Cognitive impairment in elderly people

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Cognitive Impairment in Elderly People

Predisposing Factors and Implications for Experimental Drug Studies

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Contents

Summary	459
1. Cognitive Aging in Healthy Individuals	461
1.1 Cognitive Function and Age	461
1.2 Cognitive Decline: When and at What Rate?	461
1.3 Health-Related Factors and Biological Life Events	462
1.4 A Summing Up: What is Normal Cognitive Aging?	463
2. Pathological Cognitive Aging: Concepts and Diagnostic Criteria	464
2.1 The Borderline Between Normal and Pathological Cognitive Aging	464
2.2 Rationale of the Need for Early Diagnosis of Dementia	465
2.3 Clinical Characteristics of the Prodromes of Dementia	465
2.4 Definitions	466
2.5 The Classification of Mild Cognitive Syndromes	467
2.5.1 Benign Senescent Forgetfulness and Malignant Senescent Forgetfulness	467
2.5.2 Age-Associated Memory Impairment	467
2.5.3 Mild Cognitive Changes (Subthreshold) and Cognitive Impairment Disorders	468
2.5.4 The Global Deterioration Scale	468
2.5.5 The Clinical Dementia Rating Scale	468
2.5.6 The Cambridge Mental Disorders of the Elderly Examination	469
2.6 Comparison of the Different Criteria for Mild Cognitive Syndromes	469
3. Noncognitive and Behavioural Dysfunction in Borderline States	470
3.1 Subjective Cognitive Complaints as an Early Marker of Dementia	470
3.2 Noncognitive Problems in Borderline States	470
3.3 Age and Comorbidity	471
4. Implications for Drug Therapy	471
4.1 The Impact of Cognitive Aging Research	471
4.2 Pharmacological Studies of the Treatment of Alzheimer's Disease	472
4.3 Towards the Prevention and Treatment of Cognitive Disorders	473
5. Conclusion	475

Summary

The consequences for cognitive functioning of normal aging, depression and dementia are well known. However, the borderline between normal and pathological cognitive aging is less well understood. Recently, it has been found that

it is important to differentiate between 'successful', 'usual' and pathological cognitive aging. This article reviews existing views on this borderline.

Recently, it has been found that health-related factors, or biological life events, may determine the rate of cognitive aging. Various different, but similar, diagnostic descriptions of age-related cognitive dysfunction exist simultaneously: benign senescent forgetfulness, malignant senescent forgetfulness, age-associated memory impairment, age-consistent memory impairment, late-life forgetfulness, mild cognitive changes (subthreshold) and cognitive impairment disorders are some examples of different diagnostic categories. There are also various diagnostic tools to obtain these experimental diagnoses; for example, the Global Deterioration Scale, the Clinical Dementia Rating Scale and the Cambridge Mental Disorders of the Elderly Examination. A diagnosis is considered important for the early detection of dementia.

Pharmacological treatments are still in the experimental stage. Improvement of cognitive function has particularly been studied in clinical trials with groups of patients with Alzheimer's disease as well as patient groups with age-associated memory impairment. Future strategies may orient more towards treating symptoms of cognitive dysfunction, probably also on the basis of diagnosis of health-related factors, in age-related cognitive decline and depression.

Decreased cognitive function is regarded as an inevitable consequence of advancing age. The majority of healthy elderly people complain about forgetfulness and decreased concentration, and this compromises their quality of life.^[1] These complaints are based upon objective changes in cognitive function; it is well established that virtually all aspects of cognitive functioning deteriorate with age.^[2-5] However, not all individuals show the same rate of decline; the variability of performance in cognitive tests increasing with age.

Not only does the physiological aging process influence cognition in the elderly, but various biological factors, such as medical conditions, also have an effect. There is a borderline between so-called 'normal cognitive aging' and pathological conditions such as Alzheimer's disease (AD) which are characterised by memory problems and cognitive dysfunction.^[6] Great progress has been made in our understanding of particular brain changes in elderly patients with cognitive deficits or AD, and in our understanding of the basal mechanisms of drug action in the brain. There has also been a rapid increase in the interest of clinicians, researchers and the pharmaceutical industry in the development of new classes of drugs for the palliative treat-

ment of age-related cognitive deficits and dementing conditions.^[7-9]

However, a breakthrough in the pharmacological treatment of these conditions does not seem to be at hand. There are several reasons for the lack of progress in this respect. First, the clinical diagnosis of AD and related conditions appears to be difficult, especially differentiating these conditions from 'normal' cognitive aging in the early phases of disease.^[10] Secondly, there is a lack of information concerning possible prodromes of AD in a phase in which there is a memory problem but not yet frank dementia, and longitudinal studies are sparse. Thirdly, experimental drug research in patients who are not demented and thus do not have a clearly defined medical condition has until now been less popular than drug research in patients with AD. Yet, treatment of patients with cognitive decline in a phase in which the severity of the cognitive deficit is not too profound may bear more promise than treatment of patients with frank dementia.

This article reviews the existing knowledge with respect to the borderline between normal aging and dementia with the aim to describe the domain where future drug trials should be directed. We will describe the current knowledge about so-

called 'normal' cognitive aging (section 1) and the borderline between normal aging and pathological aging, especially with respect to cognition in the elderly (sections 2 and 3). Implications for future drug development for the treatment of cognitive aging are described in section 4.

Because the focus of this article is on the borderline, there will not be an in-depth description of neurocognitive decline with age.^[1,11,12] Reviews of cognition in dementia can be found elsewhere,^[12-15] as can reviews about the pharmacological treatment of patients with dementia.^[16-19] An overview of drug treatment studies in relation to cognitive aging will be published in a forthcoming issue of this journal.^[20]

1. Cognitive Aging in Healthy Individuals

1.1 Cognitive Function and Age

There is vast literature on the relationship between age and cognitive performance. It is now generally agreed that healthy individuals are characterised by cognitive decline during the later decades of adult life.^[4,12,21] The acquisition of new information becomes less efficient, which, coupled with a diminished retention of this information, results in substantially poorer memory performance.^[1] The ability to plan new activities, solve problems and make complex decisions is noticeably diminished.^[22] In addition, attentional processes appear to be invariably poorer in older patients than in younger ones.^[23]

Over a third of all individuals aged over 60 years complain of sleep disorders.^[24] Sleeping is closely related to arousal, which is also impaired in old age. In addition, there appears to be a general cognitive slowness, appearing especially in the performance of tasks that have to be carried out under time pressure and/or in demanding situations. A general slowing down of CNS functioning may be the cause of this problem.^[3]

A fruitful model for this slowing is provided by the notion of resources and resource reduction, as discussed by Salthouse.^[25] Briefly, any cognitive

activity requires resources, which may be time, space or energy. A reduction of resources results in a diminished capacity to process information. For a thorough overview of the evidence on this issue, the reader is referred to the excellent surveys by Birren and Schaie^[21] and La Rue.^[12]

While it is quite clearly established that elderly people (i.e. over 65 years of age), show a deterioration in cognitive functioning or cognitive efficiency, there is also evidence that this deterioration may start in middle age (around the age of 40 years). It has been found that the performance of even healthy people has already deteriorated by middle-age, at least in some categories of cognitive tests.^[26,27] Age-related cognitive problems may lie dormant for decades and only become gradually or suddenly apparent as the patient realises that some aspect of his or her functioning is no longer what it used to be.

