intelligence and to have held a responsible position in society. The results give support to Thompson's view (1985) that dementia is a latent condition, often detectable only by challenge.

The introduction of a new service (e.g. the opening of a geriatric day hospital) often brings to light deficiencies in existing services. We certainly found this to be the case after the Memory Clinic had been in operation for a few months. The Report of the Royal College of Physicians on Organic Mental Impairment in the Elderly (1981) emphasises that the present 'ad hoc' crisis style of management of dementia is unsatisfactory; instead there should be a readiness to seek out problems and to respond promptly to patients' needs. Criteria which diseases should fulfil if screening in the general population is to be attempted have been stipulated by Acheson (1963) and by Wilson and Jungner (1968). Recently, Cooper and Bickel (1984) have argued that the criteria also apply to the early detection of dementing disorders in old age. It is generally recognised that for screening a single sign should carry with it a high probability that the disease is present, and eliciting the sign should be simple, economical and unobjectionable to the subject. Both these criteria are fulfilled by dementia. In the Memory Clinic, we have used memory deficit as a marker for dementia, and the assessment of this deficit is based on the history, observation and simple objective testing.

Ideally there should be reasonable prospects for cure of the disease: this does apply to the mental deterioration which can result from polypharmacy and to those with 'pseudodementia' due to affective disorder. However, in the practice of geriatric medicine, cure is not in general the sole aim of treatment, but rather early detection is a preliminary to intervention aimed at reducing disability and

postponing the need for institutional care. Bergmann (1979) has drawn attention to the difficulties in making the diagnosis of early or mild dementia. He emphasises the importance of defective memory and early behavioural impairment in the development of dementing syndromes. He also stresses the need for follow-up, since in one epidemiological study (Kay et al 1968) it was found that 30% of patients diagnosed as probable early dementia were not demented when reassessed 3-4 years later.

We have described a team of three different specialists each assessing the patient from a particular aspect. However, the focus of assessment should be on the different tasks involved, not on the different professionals represented in our clinic. These tasks are: the collection of evidence of memory deficit, the identification of detectable causes of this deficit, the detection of underlying depression, and the counselling and management of the patient and the carer(s). All these tasks could be carried out by one suitably qualified person, but in practice, at least two people should be involved to increase the reliability of the overall assessment.

The value of the Memory Clinic can be considered under three headings:

Practical value.

It offers a facility to investigate people with memory problems and to attempt to arrive at a correct diagnosis, including the revision of the original diagnosis if found to be incorrect; to establish a diagnosis in patients suffering from the early stages of a dementing illness with a view to improving the patient's management; to treat curable causes of memory loss; and to control psychiatric symptoms.

Educational value.

The general public and all health care professionals need reminding that memory failure is not a normal concomitant of old age. Older people in whom suspicion of mental impairment arises or where memory loss is a subjective or objective complaint, should be investigated. Clinics to which early cases can be referred, such as the Memory Clinic, would increase awareness that screening should be undertaken. Suitable screening tests are available and should be administered routinely by all professionals coming into contact with old people. A test which is particularly sensitive to severity of memory deficit is the ability to recall recently

learnt new material after an interval (Graham-White et al 1969; Erikson & Scott 1977). The material should contain at least five items which are to be recalled after an interval of 5 minutes during which the patient is prevented from rehearsing by involvement in other tasks. The patient should be warned about the need for subsequent recall. This type of test, the recall after a brief interval of a fictitious name and address, is included in many geriatric assessments, e.g. the Mental Test Score (Roth & Hopkins 1953) and the Cerebral Function Test (Silver 1972).

Research value.

Since the clinic offers follow-up over time to selected patients, it will be possible to describe more accurately the natural history of the various dementing illnesses. A group of patients with early dementia can be identified, from which suitable subjects for trials of potential therapeutic agents may be recruited. If such an agent should be developed, it is more likely to be effective in the early stages of dementia.

Conclusion.

This pilot project has brought to light deficiencies in the utilisation of existing services and has confirmed the point made in the Report of the Royal College of Physicians on Organic Mental Impairment in the Elderly (1981) that a readily accessible and integrated service is essential in order to arrive at a correct diagnosis in patients with early dementia and to facilitate their management. Although one of the aims of the Memory Clinic is to provide a service to family doctors, many people previously unknown to the health service referred themselves or were referred by their doctor only after prompting by others caring for the patient. We believe that memory clinics could be a valuable addition to the geriatric and psychogeriatric services within the NHS and so provide a better system of management for the vast number of elderly demented patients projected for the future.

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CHAPTER VI: DISCUSSION AND RECOMMENDATIONS FOR FUTURE STUDIES.

CHAPTER VI: DISCUSSION AND RECOMMENDATIONS FOR FUTURE STUDIES.

An update on Memory Clinics worldwide.

The difficulties in diagnosing early dementia have led to the development of specialized clinics for the evaluation and management of memory disorders in the elderly (Bayer et al 1987; Van der Cammen et al 1987). Since the first Memory Clinic was opened at the Geriatric Research Unit, University College London (Van der Cammen et al 1987), Memory Clinics have been founded all over the world, notably in the UK at the Cardiff University Hospital (Bayer et al 1987), at the Frenchay Hospital, Bristol, at the Maudsley Institute of Psychiatry, South London, at St. Mary's Hospital, London and at the Whittington Hospital, North London; in Switzerland, Basle (Stahelin et al 1989), and through the Memory Assessment Clinics Incorporation in Canada, the USA and all over Europe (Belgium, France and Switzerland) (Larrabee et al, in press). In The Netherlands, Memory Clinics have been founded at the Academic Medical Centre, Amsterdam and at the Institute of Psychiatry, Valerius Kliniek/Free University, Amsterdam, at the Hospital Gooi-Noord, Blaricum, and at the University Hospitals of Maastricht and Rotterdam.

The first Memory Clinic described used a team of three different professionals, i.e., a physician, a psychiatrist and a psychologist, each assessing the patient from a particular aspect (Van der Cammen et al 1987). However, it was pointed out that the focus of assessment should be on the different tasks involved, not on the different professionals represented in the clinic. These tasks are: the collection of evidence of memory deficit, the identification of detectable causes of this deficit, the detection of underlying depression, and the counselling and management of the patient and the carer(s). In addition, quantification of memory, intellectual, and behavioural functions is a critical component of the Memory Clinic. All these tasks could be carried out by one suitably qualified person, but in practice, at least two people should be involved to increase the reliability of the overall assessment.

Memory Clinics provide a facility for investigation and follow-up of memory impairment in old age, with the particular aim to study the early features and the natural course of Alzheimer type dementia. Memory Clinics usually have a research interest as well. They have important clinical and social relevance. Patients are typically referred by general practitioners, although with increasing public education, some are self- or family-referred. Indications for Memory Clinic referral include persons who spontaneously complain of memory loss; persons

whose memory impairment is detected after direct questioning of the patient or relative; persons who manifest word-finding problems in spontaneous speech and/or on confrontation-naming tasks; persons who manifest disorientation and problems in recent memory. Treatment of disorders such as depression, intercurrent infections, and psychiatric manifestations of the dementing illness, e.g., delusions, hallucinations, sleep disorders and wandering, is one of the major therapeutic goals of Memory Clinics. Support to patients and carers may result in a reduction in the number of hospital admissions and the length of hospital stay, and may postpone or even prevent institutionalization. Community care may be less costly than institutional care and is likely to be more acceptable to patients. Further quantification of reduction in costs is necessary.

Follow-up over time offered to selected Memory Clinic patients may lead to the discovery of identifying factors for early stages of the various dementing illnesses in old age, especially dementia of the Alzheimer type. Participation in trials of potential therapeutic agents may be offered to selected patients. These agents are more likely to be effective in the early stages of dementia.

The opening of the first Memory Clinic led to the identification of a group of patients with early dementia. It also brought to light deficiencies in the utilisation of existing services and has confirmed the point that a readily accessible and integrated service is essential in order to arrive at a correct diagnosis in patients with early dementia and to facilitate their management.

