DEMENTIA

an inventarisation of current concepts and research
on dementia in The Netherlands

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A report at the request of the Netherlands Institute for Gerontology
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PREFACE

This is a review study on the current state of research and practice with regard to biological, clinical and behavioural aspects of dementia in The Netherlands. The report is the result of a request from the Netherlands Institute of Gerontology (Nederlands Instituut voor Gerontologie; NIG) to the Netherlands Institute for Brain Research (Nederlands Instituut voor Hersenonderzoek; NIH).

The study is one of several activities in preparation for a national programme of gerontological research, to be executed over the next five years. One of the priorities of the research programme, combining scientific and societal criteria, is the phenomenon of senile dementia. The programme states that "the term 'dementia' is often used unprecisely and even incorrectly, while the diagnosis of dementia in clinical practice is also not without problems. A widespread but unjustifiable pessimism about chronic mental impairment in the elderly still impedes therapeutic efforts. The importance of preserved intellectual functioning in later life, and the prevention of dementia-like syndromes justifies an intensification of research activities within various disciplines".

We appreciate that the NIH was able to respond to our request for this study of dementia at such short notice. We wish to thank the members of the panel of experts, Prof. Dr. C.F. Hollander, Prof. Dr. F.C. Stam, Dr. H. Riet and Drs. H.F.A. Diesfeldt for their helpful comments to that institute. The study was made possible through financial support from the Directorate-General of Science Policy. We also thank all those researchers who responded in such a cooperative way to NIH's request for information.

We do hope that this study will interest potential researchers in The Netherlands, so that dementia in its various aspects will receive increasing attention in research. Through NIG a summary of this study will be made available to the public at large. We trust that this study will enable the members of the National Advisory Committee Research on Aging (Stuurgroep Onderzoek op het Terrein van de Ouder Wordende Mens, SOOM), who are responsible for the execution of the research, to stimulate research on dementia in The Netherlands.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>ACh</td>
<td>Acetylcholine</td>
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<tr>
<td>AChE</td>
<td>Acetylcholine Esterase</td>
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<tr>
<td>ACTH</td>
<td>Adrenocorticotropic Hormone</td>
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<tr>
<td>AMC</td>
<td>Academisch Medisch Centrum</td>
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<tr>
<td>BOP</td>
<td>Beoordelingsschaal voor Oudere Patienten</td>
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<tr>
<td>cAMP</td>
<td>Cyclic Adenosine Mono Phosphate</td>
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<tr>
<td>CAT</td>
<td>Choline Acetyltransferase</td>
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<tr>
<td>CCK</td>
<td>Cholecystokinin</td>
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<td>CJD</td>
<td>Creutzfeldt-Jakob Disease</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<td>CSF</td>
<td>Cerebrospinal Fluid</td>
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<td>CT</td>
<td>Computerized Tomography</td>
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<td>DDAVP</td>
<td>1-Deamino-8-D-Arginine Vasopressin</td>
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<td>EEG</td>
<td>Electro Encephalography</td>
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<td>EM</td>
<td>Electron Microscope</td>
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<td>ERP</td>
<td>Event Related Potential</td>
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<tr>
<td>ESF</td>
<td>European Science Foundation</td>
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<td>ETP-BBR</td>
<td>European Training Programme-Brain and Behavioural Research</td>
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<td>FUNGO</td>
<td>Foundation for Medical Research</td>
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<tr>
<td>GAD</td>
<td>Glutamic Acid Decarboxylase</td>
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<tr>
<td>IgG</td>
<td>Immunoglobulin G</td>
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<tr>
<td>IgGFc</td>
<td>Immunoglobulin G, fragment crystallizable</td>
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<td>MAO</td>
<td>Mono-amino Oxidase</td>
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<td>MID</td>
<td>Multi-infarct Dementia</td>
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<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
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<td>rCBF</td>
<td>Regional Cerebral Blood Flow</td>
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<td>SDAT</td>
<td>Senile Dementia of the Alzheimer Type</td>
</tr>
<tr>
<td>THA</td>
<td>1,2,3,4 Tetra-hydro-5-aminoacidine</td>
</tr>
<tr>
<td>ZWO</td>
<td>Netherlands Organization for the Advancement of Pure Research</td>
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SUMMARY

Chapter I

Dementia and, more specifically, senile dementia of the Alzheimer type (SDAT) are ill-defined at present. Many of the classical terms (e.g., acquired, irreversible, global, progressive, organic brain damage) are no longer tenable. The definition, and thus the development either of a rational therapy or of preventive measures, can be improved by (1) new developments in clinical diagnostic tools, post-mortem analysis and animal experimental research, in order to provide a better insight into the etiologic and pathogenetic mechanisms that underly this disease, or (2) the establishment beyond doubt that dementia is, in fact, nothing more than an accelerated (and thus advanced) form of the normal aging process.