Loss of neurons in the CNS may occur as early as the fourth decade of life.^[28] Problems that people aged 40 to 60 years experience may have to do with the fact that cognitive functions and abilities deteriorate, giving rise to defective memory function, decrease of cognitive energy, especially in demanding situations, and lack of concentration and attention. These problems often arise at work and can cause problems in family and other relationships, resulting in an increased use of the social security system, healthcare facilities and drugs. The problems of middle-aged people in their work or social relationships are usually ascribed to social causes, but they might also be the consequence of decreased cognitive functioning.

Emotional changes may occur in the elderly, either due to social or material losses, or as a consequence of the knowledge that many faculties have been lost or are diminished.^[3]

1.2 Cognitive Decline: When and at What Rate?

There are 2 competing theories relating to the evolution of cognitive changes.^[27] The *continuous decline hypothesis* states that the decline starts early in life and gradually goes on or accelerates

with age, whereas the *terminal drop hypothesis*^[29,30] implies that the decline manifests itself abruptly. Terminal drop may occur after a major event, e.g. related to physical health such as an infective disease, resulting in a sharp decrease in cognitive performance. Of course, terminal drop is more likely to occur in the second half of the life span, but because life expectancy has become much longer during the last century, this period can extend over the fourth to the ninth decades of life.

Unfortunately, the majority of cognitive aging research performed until now has focused on performance differences between young adults (mostly students) and elderly patients. As a consequence, there is little information about cognitive deterioration in middle-age, although some work has been done in this area.^[31,32] Studying individuals aged between 30 and 60 years is essential to gain insight into functional development during adulthood and to obtain knowledge about which functions decline when.

In this respect it is important to discern individual and group norms. As most studies of cognitive aging are cross-sectional (i.e. studying two or more age groups at one point in time), there is a distinct possibility that studies reporting gradual cognitive decline are merely an artefact of the older age groups containing more individuals who perform poorly.^[27] This could be because more elderly than younger individuals are in the period between terminal drop and death. This number increases with group age, causing the average group performance to be poorer. Incidentally, this would also result in higher group variance, a phenomenon often encountered in cross-sectional research. Individual age-performance trajectories, as Rabbitt and Go-ward^[33] put it, may differ widely and yet result in a steadily declining overall trajectory.

Another possibility is that most individuals do indeed show a gradual decline with age, perhaps as a result of the accumulation of effects of minor brain dysfunction.^[26,32] At first, these minor pathologies may have little impact but, as they accumulate with advancing age, their amassed effects result in perceivable cognitive deficits. Terminal

drop would then only occur as a result of some major pathology.

This latter possibility is clearly the more optimistic one, as it paves the way for adding life to the years. As yet, we do not know which of the two possibilities, or some combination, might apply.

Does continuous decline or terminal drop exist to a comparable extent for all different cognitive functions? This is unlikely, as it is known that even memory is not a unitary function and particular aspects of memory, e.g. recognition memory, appear to remain relatively intact in later life.^[34] The decline of sensory and perceptual performance^[35] and physical performance^[36] can have great impact on general cognitive functions, but there need not be any direct or causal relation to cognitive performance. Any loss of memory may well lag very much behind perceptual loss, or not occur at all. Likewise, 'executive function' appears an important mediator of age-related dysfunction, as it has been shown that after correction for executive function, age was not a predictor for test performance.

1.3 Health-Related Factors and Biological Life Events

With regard to the question of what factors might influence cognitive decline apart from chronological age, there is increasing interest in the factor of health. Up to a few years ago there were no reports on the influence of health-related factors on age-related cognitive decline. Of course, cognitive dysfunction in relation to well established disease states such as brain trauma, depression and alcoholism are well documented. However, the issue at stake is whether conditions with an unknown or ambiguous relationship with cognitive (dys)function, such as very mild closed head injury, social drinking, borderline hypertension, anaesthesia or diabetes mellitus, have some influence on cognitive functioning.

Recently, the term biological life events (BLE) was proposed to define 'those factors that are related to physical or mental health, experienced at any point in life and thought to be related to brain dysfunctioning, other than grossly impairing con-

ditions like dementia and brain trauma'.^[26,32,37,38] BLE are factors with potential, but until now unproven, influence on the brain. Mild head trauma, operation under general anaesthesia and history of alcohol (ethanol) consumption are examples of BLE. We have shown that the performance on particular memory tests does not decrease with age until 80 years of age in BLE-free patients, whereas performance in BLE patients is seriously compromised from the age of 60 years.^[38,39] Follow-up research showed that elderly patients with memory disorders have experienced BLE in their life significantly more often than matched controls.^[32]

Furthermore, they are more characterised by soft indices of brain dysfunction such as primitive reflexes.^[40]

Recently, researchers have called for more extensive population-based studies in which the complex interplay between health and cognition would be investigated, as well as the natural history of cognitive performance and change, in order to identify environmental factors associated with cognitive preservation or deterioration.^[41,42] Interestingly, Haxby et al.^[43] have already found that the effects of age on visual memory were much smaller than those usually reported in the literature after 'rigorous health screening' of the patients studied. Likewise, Christensen et al.^[44] provided evidence in favour of the notion that careful assessment, selection and description of patients, as well as further attention to health status, is needed to aid interpretation of cognitive aging research.

Other possible health-related factors which may influence cognitive aging are mild hypertension,^[45] medication and exposure to neurotoxic factors.^[38,46]

Subtle health-related factors are potentially important to cognitive aging. We assume that they are not severe enough to cause any acute or perceivable trouble for the individual, but that they still have some long term impact on brain functioning and cognition. Thus, although the patient is considered to have recovered, it is likely that the brain has suffered some functional damage which cannot be diagnosed. This suggests that healthy individuals with BLE may be on the border between normal

and pathological aging, and are more vulnerable to accelerated cognitive decline.