Continuing research into the early stages of dementia, especially of the Alzheimer type, calls for an integrated approach, especially between primary care, the specialists who have the task of case ascertainment, and the neuropathologists. Within this framework, Memory Clinics can play a major role.

Not all cases of early Alzheimer type dementia present with memory impairment.

One aspect of Memory Clinics that I would like to discuss further, is the fact that not all cases of early Alzheimer type dementia present with memory impairment. In the Memory Clinic at the University Hospital Rotterdam Dijkzigt we have observed that it is quite possible for patients to have normal scores on the MMSE ($\geq$ 24 points) and on further psychometric tests, while behavioural evidence of a

dementia syndrome is clearly present.
Although memory impairment is a prominent feature of early Alzheimer type dementia, there is a danger in attaching too much value to its presence in order to diagnose the condition. Since the beginning of the century, dementia has been defined in terms of the cognitive deficits, the so-called 'cognitive paradigm'. Its continuing definition in this way is reinforced by the inclusion of cognitive symptoms alone as the main criteria for the diagnosis of dementia in the major diagnostic schemes. Alzheimer's first patient had delusions and hallucinations (Alzheimer 1907), and the presence of these features was responsible for the original classification of senile dementias as 'senile psychoses' (Berrios 1989).
Future studies of early stages of Alzheimer type dementia should take into account whether behavioural disturbances and psychiatric symptoms are present, as the role of non-cognitive symptoms as early signs of the disorder has not been investigated. Their presence, as part of a dementia syndrome, may be due to an intercurrent delirium, a manifestation of cortical disinhibition, the effect of personality, or the coexistence of two mental disorders (Berrios 1989).

The differential diagnosis between normal ageing and early Alzheimer type dementia.

Further research should focus on the distinction between memory complaints due to normal ageing and memory complaints due to the early stages of Alzheimer type dementia. In the Memory Clinic described in chapter V, we identified five patients who had subjective complaints about memory problems, in whom no objective evidence of memory impairment could be obtained and in whom no underlying cause could be detected.
Four of these 5 patients have now been followed for a period of 4 years. Two patients have remained cognitively normal; one of them was a 72-year old business consultant who was working full-time and was 'overloading' his memory. His memory complaints disappeared after he had been advised to reduce his workload and to use memory aids, such as a diary. The other 2 patients have developed Alzheimer type dementia.
Follow-up of elderly people with subjective complaints about memory problems, in whom no underlying cause can be detected and no objective evidence of

memory impairment can be obtained, may lead to the identification of those who are at risk of developing Alzheimer type dementia, and to further knowledge about its early stages.

The differential diagnosis of early dementia with depression.

Further research on the symptom-profiles of early dementia and depression is required. Depression in old age may mimic dementia ('pseudodementia') (Kiloh 1961; Wells 1979; McAllister 1982, 1983), dementia may mimic depression ('pseudodepression') (Roberts 1984), depression has been quoted a 'precursor' of dementia (Reding et al 1984, 1985), and depression is known to accompany dementia, especially when insight is retained. To further complicate the matter, the diagnoses of depression and dementia are not mutually exclusive (Patterson 1986; Reifler 1982; Reifler et al 1982).

There are many well-documented cases of cognitive improvement after treatment of depression. For example, Rabins (1985) reported on 16 patients who presented with symptoms of dementia accompanying major depression. Thirteen patients (81%) had a full recovery of cognition after treatment for their depression. Most maintained this improvement after two years of follow-up, but not all patients do so. Some patients who at first seem to show improved cognition when depression is treated, ultimately manifest the presence of an underlying irreversible dementia that shows up only on follow-up, as was demonstrated in the study by Reding et al (1984). They reported on 15 patients referred to a specialized dementia clinic who were initially judged to be depressed and who were given appropriate treatment for this condition. On follow-up, 8 patients (53%) developed progressive intellectual impairment.

I consider future research on the relation between early stages of dementia, especially of Alzheimer type dementia, and depression as one of the tasks of the Memory Clinic. Counselling, treatment with appropriate anti-depressant drugs and monitoring of treatment effects can be offered to elderly depressed patients with cognitive symptomatology. Follow-up studies of such patients are needed in order to shed light on the features which will predict who will eventually develop dementia. It may prove possible to identify distinctive psychometric 'patterns' in these patients, which will facilitate the differential diagnosis between depression

'sec' and depressive symptomatology accompanying early stages of dementia, especially of the Alzheimer type.

The search for reversible causes: 'patterns' of physical comorbidity within the various types of dementia.

The percentage of patients with cognitive impairment due to reversible disorders is probably small; Clarfield (1988), in her meta-analysis of 32 publications (2889 subjects) on the subject of reversible dementias, found that only 11 of the publications reported whether the patient had improved after treatment of potentially reversible disorders. In these 11 studies, the dementia was found to reverse in 103 patients (11%), either partially (8%) or completely (3%). The most common reversible causes were drugs, 28.2%; depression, 26.2%; and metabolic, 15.5% (see Table VI.1; from Clarfield 1988).

The quality of follow-up varied, ranging from retrospective chart review by one person to careful prospective consensus committee investigation of patients followed months and even years after initial diagnosis; six publications reporting on the reversibility of the dementia syndrome did so only by giving clinical impressions such as 'improved with treatment' (Freemon 1976; Katzman 1977; Victoratos et al 1977; Smith & Kiloh 1981; Freemon & Rudd 1982; Folstein et al 1985); the other five (Fox et al 1975; Hutton 1981; Martin et al 1983; Larson et al 1984; Larson et al 1985) did include cognitive testing, but only two publications mention these tests explicitly (Larson et al 1984, 1985); although in the study by Larson et al (1985) a 7-point scale to measure treatment effects is used, none of the five studies using cognitive testing included scales to measure instrumental activities of daily living (ADL), patients' behaviour (behaviour rating scales) or the burden of care for the relatives or main carer(s) (Crevel van 1989).

At present it is not known whether the incidence of reversible causes rises with age or whether the opposite is true. Further research on this subject is required, by means of prospective intra-individual follow-up studies using appropriate standardized criteria and scales, so that treatment effects can be measured appropriately, which again can be regarded as one of the functions of the Memory Clinic.

Table VI.1: Summary of 103 Cases Reported with Partially and Completely Reversed Dementia.

Condition	Reversed Dementia		Total	Cumulative %
	Partly	Completely		
	n	n	n (%)	n (%)
Drugs	17+	12	29 (28.2)	28.2
Depression	18	9	27 (26.2)	54.4
Metabolic	10	6	16 (15.5)	69.9
Thyroid	6	1	7 (6.8)	...
B_{12}	...	1	1 (1.0)	...
Calcium	2	...	2 (1.9)	...
Hepatic	2	...	2 (1.9)	...
Other	...	4	4 (3.9)	...
Normal pressure hydrocephalus	8	3	11 (10.7)	80.6
Subdural hematoma	5	1	6 (5.8)	86.4
Neoplasm	4	...	4 (4.0)	90.4
Other	9	1	10 (9.7)	100.0
Total*	71 (68.9)	32 (31.1)	103 (100)	...

Total includes all cases of partially and completely reversed dementia.
+ Includes 4 cases of alcohol abuse.
* Figures are n(%).

From Clarfield A (1988) The reversible dementias: do they reverse? Annals of Internal Medicine 109: 476-486.
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Our own findings at the Memory Clinic in Rotterdam have been that 7 patients who had Alzheimer type dementia were found to have abnormal thyroid functions; they have now been followed up for 1-2 years; in all seven, treatment of their thyroid disorder resulted in biochemical euthyroidism but their dementia did not reverse which suggests that the thyroid disorder should be regarded as comorbidity, not as a causal factor (unpublished data).

A recent analysis of physical, mental and social comorbidity in physically ill, depressed and demented elderly patients showed distinctive patterns (Van der

Cammen et al, submitted).
Quite apart from the consideration of total reversibility, there is the need to identify conditions which may cause 'dis-ease' to the patient or aggravate the dementia. Physical ill health is often said to be 'silent' in elderly demented patients, but more often the fact is simply that the patient does not make any explicit complaints. The objectives of assessment should be directed at maintaining physical independence at home, estimating the amount of help and services required and reducing the burden on relatives by improving the patient's physical condition and by treating the patient's psychiatric symptoms. Intercurrent infections and metabolic disorders should be taken into account when the patient exhibits a sudden decline or a delirium.

Psychosocial stress and dementia.
It has been shown that mental performance of elderly patients may fluctuate due to changes in their psychosocial circumstances (Van der Cammen & Harskamp van 1989). Therefore, a history of recent life events should be included in the assessment of elderly patients with dementia. Research on psychosocial stress factors precipitating or accompanying dementia may lead to recommendations for novel models of care.

Alzheimer type dementia and pathological changes in olfactory neurones.
Deficits in odour detection and discrimination have been reported as signs of Alzheimer type dementia (Serby et al 1985) and anatomical studies suggest that olfactory pathways may be involved early in the disorder (Pearson et al 1985). Nasal epithelium tissue taken at autopsy has shown unique pathological changes in morphology, distribution and immunoreactivity of neuronal structures in patients with Alzheimer type dementia (Talamo et al 1989).
In view of these facts, we conducted a study of assessment of smell and taste in cognitively normal elderly and in elderly patients with Alzheimer type dementia (Rai et al 1989).
Fourty-two elderly patients with Alzheimer type dementia and 38 cognitively normal elderly people participated in the study. It was found that impairment of both senses occurs in normal ageing and in the process of Alzheimer type dementia.

However, impairment of both smell and taste was more marked in patients with Alzheimer type dementia, and this difference was statistically significant for impairment of smell.

None of the cognitively normal elderly who had defective smell developed any mental impairment during a one year follow-up, suggesting that impairment or loss of smell is not a universal and early feature of Alzheimer type dementia but that it can be a normal part ageing. Therefore, testing of smell cannot be used as a screening test for early Alzheimer type dementia.

However, loss of smell has many practical implications. For example, it may lead to major problems such as reduced appetite resulting in weight loss and poor nutritional status; in addition, the inability to detect noxious odours such as gas and smoke presents a practical risk, particularly to those with mental impairment.

In view of the results of this study we advise that assessment of smell should be routinely carried out in elderly patients with mental impairment. If olfactory recognition is found to be impaired in such a patient, this finding should be made known not only to the patient but also to the relatives and community workers in order to prevent potential problems.

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CHAPTER VII: SUMMARY.

CHAPTER VII: SUMMARY.

In this thesis, diagnostic approaches and management aspects of early dementia are reviewed, with particular reference to the early detection of the most common type of dementia, i.e., dementia of the Alzheimer type. This age-related disorder affects thousands of elderly people each year. An aetiological factor has not yet been determined and the diagnosis, in the present concept of dementia, can only be made with regard to clinical criteria. The victims gradually lose their intellectual functions, memory and ability to care for themselves.

Memory failure is generally acknowledged to be an early feature of Alzheimer type dementia. However, memory failure covers a wide range of medical, neurological, and psychiatric disorders. To this list, some would add normal ageing. This leads to the problem of differentiating memory complaints due to Alzheimer type dementia from memory complaints which may occur during normal ageing and from memory complaints due to other disorders, especially depression.

In the western world, the increasing number of elderly people has led to an increasing number of patients with Alzheimer type dementia, in need of care. Alzheimer type dementia is progressive and typically lasts for a number of years during which the patient is totally dependent. Thus, considerable human and financial resources are tied-up in patient care, focussing medical and public attention on the disorder. The last decade has seen an explosion of research into Alzheimer type dementia, which has been remarkable for its breadth, involving many of the disciplines of biomedical research including neuropathology, neuroanatomy, neurochemistry, neuropharmacology, neuropsychology, molecular biology, genetics and protein chemistry, together with research into risk factors, patient management and the wider social issues raised by the disorder. Although much information has been produced by these individual disciplines, the cause of the disorder and the nature of its progression are still unclear. The most recent evidence points towards a multifactorial basis. Therefore, the integration of information from all fields of research into Alzheimer type dementia is required to enhance further progress into the understanding of the disorder.

This thesis discusses the possibilities of early diagnosis and the management aspects generated by the early detection of dementia, especially of the Alzheimer type.

Chapter I.1 describes the evolution of the concept of dementia. In past centuries, living to be old was a distinctly unusual phenomenon. Very few in the population

survived to the senium, the period of life in which dementia becomes a calculable prospect rather than a chance occurrence. Gradually, the concept of dementia began to take shape, and the term 'dotage' - considered the equivalent of 'senile dementia' - was introduced by Aretaeus in the 1st century AD.

The ancient authors and mediaeval writers agreed on the inevitable decrepitude and melancholic character of old age.

Shakespeare (1564-1616) showed remarkable understanding of the psychological make-up of mankind and described forgetfulness as a possible early change of senile dementia in 'King Lear'.

In the 17th and 18th century, the medical profession began to recognise senile dementia as a medical entity.

It was Esquirol (1722-1840), who defined senile dementia in an 1838 text: 'Senile dementia is established slowly. It commences with enfeeblement of memory, particularly the memory of recent impressions. The sensations are feeble; the attention, at first fatiguing, at length becomes impossible; the will is uncertain and without impulsion; the movements are slow and impractical'. Although he was over-inclusive in his use of the term 'senile dementia', his description of cognitive changes in some of those he considered demented in the senium came close to the modern conception.

The 19th century was dense with systems of classification, and it was Emil Kraepelin (1856-1926) who, in 1899, greatly narrowed the scope of the concept of dementia by separating 'dementia praecox' (schizophrenia) from the other dementias (paralytic and organic).

Gradually, histological and clinical studies began differentiating between the various types of dementia.

In 1904, Alois Alzheimer (1864-1915) reported the presence of neuritic plaques in cases of senile dementia. In 1906, he identified neurofibrillary tangles in the brain of his famous patient - a woman presenting with dementia at age 51 - and reported his findings to a meeting of the Southwest German Society of Alienists a year later.

In 1910, Simchowicz described granulovacuolar changes in the large pyramidal cells of the hippocampus and so completed the triad of neuropathological changes which we now associate with Alzheimer type dementia.

In 1936, Jervis and Soltz advised that only clinical criteria would suffice for a

diagnosis of Alzheimer type dementia.
Modern research began in 1955, when Roth showed that conditions such as affective disorder, late paraphrenia, and confusional states were entities which were distinct from Alzheimer type dementia and vascular dementia. The neuropathological correlates of this finding were later established by Tomlinson et al (1968, 1970), who demonstrated that the histopathological diagnosis of Alzheimer type dementia is quantitative, and depends on the presence of neuritic plaques, neurofibrillary tangles and granulovacuolar changes in combination and profusion.
Until today, the aetiology of Alzheimer type dementia remains unresolved, and the nature of the neuritic plaques and neurofibrillary tangles is presently the subject of intense research.

Chapter I.2 describes the evolution of definitions and diagnostic criteria for the various dementias and for Alzheimer type dementia in particular. The term dementia refers to the clinical syndrome of global impairment of higher cortical functions including memory, the capacity to solve the problems of day-to-day living, the performance of learned perceptuomotor skills, the correct use of social skills and control of emotional reactions, in the absence of gross clouding of consciousness.
The condition is irreversible and progressive.
It is emphasized that dementia is a clinical diagnosis: for the clinician faced with an individual patient, it is usually impossible to have a diagnosis of Alzheimer type dementia confirmed before post-mortem examination of the brain has been carried out, except in those very rare circumstances where brain biopsy is thought to be justified. The clinician thus attributes dementia to dementia of the Alzheimer type during life following an assessment of probabilities and the exclusion of other causes of dementia. Similarly, a neuropathologist cannot establish at autopsy whether or not the patient had cognitive impairment during life. The diagnosis of Alzheimer type dementia therefore depends both on evidence of a dementing process in the patient and subsequently, a finding of typical neuropathological features at post-mortem examination of the brain.
In the early 1980s, the definition of dementia became the focus of attention of various working parties, which has resulted in new working models. The

application of standardized diagnostic criteria such as DSM-III-R, NINCDS-ADRDA and ICD-10, and of standardized assessment procedures have improved the ability to diagnose Alzheimer type dementia clinically, and have already led to a reduction in the overdiagnosis of Alzheimer type dementia. Newer imaging techniques such as nuclear magnetic resonance (NMR) are likely to improve upon the ability of CT scanning to assist with the diagnosis. As far as post- mortem confirmation of the clinical diagnosis is concerned, there is a need for further research, as was clearly demonstrated by two recent studies (Homer et al 1988; Duyckaerts et al 1990).
Those of us working with older people could all make a significant contribution by assessing our demented patients during life, and by helping relatives to understand the relevance of research. Researchers working on basic science investigations of dementia, and in the laboratory field in general, rely heavily on their clinical colleagues for material. Such collaborative ventures are mandatory if we are to enhance our understanding of the mechanisms underlying the disorder.