An additional problem in cognitive aging research is that the tests that are used for neuropsychological assessment of the elderly are characterised by a lack of norms for the majority of the relevant tests. Normative data, which take health-related factors and education into account, are as yet nonexistent. However, in order to differentiate normal age-related functional decline from pathological functional decline, we have to know how healthy adults of all ages perform the test used to evaluate the function. Furthermore, as there may be interactions in effects on performance between age on the one hand, and sex, education and health variables on the other, age norms should ideally be based on data obtained from various subgroups within a given age category. Lack of properly divided tests with good norms and in-parallel versions is also quite an impediment for the proper execution of drug trials aimed at treatment of cognitive decline.^[47]

1.4 A Summing Up: What is Normal Cognitive Aging?

The finding of large interindividual differences in a group of patients who can be regarded as normal by any standard used in the experimental literature raises the issue of normality.^[26,32,38] Usually, an operational, statistical definition of normality is used; observations are regarded as normal if they fall within some fixed boundaries, for instance in the middle 90% of their range.

Rowe and Kahn^[48] stressed in their theoretical review of aging that the variability of a given parameter, for instance performance on a memory test, increases with age. The authors paid attention to the heterogeneity even in normal groups, i.e. disease-free groups of elderly people. They argued that a distinction should be made between 'successful' and 'usual' aging. Successful aging refers to changes that are intrinsic to age itself, whereas usual aging is the result of aging plus all non-pathological deficiencies that occurred earlier in life. These deficiencies are not intrinsically related

to the process of aging *per se* but they are closely associated with aging because their effects are greater in old age (due to increased vulnerability or reduced resistance).^[32,38] In addition, the chance of being affected by these deficiencies increases with age.

The notion of the normality of usual aging implies the harmlessness of several possibly health-threatening factors, such as BLE. Normality also implies that what is usual is also natural and cannot, or should not, be modified. This notion of 'normality' puts too much emphasis on the level of functioning of most elderly individuals, instead of attempting to explain the reason for the increased heterogeneity. 'It tends to create a gerontology of the usual'.^[48]

Stones et al.^[49] have identified 4 different types of aging (see table I). With this model of multiple types of aging, it becomes understandable why age-associated decline can accelerate and why the variability increases with age, 2 trends often observed in aging research. The frequency of aging types 2 to 4 must increase with age, as these age-linked conditions and processes are irreversible in most cases, and any brain dysfunction that is caused by them is likely to be permanent. The onset of these age-extrinsic conditions can be assumed to vary between individuals. The aggregated deleterious effects of pathology or lifestyle on the average performance in a random sample of patients is therefore expected to accumulate with age. Conversely, processes that are age-intrinsic (primary aging) are more likely to cause a linear decline of cognition with age, if a given function is to decline at all as a result of primary aging.

It has been hypothesised that BLE constitute a biological substrate for nonpathological deficiencies that are associated with usual aging (type 2).^[38,39] Subdivision of patients based on whether they have a history of BLE can be equated to the distinction between successful and usual aging, i.e. between aging types 1 and 2. This hypothesis should be investigated further in the light of the fundamental issue about when age-associated changes can be regarded as age-intrinsic, i.e. phys-

Table I. Types of aging

Type	Characteristics
Primary (or successful) aging	Functional changes intrinsic to age
Usual aging	Nonpathological deficiencies added to the age-intrinsic processes of successful aging
Secondary aging	Pathology-related decrements added to nonpathological aging
Tertiary aging	Pathological aging plus the effects of terminal illness. Tertiary aging can thus be roughly equated to the 'terminal drop' phenomenon ^[30]

iological, and when the aging process is usual but disease-free.

2. Pathological Cognitive Aging: Concepts and Diagnostic Criteria

2.1 The Borderline Between Normal and Pathological Cognitive Aging

The borderline described in the preceding sections is especially relevant in relation to dementing conditions and their prodromes. The most common form of dementia is AD, which accounts for 50 to 70% of all cases of dementia. It is evident that an insidious and progressive disease such as AD does not manifest itself from the very beginning as the complete syndrome of dementia. Early in the course of AD, the patient may exhibit mild memory impairment and changes in other mental domains that are not sufficiently severe to merit the diagnosis of dementia. Recognising these prodromes of dementia is one of the most complex diagnostic problems to date.

This section summarises what is known about this 'grey area'. Definitions of dementia and AD are given to show the vague boundary between dementia and non-demented conditions; this is especially relevant because there is no uniformity in assessment strategies and classification systems with regard to the borderline.

2.2 Rationale of the Need for Early Diagnosis of Dementia

From a scientific point of view, the diagnosis of 'early' AD helps to clarify epidemiological aspects such as the natural history of the disease, which is of major importance for planning and developing healthcare facilities. The lack of clear diagnostic criteria for early AD is reflected by the estimates of its prevalence. In contrast to severe dementia, in which the prevalence is remarkably consistent in various studies (about 5% of the population over 65 years of age), the prevalence of mild dementia ranges from 2.6^[50] to 21.9%, and even up to 52.7% in one Japanese study.^[51] The main reason for this extreme variation is probably differences in the criteria and methods used to identify mild dementia^[51,52] and problems with regard to the definition of the boundary between normal aging and pathological conditions.

From a clinical point of view, the need for an early diagnosis is also of vital importance. A significant minority of patients with the diagnosis of dementia have treatable conditions,^[53-56] and treatment of these diseases is expected to be more successful in the early stages^[57,58] before changes in the brain have become structural.^[19,59] In addition, it is of great importance to have diagnostic methods which accurately differentiate those patients with mild dementia from those with more benign forgetfulness, because of the public's growing awareness of dementia as a major health problem and the corresponding anxiety associated with this awareness.^[60-63]

2.3 Clinical Characteristics of the Prodromes of Dementia

The onset of AD is often dated in retrospect and with imprecision. Information from relatives can provide a lot of insight into the very first prodromes but these data are largely anecdotal. Typically, predemented patients demonstrate feelings of anxiety, worry, depression and psychological vulnerability although these feelings are less pervasive than those in patients with major depres-

sion.^[64-66] Inner feelings may be more dependent on environment: patients become calm when reassured, but they may be unable to cope with even a small amount of stress.^[64,65] Passivity, loss of interests, and coarseness may be common features. Patients appear less spontaneous and extroverted, and more withdrawn.