Chapter I.3 reviews the epidemiology of dementia (all types) and of Alzheimer type dementia in particular. Dementia has become a common disorder in modern societies because of the size of their elderly populations. The prevalence of dementia (all types) and of Alzheimer type dementia rises with age, and depends on the ages of those in a population over 65; the life-time risk is estimated at 15 to 20%. Changing demographic trends show an increase of the average age of the population over 65, and the age group that is older than 80 is the fastest growing segment of the older population in the western world. Not only are more people getting older, but vaccination programmes, better economical and housing circumstances, and better health care provisions have led to a high percentage of elderly people reaching old age in good physical condition. Therefore, the phenomenon of dementia is no longer masked in modern society, as it is now able to express itself in the large proportion of people surviving into old age. The marked increase in prevalence of dementia (all types) and of Alzheimer type dementia is especially evident in the fastest growing segment of the older population, those 80 and over, where several studies have found prevalences of 10 to 20%.
The meta-analysis of the frequency and distribution of Alzheimer type dementia in

Europe by Rocca et al (1991) found an average prevalence (per 100 population) of 0.3% in those aged 60-69 years, of 3.1% in those aged 70-79 years, and of 10.8% in those aged 80-89 years. Within this meta-analysis, only the Cambridge study (O'Connor et al 1989) provided a prevalence value for those aged 90-94 years, i.e., 28.0%. The main conclusions of the meta-analysis by Rocca et al (1991) are that the prevalence of Alzheimer type dementia is similar throughout Europe, increases exponentially with increasing age, is consistently higher in women than in men, and has remained stable over time. Comparison of the European data with data from the United States and Japan indicates that international variations in the prevalence and incidence of Alzheimer type dementia are small, which points towards the possibility of age being the most important risk factor for the disorder. Prevalence values for dementia (all types) lose their consistency when the prevalence of mild dementia is focussed into. This is most likely due to differences in the criteria and in the methods and instruments used to identify cases of mild dementia. Mild dementia constitutes a special research entity which is already receiving the attention it deserves.

Chapter I.4 addresses the challenging problems surrounding the diagnosis of early and mild dementia, especially of the Alzheimer type. There are now sufficient methods and instruments available for the diagnosis of dementia and for the assessment of its severity. Their ability to detect early diagnostic features remains a field open to further research. Early diagnosis of dementia is hindered by the variety of symptoms with which the condition may present and by the lack of valid tests to identify early stages. Early dementia is still a vague, not well-defined entity which may resemble cognitive changes occurring during normal ageing and which can only be ascertained by future decline found during intra-individual follow-up over time. In addition, there is the problem of distinguishing early dementia from depression.
In the assessment of an elderly patient with cognitive impairment, informant data should be obtained whenever possible. Tests relevant to everyday life deserve further research attention and should be included in future studies of early dementia as they may well be sensitive to the earliest changes in memory function, and thus be a better predictor of memory impairment than laboratory memory tests.

Rather than continuing the search for the identifying test for early and mild dementia it seems wise that researchers worldwide should now make use of the existing diagnostic criteria in combination with well-tested screening instruments and rating scales in an attempt to achieve consistency in prevalences of early and mild dementia across nations.

Chapter III discusses the value of the Mini-Mental State Examination (MMSE) for the detection of cognitive impairment in a geriatric outpatient population in the Netherlands. One hundred and thirty-eight elderly patients, who were referred to the geriatric outpatient clinic at the University Hospital Rotterdam Dijkzigt for a variety of reasons, were enrolled as participants in the study.
The dutch version of the MMSE (Rooymans 1984) was found a valid screening instrument for the detection of cognitive impairment in this patient population. An optimal cutting point of 23/24 out of a total score of 30 was found for the detection of cognitive impairment. This corresponds with the cutting point found by Anthony et al (1982) in their psychiatric sample and by Nissen et al (1989) in their neurological sample. Moreover, we found a similar sensitivity and specificity at this cutting point as Anthony et al (1982) did, although, contrary to our patient sample, their sample included patients with delirium. These data indicate that the MMSE score is representative for the cognitive status of elderly patients referred to a geriatric outpatient clinic.
The discriminative validity of the MMSE was not influenced by level of education. However, we found a significantly higher percentage of patients with a psychiatric disorder other than dementia among the false positives in comparison to the sample as a whole. Therefore, the MMSE should not be used as a sole criterion for diagnosing dementia.
We also found that suffering from dementia or amnestic syndrome is associated with the presence of complaining informants.

Chapter IV describes the pros and cons of case finding for dementia in general practice and provides guidelines for patient management in general practice.
Early detection of dementia in general practice is hindered by the fact that most elderly people do not contact their general practitioner about their intellectual decline, and their relatives commonly present only when the burden of care

becomes too high. Moreover, not all elderly people have a relative or key helper available to them, so that their dementia may not be detected until the mental deterioration has reached an advanced stage. Especially the very old may be at risk of late detection, since society at large seems to accept a degree of social and cognitive dysfunction in more elderly individuals, as was recently demonstrated by Ashford et al (1989).

Despite these worrying facts, the evidence collected and discussed in chapter IV indicates that at present the advice must be against screening and case finding for dementia in routine general practice until further studies on its feasibility have been carried out. Early dementia is still a vague, not well-defined entity which may present with a variety of symptoms. There is extensive overlap in symptom-profiles between dementia and depression, especially in the earlier stages. In addition, there is the important problem of distinguishing early and mild dementia from what may be normal ageing.

However, general practitioners should take the initiative to screen their patients for dementia whenever circumstantial evidence for the presence of the condition exists. Recent studies have shown that general practitioners are able to recognize dementia in a significant number of cases (O'Connor et al 1988; Sandholzer 1989). General practitioners have usually known the patient for a number of years, so they are able to judge whether a decline from a previously higher level of functioning has taken place. In addition, they are in an excellent position to interview the patient's relatives or main carers and so obtain early behavioural evidence of a dementing illness.

Early detection has important implications not only for patients and their carers but also for the health care services. Cognitive impairment due to correctable causes is reversible only if detected and treated at an early stage. However, cure is only a minor aspect, applicable to a small proportion of patients. Rather, early detection is a preliminary to intervention aimed at reducing disability and postponing the need for institutional care. Demented elderly people are disproportionately heavy users of hospital services. The fact that the general practitioner is aware of the dementia has been shown to relieve the burden of care for the relatives. Timely support may prevent hospital admissions, reduce the need for institutionalization and improve the quality of life for the patient and his carers.

Chapter V discusses the position of a Memory Clinic as a tool in the diagnosis and follow-up of cognitive disorders in the elderly.
Memory impairment is a salient and early feature of developing dementia, but in practice is often not recognised until it has reached an advanced stage. The operation described is of a Memory Clinic opened on an experimental basis at the Geriatric Research Unit, University College London, in 1983, with the aim of identifying the causes of memory impairment in the elderly, with particular reference to the early detection of dementia. It proved possible to identify a group of people with early dementia who had previously been undiagnosed, and also to reveal deficiencies in the utilisation of existing services.
It is concluded that Memory Clinics could be a valuable addition to the geriatric and psychogeriatric services and so provide a better system of management for the vast number of elderly demented patients projected for the future.

In Chapter VI, recommendations for future research on the early stages of Alzheimer type dementia are discussed.
It is pointed out that future studies of early Alzheimer type dementia should take into account the presence of behavioural disturbances and psychiatric symptoms as possible early manifestations of the disorder. The current screening tests and diagnostic criteria carry the danger of overemphasizing memory impairment as an early feature of dementia, thereby losing important evidence provided by other symptoms.
In addition, further research is required on the differential diagnosis between normal ageing and early Alzheimer type dementia, and on the differential diagnosis between depression and early dementia, especially of the Alzheimer type. Depressive symptoms constitute a separate entity within the early diagnosis of Alzheimer type dementia. Psychometric profiles of elderly patients with depression may reveal specific patterns for depression associated with Alzheimer type dementia.
Studies of physical comorbidity in elderly patients with the various types of dementia may tell us which causes of dementia are truly reversible and which 'patterns' of physical disease exist within the various types of dementia.
Lastly, research on psychosocial stress factors precipitating or accompanying dementia may lead to recommendations for novel models of care.

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SAMENVATTING

In dit proefschrift worden de diagnostische benaderingen en de management aspecten van vroege dementie besproken, speciaal vanuit het oogpunt van de vroegdiagnostiek van de meest voorkomende vorm van dementie: namelijk de Alzheimer dementie. Ieder jaar worden duizenden ouderen door deze leeftijds-afhankelijke aandoening getroffen. Een oorzakelijke factor is nog niet vastgesteld. De diagnose kan, binnen het huidige concept van dementie, alleen gesteld worden op grond van klinische criteria. De patiënten verliezen geleidelijk hun intellectuele functies, hun geheugen en het vermogen om voor zichzelf te zorgen. Geheugenfunctiestoornissen worden in het algemeen beschouwd als een vroeg kenmerk van de Alzheimer dementie. Echter, geheugenfunctiestoornissen komen voor bij velerlei aandoeningen op internistisch, neurologisch en psychiatrisch gebied, en worden door sommigen beschouwd als een onderdeel van normale veroudering. Dit leidt ertoe dat geheugenfunctiestoornissen die optreden ten gevolge van een Alzheimer dementie gedifferentieerd dienen te worden van geheugenfunctiestoornissen, die kunnen optreden tijdens normale veroudering, en van geheugenfunctiestoornissen, die kunnen optreden ten gevolge van andere aandoeningen, met name de depressie.

In de westerse wereld heeft het toenemende aantal ouderen geleid tot een toenemend aantal patiënten met Alzheimer dementie, die zorg behoeven. Alzheimer dementie is progressief en in het klassieke geval is de patiënt gedurende een aantal jaren totaal afhankelijk van anderen, zodat er voor de patiëntenzorg aanzienlijke menselijke en financiële inspanningen nodig zijn. Hierdoor hebben zowel de medische professie als de maatschappij in het algemeen hun aandacht op de aandoening gevestigd. Gedurende de laatste tien jaar heeft een explosie van onderzoek naar de verschillende aspecten van Alzheimer dementie plaatsgevonden, waaraan, naast de psychiatrie en de neurologie, vele disciplines hebben deelgenomen, onder andere de neuropathologie, neurochemie, neurofarmacologie, neuropsychologie, klinische genetica. Tevens vindt onderzoek plaats naar risicofactoren en wordt aandacht besteed aan aspecten van begeleiding van de patiënt en aan de uitgebreide sociale problematiek, die door de aandoening veroorzaakt wordt. Alhoewel zeer veel informatie door al dit onderzoek verkregen is, zijn de oorzaak van de aandoening en de aard van de progressie van de aandoening nog onduidelijk. De meest recente onderzoeken wijzen in de richting van een multifactoriële oorzaak. Daarom is het nodig, dat een integratie van informatie vanuit alle

onderzoeksgebieden die zich bezig houden met Alzheimer dementie plaats vindt om een verdere uitbreiding van onze kennis van de aandoening mogelijk te maken. Dit proefschrift bespreekt de mogelijkheden van vroegdiagnostiek en de management aspecten die gegenereerd worden door de vroege detectie van dementie, in het bijzonder de Alzheimer dementie.

Hoofdstuk I.1 beschrijft de evolutie van het concept dementie. In vroegere eeuwen was het uiterst ongebruikelijk om een hoge leeftijd te bereiken. Weinig mensen in de bevolking overleefden tot het senium, de periode in het menselijk leven waarin dementie een niet onwaarschijnlijk vooruitzicht wordt in plaats van een toevallige gebeurtenis. Langzamerhand begon het concept dementie duidelijker vormen aan te nemen . De term 'kindsheid' - beschouwd als het equivalent van 'seniele dementie' - werd geïntroduceerd door Aretaeus in de eerste eeuw na Christus. De schrijvers uit de oudheid en de middeleeuwen waren het eens over de onvermijdelijke aftakeling en het melancholische karakter van de oude dag.
Shakespeare (1564-1616) toonde een opvallend inzicht in de psychologische samenstelling van zijn medemens. Hij beschreef vergeetachtigheid als een mogelijk vroege uiting van seniele dementie in zijn toneelstuk 'King Lear'.
In de 17° en 18° eeuw begon de medische professie seniele dementie te onderkennen als een medische entiteit. Esquirol (1722-1840) definieerde seniele dementie in een tekst geschreven in 1838: 'Seniele dementie ontstaat langzaam. Het begint met een verzwakking van het geheugen, vooral het geheugen voor recente indrukken. De gewaarwordingen zijn zwak. De concentratie is aanvankelijk wisselend, later onmogelijk. De wil is onzeker en zonder impuls. De bewegingen zijn traag en ongericht.' Hoewel Esquirol te veel aandoeningen in zijn beschrijving van de term 'seniele dementie' op nam, komt zijn beschrijving van de cognitieve veranderingen bij sommige bejaarden die hij als dement beschouwde, dicht bij het moderne concept.
In de 19° eeuw werden vele classificatiesystemen ontworpen; het was Emil Kraepelin (1856-1926), die in 1899 het concept dementie verder specificeerde door 'dementia praecox' (schizofrenie) te onderscheiden van de andere typen dementie (paralytisch en organisch). Langzamerhand begonnen histologische en klinische onderzoekers te differentiëren tussen de verschillende typen van dementie.

In 1904 rapporteerde Alois Alzheimer (1864-1915) de aanwezigheid van neuritische plaques bij patiënten met seniele dementie. In 1906 identificeerde hij de neurofibrillaire degeneratie in de hersenen van zijn beroemde patiënt, een vrouw die op 51-jarige leeftijd dementie ontwikkelde, en één jaar later rapporteerde hij zijn bevindingen op een vergadering van de Zuidwestduitse Vereniging van Psychiaters.
In 1910 beschreef Simchowicz de granulovacuolaire degeneratie in de grote pyramidale cellen van de hippocampus en completeerde zo het trias van neuropathologische veranderingen, dat wij heden ten dage met Alzheimer dementie associëren.
In 1936 adviseerden Jervis en Soltz, dat de diagnose Alzheimer dementie alleen gesteld mocht worden op grond van klinische criteria. Het moderne onderzoek begon in 1955, toen Roth aantoonde dat condities zoals depressie, late parafrenie en delirium entiteiten waren, die onderscheiden konden worden van Alzheimer dementie en vasculaire dementie. De neuropathologische correlaties van deze bevinding werden later bevestigd door Tomlinson et al (1968, 1970), die aantoonden dat de histopathologische diagnose van Alzheimer dementie kwantitatief is, en pas gesteld mag worden als neuritische plaques, neurofibrillaire degeneratie en granulovacuolaire degeneratie, in combinatie en in overvloed aanwezig zijn.
Tot op heden blijft de aetiologie van Alzheimer dementie onopgelost en de aard van de neuritische plaque en de neurofibrillaire degeneratie is op het ogenblik het onderwerp van intensief onderzoek.