Some features of this syndrome reflect disruption of compensating abilities, such as a tendency to tire easily and difficulty adjusting to events that are not part of a daily routine, whereas other features are more likely to be secondary phenomena, such as withdrawal, anxiety and a tendency to worry.^[65,67-70] Although the predemented patients themselves may not notice these changes, their relatives probably do.^[71,76]

This picture of 'predementia' or prodromes of dementia should be regarded as tentative. It is not known if all patients with AD present with a similar picture to the one described here. Moreover, we do not know the predictive value of predementia. To date, no clear diagnostic categories adequately classify this clinical picture. The patient's state may be too subtle to be described in reliable research criteria. A qualitative approach, i.e. a detailed psychopathological description, is probably the most adequate approach. The importance of a qualitative assessment is underlined by the relative lack of specificity of the traditional psychometric tests.^[15]

Neurological examination probably does not reveal any abnormalities, nor do ancillary data such as those obtained from laboratory or neuro-imaging investigations,^[77,78] although there may be an increase in 'soft' neurological signs early in the course of illness.^[40] The patients may perform within normal ranges on traditional psychometric tests of memory, but may need more time to complete tasks and show a tendency to tire and slow down when testing takes too long.^[13,15,51,79]

If memory is impaired, this can usually be identified by tasks measuring delayed recall.^[64,65,79,80] With respect to the search for biological markers to distinguish between AD, and normal and borderline states, until now none of these markers has proven successful in individual patients given the

findings obtained by computed tomography (CT),^[81] single photon emission computed tomography (SPECT)^[82] and magnetic resonance imaging (MRI).^[83,84] Given the lack of reliable and valid aetiologically based objective tests, the diagnosis of early AD is still based on detailed clinical description, differentiation from normality and other behavioural diagnoses (e.g. depression), neuropsychological examination, and follow-up studies.^[74,85,86]

2.4 Definitions

Considerable progress in the accurate diagnosis of dementia has been made in the last decade. Consensus procedures have yielded operational criteria for the clinical diagnosis of dementia and the main dementing illnesses.^[87-90] Although dementia is now generally regarded as a clinical syndrome and not as a disease, important differences exist in the interpretation of this notion.

The term dementia is used by some researchers to denote a clinical condition defined only by observable behaviour, irrespective of its aetiology. For instance, in the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Diseases Association (NINCDS-ADRDA) criteria for clinical AD states it is proposed that 'dementia is a diagnosis based on behaviour and cannot be determined by computerised tomography, electroencephalography, or other laboratory instruments, although specific causes of dementia may be identified by these means'.^[89] The consequence of this definition is that dementia can be caused by both organic and functional disorders.

Other researchers limit the definition of dementia to organic aetiologies. For instance, the DSM-IV states that 'either there is evidence . . . of specific organic factor(s) judged to be aetiologically related to the disturbance, or, in the absence of such evidence, an aetiological factor can be presumed if the disturbance cannot be accounted for by any nonorganic mental disorder, e.g. major depression accounting for cognitive impairment'.^[91] Still, others have extended the definition of dementia to in-

clude characteristics of irreversibility or a progressive course.^[92]

The most widely used definitions of dementia to date are those of the DSM-III-R and DSM-IV.^[87,91] In short, the DSM definition involves a combination of memory impairment with impairment in at least one of the domains of abstract thinking, judgement, aphasia, apraxia and agnosia, constructional difficulty, or deficits in executive function. The impairment must be severe enough to interfere with social functioning. It is important to note here that the DSM-IV definition implies the acceptance of some degree of heterogeneity; not all cognitive domains are necessarily affected. Virtually all current research studies make use of the DSM-IV criteria, except for the last criterion concerning the presumed organic aetiology.

With respect to criteria for the diagnosis of AD, 2 sets are widely used: the DSM-IV criteria for Primary Degenerative Dementia of the Alzheimer type (PDD)^[91] and the so-called NINCDS-ADRDA criteria.^[89] The latter criteria are comparable with those of the DSM-IV, but are more elaborate and better operationalised.

The NINCDS-ADRDA criteria differentiate between possible, probable and definite AD. A diagnosis of definite AD can only be made when the criteria for probable AD are fulfilled and when there is histopathological evidence from biopsy or autopsy. Probable AD is defined by the presence of dementia, an onset between 40 and 90 years of age, and the absence of systemic disorders that themselves could account for progressive deficits in memory and cognition. A diagnosis of possible AD is made when there are variations in onset, presentation, clinical cause or in the presence of a second possible dementing disorder, which is clinically not considered to be the course of dementia. Allowance is made for plateaus in the course of progression or in the presence of associated psychiatric, somatic or neurological symptoms.

The most widely used clinical criteria for vascular dementia are those of the DSM, based on clinical description. The features are not defined in detail and leave much room for interpretation.

Ischaemic scales have long been used for the diagnosis of vascular dementia.^[93,94] More recent criteria have also paid attention to the temporal relationship between dementia and stroke, the number of strokes, and brain imaging data.^[88,90,95,96]

2.5 The Classification of Mild Cognitive Syndromes

The differentiation between dementia and normal states has been especially problematic. In the past 30 years, several attempts have been made to define the clinical and neuropsychological features

the borderline state between normality and frank dementia. As early as 1958, Kral^[97] introduced the terms benign and malignant senescent forgetfulness (BSF and MSF) to describe memory complaints of the elderly people he studied. Since then, investigators have tried to describe these states in more detail, e.g. very mild or mild cognitive decline,^[98] questionable dementia,^[99] minimal dementia,^[92] age-associated memory impairment (AAMI),^[100] age-consistent memory impairment and late-life forgetfulness.^[101] In addition, the DSM-IV includes a new category, age-associated cognitive decline.^[102,103] However, the nosological status of many of these proposals is still unclear, especially regarding the extent to which they are related to dementia.^[104]

Nevertheless, the concepts provide a good starting point especially because clear and unequivocal diagnostic criteria are a prerequisite for development of therapeutic strategies for patients with cognitive complaints. The main concepts are described below.

2.5.1 Benign Senescent Forgetfulness and Malignant Senescent Forgetfulness

The concepts of BSF and MSF were introduced more than 30 years ago and probably represent the earliest attempt to distinguish clinically between normal age-related memory changes in the elderly and those forms of memory change with a worse prognosis.^[97] The terms have often been used in the medical literature and have become a generally accepted notion among clinicians.

The presentation of BSF is '... patchy and variable, with difficulties remembering details of experiences (names and places), but with relative ease in recalling the experiences itself. Usually, the forgotten details are recalled later'.^[97] The condition is not progressive and does not increase the risk of developing dementia. In contrast, MSF is characterised by an inability of the patient to recall events in the recent past, disorientation with regard to personal data, and retrogressive loss of remote memories. Patients with MSF remain unaware of their deficit and frequently produce confabulations.

BSF and MSF were never appropriately defined in operational terms. As a consequence, research data on the reliability of the criteria are sparse; few data exist on the prognostic value of BSF. Kral carried out a 4-year follow-up study with 20 patients with BSF and 34 with MSF; only 1 patient with BSF deteriorated cognitively, whereas all patients with MSF did.^[105] Death rates in BSF and MSF also differed significantly from one another: 38% vs 61.7%, respectively, after a 4-year observation period. Recently, a 3-year follow-up study of patients with supposed BSF was reported by O'Brien et al.^[74]: 6 of the 68 patients with BSF (9%) became demented, which was about twice the expected rate. These findings cast doubt on the view that BSF always follows a benign course. Because of the ill-defined criteria and their uncertain nosological status, the use of the terms BSF and MSF cannot be recommended for research and clinical purposes, in spite of their widespread popularity.

2.5.2 Age-Associated Memory Impairment

The term AAMI was introduced by Crook et al.^[100] and denotes a condition in otherwise healthy middle-aged or elderly individuals (50 years or older) who complain about memory loss and who score at least 1 standard deviation (SD) from the mean for younger adults on neuropsychological tests of secondary memory. The AAMI criteria were provisionally established in order to have an operational definition of 'normal' cognitive aging. In relation to the discussion on 'normality' in section 1.7, AAMI is partly associated with usual

aging and partly with secondary aging. In addition, patients who are in the prodromes of dementia may be diagnosed with AAMI.

Blackford and LaRue^[101] criticised certain aspects of the AAMI concept, including the omission of an upper age limit, the omission of any means of quantification of subjective complaints, the criterion that 'performance is 1 SD below the mean established for young adults on a standardised test for secondary memory' (which precludes the use of tests developed especially for old-aged populations), and the likelihood of meeting the above-mentioned criterion when more tests are administered. Besides, the AAMI criteria provide a minimum for the deviation in memory performance (at least 1 SD), but no maximum, although dementia should be ruled out.

Blackford and LaRue^[101] added to AAMI the following new categories: age-consistent memory impairment (ACMI) for performance within 1 SD of the mean established for age on 75% or more of the tests administered, and late-life forgetfulness to denote performance between 1 and 2 SD below the mean established for age on 50% or more of the tests administered.

Data on the reliability and validity of the AAMI criteria have not been published yet. Furthermore, no longitudinal data have been reported and, therefore, the prognostic significance of the AAMI concept remains unsettled. The use of the term AAMI in clinical practice is limited. Nevertheless, the criteria are well defined operationally and provide a basis for selecting study participants in order to study the epidemiology, course and clinical significance of normal aging, and to evaluate the effect of pharmacological or other forms of intervention.^[106,107] More refined criteria have been proposed which may make the AAMI concept, in a revised form, more fruitful for clinical use.^[108]

2.5.3 Mild Cognitive Changes (Subthreshold) and Cognitive Impairment Disorders

The DSM-IV includes a new category of 'mild cognitive changes (subthreshold)' as part of the class of cognitive impairment disorders.^[103,109,110] In contrast to the DSM-III, the DSM-III-R speci-

fies the severity of dementia in terms of functional capacity.^[87] The prognostic value of the DSM-III criteria for the mildest stages of dementia is high when applied by experienced clinicians in selected patient groups.^[111,112] In field studies, however, the criteria seem to be less accurate.^[113]

2.5.4 The Global Deterioration Scale

In 1982, Reisberg and co-workers^[98] presented the Global Deterioration Scale (GDS) for the grading of primary degenerative dementia. The GDS is one of the most widely used clinical instruments to stage the course of cognitive decline and AD. The scale describes cognitive and behavioural changes in 7 stages.

- Stage 1 describes 'normality' (no complaints, no deficits).
- The description of stage 2 ('very mild cognitive decline') is rather nonspecific.
- The characteristics of stage 3 ('mild cognitive decline') are more specific, but they refer almost exclusively to memory or related cognitive domains.
- From stage 4 onwards the DSM-III criteria for dementia are amply met.

The prognostic properties of the various stages are reasonably established. Generally, GDS stage appears to be a major predictor of decline: patients in stage 2 have a low risk of declining in the following years, whereas a large proportion of the patients in stage 3 and more so in stage 4 show cognitive decline. It has been suggested that a GDS score of 2 reflects normal aging (i.e. 'usual' aging in terms of the earlier discussion) in practically all patients, whereas GDS stage 3 represents borderline cognitive functioning. From stage GDS 4 onwards, a progressive course of decline is likely.^[98]

2.5.5 The Clinical Dementia Rating Scale

The Clinical Dementia Rating Scale (CDR)^[99] rates the severity of dementia as questionable, mild, moderate or severe (scores of 0.5, 1, 2 or 3, respectively). The individual performance is rated separately in each of the categories of memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. From these ratings, an overall CDR score is calcu-

lated according to a complicated algorithm. The criteria carry high face validity and are based on a wide range of cognitive activities in daily life. Memory performance in daily life is considered to be the central criterion, while the other features are regarded as secondary.

Interrater reliability and construct validity of the CDR have been demonstrated.^[114] The scale has been documented by several longitudinal studies, which make the CDR probably the best-tested rating scale for staging dementia to date.^[115] The CDR is considered to be a well-documented scale for rating dementia in selected samples. The CDR is more difficult to administer than the GDS. From CDR stage 1 onwards a deterioration of cognitive functioning can be reliably predicted, whereas CDR stage 0.5 reflects the borderline state.^[99]

2.5.6 The Cambridge Mental Disorders of the Elderly Examination

The Cambridge Mental Disorders of the Elderly Examination (CAMDEX) consists of a standardised psychiatric interview with the patient and caregiver, and a brief neuropsychological battery (the CAMCOG).^[92,116] The CAMDEX was especially designed for the detection of early dementia and describes 4 syndromes as guidelines for the staging of dementia: minimal, mild (early); moderate and severe dementia. In contrast to the GDS and the CDR, the CAMDEX can be used to obtain a syndromal and aetiological diagnosis. The CAMDEX criteria should be used in a 'flexible manner', leaving 'some room for clinical judgement'.^[116]

The face validity of the CAMDEX is high and the interrater reliability is good.^[92]

In some recent studies of longitudinal follow-up design in which the CAMDEX was used to assess patients, it was concluded that, although the CAMDEX criteria were in general feasible, the criteria for minimal dementia were difficult to apply in clinical practice.^[117,118] Errors in the diagnosis of minimal dementia occurred, especially in people of below-average intelligence, in the old and frail, and in patients with sensory impairments. The need for repeated assessments over lengthy periods was

stressed in order to document the natural history of dementia correctly.