Hoofdstuk I.2 beschrijft de evolutie van de definities en de diagnostische criteria voor de verschillende typen dementie en in het bijzonder voor de Alzheimer dementie. De term dementie verwijst naar het klinische syndroom van globale stoornissen van hogere corticale functies, inclusief geheugen, de capaciteit om de problemen van het dagelijks leven op te lossen, het uitvoeren van aangeleerde perceptuo-motorische vaardigheden, het correcte gebruik van sociale vaardigheden en het beheersen van emotionele reacties, zonder dat er een verlaging van het bewustzijnsniveau aanwezig is. De aandoening is irreversibel en progressief. Dementie is zeer nadrukkelijk een klinische diagnose. De clinicus die de individuele patiënt moet beoordelen, kan in het algemeen de diagnose

Alzheimer dementie niet bevestigd zien, totdat een post-mortem onderzoek van de hersenen heeft plaatsgevonden, met uitzondering van de zeer zeldzame gevallen, waarin een hersenbiopsie tijdens het leven van de patiënt gerechtvaardigd wordt geacht. De clinicus schrijft dus tijdens het leven van de patiënt de dementie toe aan een dementie van het Alzheimer type op grond van een uitgebreide beoordeling van waarschijnlijkheden en het uitsluiten van andere oorzaken van dementie. Evenzo is het voor de neuropatholoog onmogelijk om bij post-mortem onderzoek van de hersenen vast te stellen of de patiënt gedurende zijn leven wel of geen cognitieve functiestoornissen had. De diagnose Alzheimer dementie hangt dus af van de aanwezigheid van klinische aanwijzingen voor een dementiesyndroom tijdens het leven van de patiënt en het vervolgens aantonen van de typische neuropathologische kenmerken bij het post-mortem onderzoek van de hersenen. In het begin van de jaren '80 concentreerden verschillende werkgroepen zich op de definitie van dementie, hetgeen resulteerde in nieuwe werkmodellen. Het toepassen van gestandaardiseerde diagnostische criteria, zoals DSM-III-R, NINCDS-ADRDA en ICD-10, en van een gestandaardiseerde beoordelingsprocedure, hebben de vaardigheid om een klinische diagnose van Alzheimer dementie te stellen, verbeterd en hebben reeds geleid tot een reductie van de overdiagnostiek van de aandoening. Nieuwere beeldvormende technieken, zoals de nucleaire magnetische resonantie (NMR), zullen waarschijnlijk de diagnostische mogelijkheden van de gecomputeriseerde tomografie (CT-scan) overtreffen. Ten aanzien van de bevestiging van de klinische diagnose door middel van hersenobductie blijkt uit recente studies dat verder onderzoek nodig is, zowel in een samenwerkingsverband tussen de kliniek en de neuropatholoog (Homer et al 1988) als tussen de neuropathologische laboratoria onderling (Duyckaerts et al 1990). Diegenen die oudere patiënten behandelen, kunnen een belangrijke bijdrage aan het dementie-onderzoek leveren door hun demente patiënten gedurende het leven zo goed mogelijk te diagnostiseren en te begeleiden, en door aan de familieleden uit te leggen hoe belangrijk onderzoek is. Onderzoekers die zich bezig houden met basaal wetenschappelijk onderzoek van dementie en in het algemeen diegenen die in het laboratorium werken, zijn in zeer grote mate afhankelijk van hun klinische collega's voor materiaal en informatie. Dergelijke samenwerkingsverbanden zijn vereist als wij ons begrip van de mechanismen die dementie veroorzaken willen vergroten.

Hoofdstuk I.3 bespreekt de epidemiologie van dementie (alle typen) en van de Alzheimer dementie in het bijzonder. Dementie is een zeer frequent voorkomende aandoening in de westerse maatschappij vanwege de grote toename van het aantal (hoog)bejaarden. De prevalentie van dementie (alle typen) en van de Alzheimer dementie neemt toe met de leeftijd en hangt af van het aantal mensen in de bevolking dat ouder is dan 65 jaar; de 'life-time risk' wordt geschat op 15 tot 20%. Veranderingen in de demografie van de westerse wereld tonen een toename van de gemiddelde leeftijd van de bevolking boven de 65 jaar, en binnen deze groep neemt de leeftijdsgroep ouder dan 80 jaar het snelst toe. Niet alleen worden meer mensen ouder, maar ook hebben vaccinatieprogramma's, betere economische omstandigheden, betere behuizing en betere gezondheidszorgvoorzieningen ertoe geleid, dat een hoog percentage ouderen in een goede lichamelijke conditie de oude dag bereikt. Daarom is het fenomeen dementie niet langer onbekend in onze moderne samenleving, aangezien de aandoening tot uiting kan komen in het hoge percentage personen dat een hoge leeftijd bereikt. De sterke toename in de prevalentie van dementie (alle typen) en van de Alzheimer dementie is vooral evident in de snelst groeiende groep van de oudere populatie, degenen van 80 jaar en ouder; verschillende studies hebben in deze laatste leeftijdsgroep prevalenties van 10 tot 20% gevonden.
De meta-analyse van de frequentie en distributie van Alzheimer dementie in Europa door Rocca et al (1991) vond een gemiddelde prevalentie (per 100 van de bevolking) van 0.3% in de leeftijdsgroep van 60-69 jaar, van 3.1% in de leeftijdsgroep van 70-79 jaar en van 10.8% in de leeftijdsgroep van 80-89 jaar. Binnen deze meta-analyse gaf alleen de Cambridge studie (O'Connor et al 1989) een prevalentiewaarde voor de leeftijdsgroep van 90-94 jaar, namelijk 28.0%. De voornaamste conclusies van de meta-analyse van Rocca et al (1991) zijn dat de prevalentie van Alzheimer dementie door heel Europa gelijk is, exponentieel toeneemt met het toenemen van de leeftijd, constant hoger is in vrouwen dan in mannen, en in het beloop van de tijd stabiel is gebleven. Vergelijking van de Europese gegevens met gegevens uit de Verenigde Staten en Japan wijst erop dat internationale variaties in de prevalentie en incidentie van Alzheimer dementie klein zijn, hetgeen duidt op de mogelijkheid dat leeftijd de voornaamste risicofactor voor de aandoening is. Prevalentiewaarden voor dementie (alle typen)

verliezen hun consistentie wanneer men kijkt naar milde dementie. Dit is waarschijnlijk het gevolg van verschillen in de criteria, methoden en instrumenten, die gebruikt worden om gevallen van milde dementie te identificeren. Milde dementie vormt een speciale entiteit, die binnen het dementie-onderzoek reeds de aandacht krijgt, die het verdient.

Hoofdstuk I.4 bespreekt de interessante problemen die de diagnose van vroege en milde dementie, vooral die van het Alzheimer type, omringen. Er zijn nu voldoende methoden en instrumenten beschikbaar om de diagnose dementie te stellen en de ernst van de dementie te beoordelen. Echter, hun vermogen om vroege diagnostische symptomen te ontdekken, blijft een gebied dat open ligt voor verder onderzoek. De vroege diagnose van dementie wordt bemoeilijkt door de verscheidenheid aan symptomen, waarmee de aandoening zich kan presenteren en door het gebrek aan valide testen om vroege stadia te identificeren. Vroege dementie is tot nu toe een vage, niet goed omschreven entiteit, die gelijkenis kan vertonen met cognitieve veranderingen die optreden tijdens normale veroudering, en die alleen gediagnostiseerd kan worden door het vaststellen van cognitieve achteruitgang in het beloop van de tijd. Bovendien is het moeilijk om onderscheid te maken tussen een vroege dementie en een depressie.
Bij de beoordeling van een bejaarde patiënt met cognitieve functiestoornissen moet men, indien mogelijk, een hetero-anamnese afnemen. Testen die het functioneren in het dagelijks leven meten, zoals de BDL-schalen (Bijzondere activiteiten van het Dagelijks Leven), verdienen verdere aandacht en zouden opgenomen moeten worden in toekomstige studies van vroege dementie, aangezien zij wel eens zeer sensitief zouden kunnen blijken voor de vroegste stoornissen in geheugenfunctie.
Het verdient aanbeveling dat onderzoekers over de hele wereld gebruik maken van de bestaande diagnostische criteria in combinatie met goed geteste screeningsinstrumenten en beoordelingsschalen in een poging om consistentie in prevalentiewaarden van vroege en milde dementie op internationaal niveau te bereiken, in plaats van te blijven zoeken naar de identificerende test voor vroege en milde dementie.