2.6 Comparison of the Different Criteria for Mild Cognitive Syndromes

Comparison of the different concepts and criteria discussed above shows that there is considerable overlap in clinical characteristics. At the outset, there are few differences between Kral's BSF and Reisberg's very mild cognitive decline (GDS stage 2). Likewise, stage 3 of the GDS closely resembles the description of very mild cognitive impairment of the CDR (CDR score of 0.5) and the CAMDEX definition of minimal dementia, whereas GDS stage 4, CDR stage 1 and CAMDEX mild dementia are all highly compatible with the criteria for mild dementia as defined by DSM-III-R. However, the concepts differ,^[119,120] and thus the comparison of the results of these studies should be approached with some caution.

From the results of the follow-up studies on the prognosis of early AD, as defined by the different criteria, it can be concluded that the likelihood of further cognitive decline is low (but not zero) for patients with mere memory complaints classified as BSF or GDS stage 2; intermediate for patients with questionable dementia, GDS stage 3 or CAMDEX minimal dementia; and high for patients with GDS stage 4, DSM mild dementia, CAMDEX mild (early) dementia and CDR stage 1. Stated in another way, patients who complain only about poor memory, without objective evidence of impaired memory and who perform well in daily activities cannot be regarded as being at high risk of developing dementia. In contrast, those who demonstrate objective cognitive impairments that interfere with social functioning probably will develop dementia.

It should be considered that these studies were performed with selected samples. It is still impossible to accurately predict the outcome in individuals with mild cognitive changes.

3. Noncognitive and Behavioural Dysfunction in Borderline States

3.1 Subjective Cognitive Complaints as an Early Marker of Dementia

With respect to the differentiation of a dementing condition from 'normal' aging, it is important to know whether the judgement of one's own memory (often referred to as metamemory)^[121,122] reflects objective cognitive functioning and whether memory complaints have diagnostic meaning. Complaints of memory are quite common in elderly and middle-aged individuals. In fact, in 1 study no less than 73% of the 40-year-old patients and 91% of the 70-year-old patients reported difficulties in remembering.^[71]

Although the growing interest of the public media in dementia and AD may have increased the awareness of memory deficits as a possible first sign of mental deterioration,^[60-62] much evidence suggests that memory complaints in older adults correlate to a large extent with depression, but only modestly with their performance on objective memory tests.^[71,73,123] However, the finding that the association of subjective complaints with depression is stronger than with dementia should not be interpreted too dichotomously, since depression may also be a presenting symptom of AD.^[124] Moreover, a recent study reported that relatives' assessments of patients' memory, measured by standardised questionnaires, were a reasonable predictor of dementia, with an overall classification accuracy rate of 74%. This rate was improved by 11% when objective memory tests were also used.^[73]

These findings emphasise the diagnostic importance of taking a history from a relative or other informant who can report on the premorbid behaviour of the patient. Because metamemory is a poor predictor of cognitive decline in patients who are already demented, it would be of interest to investigate whether complaints of one's decreasing cognitive functions anticipate manifest dementia.

3.2 Noncognitive Problems in Borderline States

There is good evidence that deficits of memory are among the earliest features of AD.^[94,112,125] However, this does not mean that impaired memory is a prerequisite for the diagnosis of AD in its prodromal stage. That which has to be proven is accepted as proof when memory impairment is considered to be the main characteristic of the preceding stages of dementia.^[79] Interestingly, a large amount of evidence from epidemiological and descriptive studies shows that noncognitive symptoms are equally prominent in the disintegration of psychological organisation. These symptoms involve perception, motility, personality organisation, emotional experience and volition.^[126-128] In addition, the continuum between patients characterised as normal and those with pathological cognitive decline is also found for noncognitive behaviour. For instance, a study of randomly selected women aged from 70 to 79 years yielded a smooth and unimodal distribution of cognitive function and behavioural changes.^[129] Recently, Berrios has challenged the view that prodromes of dementia should be defined as a form of 'minidementia', i.e. only differing quantitatively from dementia.^[126]

The most frequently studied noncognitive aspects of early AD are changes in affectivity and personality. Depression can be related to age-related cognitive decline and prodromes of dementia in several ways: depression may present with the clinical picture of dementia ('pseudodementia'),^[130] it may coexist with dementia, or depression may precede dementia.^[124,131] Furthermore, dementia, notably the subcortical types, can mimic depression, and both conditions may develop independently from one another.^[132]

The notion of depression being an early manifestation of dementia is still under debate. In a retrospective study, the relatives of patients with AD reported depression and agitation as being the first symptoms of dementia in about 40% of the patients.^[133] In prospective studies, depressive symptoms in combination with cognitive deficits

in elderly patients were also found to increase the risk of the patient developing subsequent dementia.^[124,131] However, other studies did not report an increased prevalence of depressive symptomatology in patients who subsequently developed dementia.^[128,134]

The results of these studies have to be evaluated carefully, because the definitions used for depression and dementia may be different from those adhered to today.^[86]

In summary, patients with depressive symptoms and cognitive deficits may often have prodromes of AD. However, these patients have unfortunately been rejected from participation in most studies of AD, probably due to a dichotomous view in which depression and dementia are regarded as mutually exclusive. More refined clinical and neuropsychological descriptions and prospective neuroimaging and neurochemical studies should be carried out in order to elucidate the relationship between depressive symptoms and mild dementia.

With respect to studies into personality changes in AD, it has recently been shown that AD patients become more passive, more coarse and less spontaneous. The personality changes occurred early in the course of the disease and could not be attributed to the decline in intellectual function.^[69] Similar profiles (diminished initiative, loss of self-confidence, decreased extroversion, growing apathy, relinquishment of hobbies, and increased rigidity) have also been found in other studies.^[64-68] Many patients had subtle personality changes long before dementia became clinically manifest.

Thus, personality changes are likely to be among the earliest features of AD and are evident in the phase preceding dementia. Although the assessment of personality in patients with dementia presents unusual and difficult methodological problems, personality changes should be seen as a marker of early AD and warrant further investigation.

3.3 Age and Comorbidity

It should be noted that most of the research into AD has been carried out in relatively young, healthy patients even though dementia is more prevalent

among the older and more diseased population. Older populations show higher levels of comorbidity. The relevance of this aspect has been noticed in field studies in which particular diagnostic errors in very old patients and those with significant comorbidity were noted.^[117]

Older patients are more difficult to investigate appropriately. Many of these patients live in nursing homes or other protected environments, where criteria for social and functional decline are harder to meet than in younger patients who are still working.^[135] Moreover, samples of older patients will inevitably suffer more from methodological flaws such as higher mortality figures and more loss at follow-up. Therefore, data from studies using relatively young patients cannot be directly applied to a typical geriatric population. It seems likely that the detection of a prodrome of AD and early AD in young, healthy patients requires a different approach to that for older patients. These aspects have generally been neglected so far in research of the borderline between normal aging and dementia, and the earliest stages of AD.

4. Implications for Drug Therapy

4.1 The Impact of Cognitive Aging Research

Research into cognition in usual aging, AAMI and dementia has a common problem, namely the profound heterogeneity within groups of patients.^[136] Many health-related factors and disease states, as well as education and psychosocial factors, contribute to the pattern of cognitive and noncognitive deficits and complaints.^[137] The clinical syndrome of dementia is heterogeneous whereas AD may consist of several different nosological entities.^[138,139]

Unlike primary aging (see table I), secondary and tertiary aging are associated with other factors in addition to age. As discussed in sections 2.3, 3.1 and 3.2, the syndrome of complaints and functional deficits in usual aging and in the putative prodromes of dementia are not uniform in the sense that 'only' memory or 'primarily' memory is affected.

On the contrary, a number of cognitive and noncognitive functions are affected (section 3).

This has considerable implications for therapeutic strategies in the field of age-related cognitive deficits. A major point concerns the choice of patient population as a target. Patient groups with AAMI or ACMI may contain quite a number of individuals who have very early AD. Drug treatment of this group may be of relevance in order to prevent or postpone the onset of AD. Another relevant aim may be the treatment of noncognitive behavioural problems in this group (e.g. symptoms of mood disorder or lethargy) as these have an important impact on the functional capacity of the patient and his or her quality of life. A third aim may be the development of strategies for patients who complain of cognitive dysfunction but who may never develop dementia, yet are handicapped in their daily life.

There is increasing evidence that patients who are not demented but who do have objective cognitive deficits on neuropsychological investigation should be characterised as a disease group: the new classification of the DSM-IV, 'age-associated cognitive decline',^[102] may improve the possibility of targeting these patients for drug development.

It may be important to discern various subgroups within the heterogeneous group of non-demented patients with impaired cognitive functioning, e.g. those with BLE and those without (see section 1.3). Patient groups for drug studies can be made more homogeneous, which would improve the detection of possible drug effects. The rationale is that the pathogenesis of the cognitive decline can be expected to differ for the various subgroups.

Similarly, it may be of interest to search for drug effects in non-demented elderly people who have an abnormal profile of apolipoprotein E4 (Apo E4), as this substance has been implicated in AD.^[140] Likewise, other biological markers could be used to select non-demented individuals with cognitive impairment for experimental drug studies. Measurement of hippocampal atrophy or pupillometry could be relevant in this respect because of findings in recent years, which suggest that patients with

hippocampal atrophy^[84] or with abnormal pupil reaction to low doses of tropicamide^[141] may be individuals in the borderline between normal aging and dementia.

4.2 Pharmacological Studies of the Treatment of Alzheimer's Disease

Current research into the effects of experimental drugs in the treatment of AD and AD-related conditions has met with difficulties. Through the years, it has appeared that the majority of studies have been characterised by methodological flaws.^[142] The patient groups tend to be too heterogeneous, particularly with regard to symptoms and severity, there is a lack of sensitive and reliable evaluation measures, and the length of the treatment period may differ considerably from study to study (see also Hijman et al.^[47] for discussion). Furthermore, no reference or benchmark drug exists and patients often experience adverse effects in these studies.

The tacrine experience illustrates these problems. Although tacrine has been given the benefit of the doubt by many world markets,^[143] it is not registered in several countries, including The Netherlands, because of its adverse effect profile. A 40% chance of a positive response set against a 60% chance of severe adverse events is a cost-benefit problem.

Finally, statistically significant results on some psychometric measures are not always reflected by clinically relevant findings. For instance, an improved score on a memory test without a concomitant improvement in daily life activities is not relevant from a clinical point of view.

AD drug studies performed in the last decade have shown that it is not a fruitful strategy to treat AD as a disorder of memory. Memory is not a unitary function but consists of various subprocesses which are dependent on different neurotransmitters and centres in the brain. Thus, many classes of drug can be used for the treatment of memory disorders.^[144] Besides, AD is not a one-neurotransmitter disease; various neurotransmitters are affected and these are related to a variety of cognitive behaviours from memory to problem solving.^[145,146]

Drugs with possible treatment efficacy could thus be based upon an action at various different neurotransmitter systems. This is especially the case because behavioural problems in AD and related conditions such as mood disorders, lethargy, personality changes, anxiety, and in patients with more severe disease, restlessness, wandering, psychosis and aggression require treatment as much as the cognitive problems do.^[147,148] Until now, researchers involved in drug development have been disproportionately interested in the cognitive symptomatology.

Finally, there is a lack of research directed at the early stages of AD (e.g. GDS stage 3). In addition, there have not been many clinical trials on possible prodromes of dementia.^[149] It has been argued that this is the best time to treat patients with agents which can halt or slow the deterioration, but researchers have been somewhat reluctant to go deeper into this matter. It is possible that the fact that mild cognitive disorder has until now not been regarded as a nosological or disease entity is the reason for this reluctance.^[16] The development of strict criteria for the prodromal or 'predementia' phase of AD and of methods for its clinical diagnosis would be an important step in the right direction. The treatment of AD in its predementia phase would then be possible because AD is a nosological entity.

Table II summarises the various aims which are explicitly and implicitly present in drug treatment studies. Many have hoped to find a treatment for the cause of AD. This is something other than the symptomatic or palliative treatments which are currently the norm. Of course, a cure for the disease should be actively sought, but treatment of one or more symptoms remains of major importance. Finally, as mentioned above, the majority of studies have focused on cognitive symptoms, but the aims of treatment are different depending on whether the clinical psychopharmacological researcher sets out to reverse the course of the disease, or to postpone or slow further decline. The prevention of dementia by treatment in a very early stage is a specific example of postponing or slow-

Table II. Future intervention strategies

Causal pharmacological treatment ('cure')
Pharmacological treatment for one or more symptoms (cure, or postponing or slowing the process)
Prevention of dementia by pharmacological treatment in a predementing stage (e.g. age-associated memory impairment or related condition)
Prevention of age-related cognitive disorders by means of nutrients, vitamins, dietary supplements and/or herbal extracts
Improved pharmacological treatment, during adulthood, of depression, anxiety, insomnia, anaesthesia, neurotoxic exposure, alcohol abuse, neurotrauma with drugs that do not produce or aggravate cognitive disorders
Psychological treatment of the dementing patient, e.g. function-oriented guidance
Psychological treatment of primary care-giver
Home training of primary care-givers

ing decline. However, much research is still needed to improve the methodology of the early identification of AD.