In hoofdstuk III wordt de waarde van de Mini-Mental State Examination (MMSE) voor het ontdekken van cognitieve functiestoornissen in een populatie van geriatrische polikliniekpatiënten in Nederland besproken. Honderdachtendertig oudere patiënten, die om verschillende redenen verwezen werden naar de polikliniek Geriatrie van het A.Z.R.-Dijkzigt, namen aan de studie deel. De Nederlandse versie van de MMSE (Rooymans 1984) bleek een valide screeningstest voor het ontdekken van cognitieve functiestoornissen in deze patiëntenpopulatie. De optimale cut-off waarde voor het ontdekken van cognitieve functiestoornissen bleek te liggen bij een score van 23/24 punten (bij een maximale score van 30 punten). Dit komt overeen met de cut-off waarde gevonden door Anthony et al (1982) in hun psychiatrische patiëntenpopulatie en door Nissen et al (1989) in hun neurologische patiëntenpopulatie. Bovendien vonden wij voor deze cut-off waarde een sensitiviteit en specificiteit die overeen kwamen met de sensitiviteit en specificiteit gevonden door Anthony et al (1982), alhoewel deze laatste studie, in tegenstelling tot onze studie, patiënten met delirium bevatte. Deze resultaten tonen aan dat de MMSE-score representatief is voor de cognitieve status van bejaarde patiënten, verwezen naar een geriatrische polikliniek. Het discriminerend vermogen van de MMSE werd niet beïnvloed door opleidingsniveau. Onder de vals-positieven werd een significant hoger percentage patiënten met een psychiatrische aandoening anders dan dementie gevonden. Hieruit kan geconcludeerd worden dat de MMSE niet gebruikt moet worden als het enige criterium voor de diagnose van dementie. Ten aanzien van de presentatie van geheugenklachten werd gevonden, dat groepen waarin de informanten klaagden over het geheugen van de patiënt, significant lagere MMSE-scores hadden dan groepen waarin alleen de patiënt zelf klaagde over zijn geheugen of waarin geen geheugenklachten bestonden. De diagnose dementiesyndroom/amnestisch syndroom bleek geassocieerd te zijn met de aanwezigheid van klagende informanten.

Hoofstuk IV beschrijft de pro's en contra's van case finding voor dementie in de huisartsenpraktijk en geeft richtlijnen voor het management van patiënten in de huisartsenpraktijk.
De vroege detectie van dementie in de huisartsenpraktijk wordt belemmerd door het feit, dat de meeste oudere patiënten hun huisarts niet consulteren over een

achteruitgang van hun intellectuele vermogens en dat hun familieleden pas klagen, wanneer de zorg voor de patiënt te veel van hen vergt. Bovendien hebben niet alle ouderen een familielid of sleutelfiguur tot hun beschikking, zodat hun dementie vaak niet ontdekt wordt, totdat er sprake is van een vergevorderd stadium. Het zijn vooral de hoogbejaarden, die het risico lopen van een late ontdekking van hun dementie, aangezien de maatschappij in het algemeen een zekere mate van sociale en cognitieve dysfunctie bij bejaarde individuen lijkt te accepteren, zoals werd aangetoond door de studie van Ashford et al (1989).
Alhoewel deze gegevens zorgwekkend zijn, wordt door middel van de bewijsvoering in hoofdstuk IV geconcludeerd, dat op het ogenblik het advies moet zijn om geen screening en case finding voor dementie in de routine van de huisartsenpraktijk te verrichten, totdat verder onderzoek over de haalbaarheid ervan is uitgevoerd. Vroege dementie is een vage, niet goed gedefinieerde entiteit die zich kan presenteren met een verscheidenheid aan symptomen. Er bestaat een uitgebreide overlapping in symptoom-profielen tussen dementie en depressie, vooral in de vroege stadia. Bovendien is het moeilijk om onderscheid te maken tussen vroege en milde dementie en normale veroudering. Echter, huisartsen moeten proberen het initiatief te nemen om die oudere patiënten te screenen voor dementie, bij wie verdenking op de aandoening bestaat.
Recente onderzoeken hebben aangetoond dat huisartsen, in een aanzienlijk aantal van de gevallen, in staat zijn om een dementiesyndroom te herkennen (O'Connor et al 1988; Sandholzer 1989). Huisartsen kennen in het algemeen de patiënt een aantal jaren, dus zijn zij meestal in staat te beoordelen of een achteruitgang ten opzichte van een vroeger bestaand hoger niveau van functioneren heeft plaatsgevonden. Bovendien verkeren zij in een uitstekende positie om de familieleden te interviewen over het functioneren en het gedrag van de patiënt, en om op die manier vroege aanwijzingen voor het bestaan van een dementiesyndroom te verkrijgen.
Vroege detectie heeft belangrijke implicaties, niet alleen voor de patiënt en zijn verzorgers, maar ook voor de gezondheidszorg. Cognitieve functiestoornissen ten gevolge van corrigeerbare oorzaken zijn alleen reversibel, als ze ontdekt en behandeld worden in een vroeg stadium. Echter, genezing is slechts bij een klein gedeelte van patiënten met dementie mogelijk. In het algemeen is vroege detectie een voorwaarde voor interventie, die tot doel moet hebben om invaliditeit te

beperken en de noodzaak voor institutionele verzorging uit te stellen. Oudere patiënten maken in het algemeen frequent gebruik van ziekenhuisvoorzieningen. Het feit dat de huisarts op de hoogte is van de dementie van de patiënt vermindert de draaglast voor de familieleden en verzorgers. Tijdige ondersteuning kan de noodzaak voor ziekenhuisopnames en institutionalisering mogelijk reduceren en de kwaliteit van leven voor de patiënt en diens verzorgers verbeteren.

Hoofstuk V bespreekt de positie van een Geheugenpolikliniek in de diagnose en follow-up van cognitieve functiestoornissen bij oudere patiënten.
Geheugenfunctiestoornissen worden in het algemeen beschouwd als een sluipend en vroeg symptoom van een zich ontwikkelende dementie, maar in de praktijk worden zij dikwijls niet herkend totdat de dementie ver gevorderd is. In dit hoofstuk wordt de functie van een Geheugenpolikliniek beschreven, die in 1983 geopend werd bij de geriatrische research-afdeling van University College London, met als doel de oorzaken van geheugenfunctiestoornissen bij oudere patiënten te identificeren, vooral vanuit het oogpunt van de vroege detectie van dementie. Het bleek mogelijk om een groep oudere personen met vroege dementie te identificeren, die tot dan toe niet gediagnostiseerd waren, en om tekortkomingen in het gebruik van bestaande voorzieningen aan te tonen.
Geheugenpoliklinieken kunnen een waardevolle toevoeging zijn voor de geriatrische en psychogeriatrische voorzieningen en bijdragen aan het bepalen van een beter beleid voor het grote aantal dementerende ouderen, nu en in de toekomst.

In hoofdstuk VI worden aanbevelingen gedaan voor toekomstig onderzoek naar de vroege stadia van Alzheimer dementie. Er wordt op gewezen, dat in toekomstige studies van vroege Alzheimer dementie rekening gehouden moet worden met de aanwezigheid van gedragsstoornissen en psychiatrische symptomen als mogelijke vroege manifestaties van de aandoening. De huidige screeningstesten en diagnostische criteria leggen sterk de nadruk op geheugenfunctiestoornissen als een vroeg symptoom van dementie en brengen daardoor het risico met zich mee dat belangrijke bewijzen voor het bestaan van een dementiesyndroom, die door andere symptomen dan geheugenfunctie-

stoornissen geleverd worden, over het hoofd gezien worden. Verder onderzoek naar de differentiaal diagnose van depressie en vroege dementie, met name van het Alzheimer type, is noodzakelijk. Depressieve symptomen vormen een aparte entiteit binnen de vroegdiagnostiek van Alzheimer dementie. Psychometrische profielen van oudere patiënten met depressie zouden wel eens specifieke patronen kunnen tonen voor depressies die geassocieerd zijn met een Alzheimer dementie.

Studies van de somatische comorbiditeit bij bejaarde patiënten met verschillende typen dementie kunnen ons leren welke oorzaken van dementie werkelijk reversibel zijn en welke 'patronen' van lichamelijke ziekten bestaan binnen de verschillende typen dementie.

Tenslotte is verder onderzoek nodig naar de mogelijke invloed van psychosociale stress factoren op het ontstaan of het verergeren van een Alzheimer dementie.

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DANKWOORD

Velen hebben bijgedragen aan het tot stand komen van dit proefschrift. Hen allen wil ik daarvoor hartelijk danken. Een aantal mensen en groepen wil ik speciaal noemen.

Allereerst heeft het enthousiasme van mijn beide promotoren, Prof. Dr. F.J.G. Oostvogel en Prof. Dr. W.J. Schudel, mij gestimuleerd om, uitgaande van het concept van een Geheugenpolikliniek, dit proefschrift te wijden aan de problemen rondom de vroegdiagnostiek van dementie.

Beste Frits, jij was degene die in 1984, gesteund door de Stichting Katholieke Verplegings- en Verzorgingsinstellingen Rotterdam, de grondslagen voor de klinische geriatrie in het Academisch Ziekenhuis Rotterdam Dijkzigt en aan de Erasmus Universiteit Rotterdam legde, en begrip en enthousiasme voor dit nog nieuwe specialisme wist te creëren. Je continue belangstelling en steun, gepaard aan je grote kennis van het vakgebied, leidde regelmatig tot inspirerende discussies en ideeën, die over de grenzen van dit proefschrift heen, vele aspecten van de geriatrie bestreken. Eveneens wil ik je hartelijk danken voor je continue steun voor de subafdeling Klinische Geriatrie in het Academisch Ziekenhuis Rotterdam Dijkzigt.

Beste Joost, dat de psychiatrische aandoeningen op oudere leeftijd bijna dagelijks het pad van de klinisch geriater doorkruisen, is jou welbekend. Onze samenwerking wordt weerspiegeld in dit proefschrift. Mede dankzij jouw nimmer aflatende steun kwam de Geheugenpolikliniek aan het Academisch Ziekenhuis Rotterdam Dijkzigt tot stand. Ik hoop de goede samenwerking met jou en je medewerkers in de toekomst te kunnen voortzetten.

De overige twee leden van de leescommissie, Prof. Dr. M.A.D.H. Schalekamp en Prof. Dr. A. Hofman, wil ik eveneens danken voor de vaak verhelderende discussies over de verschillende onderwerpen in dit proefschrift.

Beste Maarten, van deze gelegenheid maak ik graag gebruik om nog eens mijn dank uit te spreken voor je continue steun voor de subafdeling Klinische Geriatrie, die binnen jouw afdeling Inwendige Geneeskunde I zo gastvrij werd opgenomen. Ik hoop de goede samenwerking nog jarenlang te continueren.

Beste Bert, ook jou wil ik danken voor je enthousiaste steun voor de klinische geriatrie. Ik hoop dat de samenwerking tussen de Geheugenpolikliniek van het Academisch Ziekenhuis Rotterdam Dijkzigt en jouw grote ERGO-project in de toekomst nog verder tot bloei zal komen.

De co-auteurs van hoofdstuk III en V dank ik voor hun continue bereidheid tot

discussie. Ik prijs mij gelukkig met Prof. A.N. Exton-Smith, Janet Simpson en Morris Fraser, die deel uitmaakten van het team van de "Memory Clinic" aan de Geriatric Research Unit van het University College London, gewerkt te mogen hebben. De "Memory Clinic" in Londen vormde de basis voor het oprichten van de Geheugenpolikliniek aan het Academisch Ziekenhuis Rotterdam Dijkzigt. Mijn speciale dank gaat uit naar Frans van Harskamp van de afdeling Neurologie en Neuropsychologie, die de oprichting van de Geheugenpolikliniek aan het Academisch Ziekenhuis Rotterdam Dijkzigt vanaf het eerste begin gesteund heeft.
Dick Stronks en Jan Passchier, jullie ideeën waren van grote waarde bij het tot stand komen van hoofstuk III. Dank!
De Stichting Katholieke Verplegings- en Verzorgingsinstellingen Rotterdam wil ik danken voor hun continue, materiële en immateriële, steun voor de ontwikkeling van de klinische geriatrie in het Academisch Ziekenhuis Rotterdam Dijkzigt en aan de Erasmus Universiteit Rotterdam.
De Geheugenpolikliniek en de polikliniek Geriatrie van het Academisch Ziekenhuis Rotterdam Dijkzigt waren nooit van start gegaan zonder de medewerking van Prof. Dr. C. Hilvering, die nu alweer vier jaar lang werkruimte op de polikliniek Longziekten beschikbaar stelt. Mijn hartelijke dank, ook aan de staf van de polikliniek Longziekten, die altijd met veel tact en geduld de oudere patiënten te woord staat.
Tevens dank ik de hoogleraren, stafleden, arts-assistenten, verpleegkundigen en overige medewerkers van de afdelingen Inwendige Geneeskunde, vooral van de afdeling Inwendige Geneeskunde I, voor hun goede zorgen voor de oudere patiënten, die via de polikliniek Geriatrie opgenomen worden.
De medewerkers van de subafdeling Klinische Geriatrie hebben gedurende het laatste jaar buitengewoon veel geduld gehad en een continue belangstelling voor de vordering van dit proefschift getoond. Zonder de hulp en het doorzettingsvermogen van Ellen van der Heiden was dit proefschrift nooit in druk verschenen. Hartelijk dank voor de vanzelfsprekendheid van je inzet en voor de geboden steun!
De medische studenten, die met veel interesse aan geriatrisch onderzoek deel namen, dank ik voor hun enthousiasme.
Specialisten, huisartsen, verpleeghuisartsen, RIAGG's en patiënten dank ik voor het in mij gestelde vertrouwen.
"Last but not least" gaat mijn dank uit naar mijn ouders, die mij in de gelegenheid stelden om te studeren en die een voortdurende stimulans zijn. Dank ook aan alle familieleden en vrienden, die in de afgelopen jaren het thuisfront steunden.

Gedurende de jaren in Engeland waren Mel's steun en enthousiasme voor mijn carrière en voor het project van de "Memory Clinic" een onontbeerlijke stimulans. De eremedaille verdient Johanna, die door haar continue belangstelling en aanmoediging in zeer sterke mate bijdroeg aan het tot stand komen van dit proefschrift. Je was voortdurend een bron van inspiratie!

CURRICULUM VITAE

The author was born on 23rd February 1947 in Rotterdam, the Netherlands. In 1965 she obtained the diploma Gymnasium-beta in Rotterdam and commenced Medical School at Leiden University, where she graduated in 1973. After six months as a Registrar in General Surgery at the Nebo Hospital in The Hague, she started her training in General (Internal) Medicine at the Westeinde Hospital in The Hague in 1974. Having completed this training in March 1979, she moved to London, UK, where she worked at the National Heart Hospital, the Paddington and Kensington Chest Clinic, and the Brompton Hospital until October 1982.

From October 1982 till October 1984, she received her training in Geriatric Medicine with Prof. A.N. Exton-Smith at the Department of Geriatric Medicine, University College Hospital London, UK.

From October 1984 till October 1986, she was Locum Consultant in Geriatric Medicine at Lewisham and Hither Green Hospitals, London.

Her appointment as internist/geriatrician at the University Hospital Dijkzigt, Rotterdam, The Netherlands, followed in April 1987.