Relevant future development may involve drugs which act upon particular brain mechanisms which underlie age-related deficits, for example, drugs acting upon the aggregation of amyloid, on the cleavage of β /A4-amyloid protein, and on the Apo E4 chaperones.

4.3 Towards the Prevention and Treatment of Cognitive Disorders

The prescription of psychoactive drugs seems to become more and more dependent on cost-benefit rationales. If it can be proven that chronic use of certain psychoactive substances accelerates cognitive aging, then clinicians should be more cautious in prescribing these drugs even when patients are still young adults.

It must be kept in mind, however, that there are many good reasons to prescribe psychoactive drugs, such as for persistent sleep disorders, anxiety, depressed mood, etc. As these conditions themselves may be accompanied by cognitive disorders,^[150,151] treatment with cognition enhancers, as opposed to classical treatments with hypnotics, anxiolytics and antidepressants, may be justified. Nevertheless, it has been argued that in many cases alternatives do exist, for example, antidepressants without

anticholinergic adverse effects (such as selective serotonin reuptake inhibitors or reversible inhibitors of monoamine oxidase type-A).^[152] Another example is the serotonin 5HT_{1A} agonist anxiolytics which act without impairing memory, and 5HT₃ antagonist anxiolytics that may even improve cognition.^[153]

Although the adverse effect profile of anti-AD drugs should be benign, in the case of treatment of cognitive disorders which are not as severe as AD, it seems reasonable to demand a total absence of adverse effects. This is another expression of the 'cost-benefit' attitude towards treating cognitive disorders that are not primarily associated with accepted pathology. Such cognition enhancers could also be used as co-medication to prevent the 'sedating' or 'cognition impairing' effects of psychoactive drugs. Examples from other disciplines illustrate this point.

In the area of allergy treatment, in the last decade there has been a major shift towards the prescription of antihistamines that lack anticholinergic adverse effects, antihistamines that do not readily penetrate the blood-brain barrier, and even antihistamines combined with CNS stimulants.^[154,155] Major reasons for the development of these 'new' antihistamines were not so much to increase their anti-allergic efficacy, but to increase their specificity so as to prevent patients with allergies from experiencing drug-induced cognitive impairment on a daily basis and hence to maintain an optimal quality of life.

In general, there is neither a wealth of research nor of clinical experience with drugs to combat the cognitive impairment induced by BLE. However, there are many interesting theoretical possibilities such as a combination of benzodiazepine anxiolytics, anticholinergic antidepressants, anaesthetic agents, alcohol (ethanol) and neurotoxic exposure with nootropic drugs or cognition enhancers. The latter category of drugs reverses or attenuates syndromes of cognitive impairment induced by cholinergic dysfunction.^[156-159]

Several piracetam analogues, i.e. tenilsetam, aniracetam, and oxiracetam,^[160,161] have been shown

to attenuate anticholinergic and hypoxic effects on cognition. The piracetam-like nootropic compounds have few adverse effects and hence could be candidate substances for co-prescription with psychoactive drugs known to impair cognition.

Finally, it is worth mentioning that many patients who are treated with antidepressant, anxiolytic or hypnotic drugs are probably attenuating their drug-induced cognitive impairment by habitually consuming products containing nicotine and caffeine, i.e. smoking tobacco and drinking coffee. Nicotine, a nicotinic cholinergic agonist, has been repeatedly demonstrated to possess the property of antagonising the effects of anticholinergic agents on cognition.^[162-164] Caffeine attenuates the memory impairment induced by cholinergic blockade,^[162] benzodiazepine-induced cognitive impairment,^[165] and even the cognitive-impairing effects of alcohol.^[166]

However, chronic use of caffeine has been shown to be associated with an improvement of cognitive performance.^[167] Also the use of nicotine, despite its known association with an increased risk of cancer, has been shown to be associated with improved cognitive performance^[168] and even with a lower incidence of AD.^[169]

Dietary supplements, vitamins, trace elements and flavonoids may prevent cognitive disorders, particularly those associated with aging, fatigue or daily intake of alcohol. Studies have demonstrated an association between the use of thiamine (vitamin B1),^[170] pyridoxine (vitamin B6)^[171] or cyanocobalamin (vitamin B12),^[172] and cognition. However, one has to assume that a depletion, whether experimental, clinical or subclinical, of those vitamins must exist to explain these effects.

Altered levels of trace elements may play a role in the development of cognitive disorders, and memory complaints may be the clinical expression of a disturbed balance in micronutritional elements, such as trace elements or minerals. We have found that, among other elements, decreased levels of zinc are associated with increasing age.^[173] Furthermore, zinc blood level and psychological performance were positively correlated, independent

of age.^[174] However, when we searched for the reverse association, i.e. lowered levels of zinc or other trace elements as putative biological markers in persons with AAMI as compared with age-matched controls, we could not find one.^[175]

5. Conclusion

Research into the borderline states between normal aging and dementia is underdeveloped compared to the vast amount of knowledge which has been gained on normal cognitive aging and on dementing conditions (especially AD). A major problem may be the fact that the nosological status and clinical characteristics of these intermediary stages have only recently been elucidated. This has prevented clinicians from developing diagnostic and treatment programmes, and drug companies have not been stimulated to put much effort in developing drugs for a nonexistent disease.

Until now, many consider the development of drugs for a normal physiological process (i.e. the aging process) not rational. However, the view that 'normal' aging needs no treatment should in our view be replaced by more subtle options, e.g. a distinction between primary and secondary aging.

The borderline between primary aging, which is exclusively determined by chronological age, and clear-cut dementia is very subtle: many people experience secondary aging, the symptoms of which are only normal in a statistical sense but not in a physiological sense. This is a good reason to develop specific drugs for the nondemented population experiencing age-related cognitive decline. The recent incorporation of the classes of 'cognitive disorder' and 'age-related cognitive decline' in DSM-IV may herald a positive change of attitude in this respect.^[108,176] Otherwise it might be worthwhile to target subgroups of cognitive disorders in terms of recognised factors that compromise successful aging. Clinical trials with nootropic drugs to prevent cognitive impairment after BLE such as closed head injury that are currently being carried out are an example. Nootropic drugs or cognition enhancers as co-medication against the cognitive impairment caused by psychoactive drugs used to

treat depression, anxiety, insomnia or allergy could be a positive contribution in the struggle to achieve successful aging.

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