Chapter II

It was not until the 19th century that senile dementia was recognized as a disease related to senescence. Around 1900, the major presenile dementias (Huntington’s chorea, Pick’s disease and Alzheimer’s disease) were described as separate entities for the first time. More recently, the classification of various types of dementia as distinct diseases on purely clinical grounds has lost much of its meaning (e.g. Alzheimer’s disease and Senile Dementia are no longer considered to be two distinct diseases). By contrast, more emphasis has been put upon different etiological and pathogenetic mechanisms that may lead to clinical syndromes which are quite similar.

Chapter III

Dementia can be classified (1) according to the age at which it emerges, (2) according to its gravity and (3) according to its etiology. Arbitrarily, two groups are distinguished: irreversible dementias (‘dementia diseases’) and reversible dementias (diseases associated with dementia, secondary dementias).

Chapter IV

Current diagnostic tools are not capable of positively diagnosing SDAT. The validity of clinical diagnostic criteria is dubious, so that relevant psychometric test batteries will have to be developed. Neurological diagnosing tools are capable of excluding no more than a small number of conditions which are capable of leading to dementia. However, this applies only to 5-10% of the demented patients. The diagnosis ‘SDAT’ means, in fact, simply that the patient is older than 65 years, while no clearcut cause of the dementia can been identified. Positron
emission tomography (PET scan) and the application of 'sophisticated' new techniques in neuropathology may open the possibility of revealing local, positive signs of SDAT. On the other hand, there is little reason to expect any signs that are qualitatively different from the changes observed during normal aging (see below).

Chapter V

The pathological abnormalities found in SDAT are qualitatively similar to those found during normal aging, but quantitatively much more pronounced. On pathological grounds SDAT may be considered to be a mere aggravation of the normal aging process, suggesting that research on the normal aging process is essential for our understanding of SDAT and for the development of a rational therapy.

Chapter VI

Various neurochemical changes have been reported to occur in dementia. A cortical presynaptic degeneration of cholinergic nerve terminals is supposed to be one of the early features, but these changes have also been found, although to a lesser degree, during normal aging. In addition, most of the other neurotransmitters (i.e. amines, amino acids and peptides) show degenerative changes as well. Consequently, there seems to be no truly 'specific' biochemical change in dementia, in spite of the fact that a cell loss of the ascending cholinergic system, originating from the substantia innominata, has recently been proposed as such. The central problem in establishing what is cause and what is effect among the neurochemical and other changes is the lack of a suitable animal experimental model for dementia. This problem would become trivial, however, if it could be established that dementia is an accelerated form of aging.

Chapter VII

Various causal factors of dementia have been proposed.
(a) A number of toxic compounds have been suggested, although none of them have been properly validated. Intracerebral aluminium levels have been reported to be elevated in SDAT, but again it is not clear whether this is cause or effect of the disease, since this metal is also accumulated during normal aging.
(b) The role of other environmental factors (e.g. disturbed brain function resulting from a chronic decrease in sensory stimulation) is an intriguing possibility which has only recently begun to be studied. (VII,1).
(c) It is not likely that the presence of auto-antibodies to CNS components in the sera of demented patients and of gamma-globulins in senile plaques reflect a primary pathogenetic
mechanism. Auto-antibodies against CNS structures occur also in a number of other pathological conditions. The intracerebral presence of immunoglobulins may reflect an increase in vascular permeability (VII, 2).

(d) There is evidence for a causal hereditary factor in Huntington's chorea. The search for markers identifying the causative gene, which would open the possibility of prenatal genetic counseling, should be encouraged. Also in a number of cases of Alzheimer's disease with early onset, a hereditary factor seems to be of importance (VII, 3).

(e) In Kuru and Creutzfeldt-Jakob disease a slow virus is responsible for the disease. At present there is no evidence for virus involvement in SDAT (VII, 4).

Chapter VIII

At the present moment therapeutic possibilities are very limited. Classical psychopharmaca only act symptomatically, and may even induce 'pseudodementia'. Geronto-psychiatric medicines, claimed to counteract specifically the symptoms and progression of the disease, have so far given disappointing results. Their positive effects may be due not so much to their specific geronto-psychiatric action but rather to their effects on mood and motivation. Therapies directed towards neurotransmitter normalization have also been disappointing, possibly because mere replenishment of the transmitter is no substitute for the integrative properties of the affected neurons. Non-pharmacological therapies (e.g., environmental stimulation) are at least as promising as the pharmacological ones.

Chapter IX

Research on dementia is only a minor branch of the Dutch scientific effort. Research on Huntington's chorea is performed in Leyden (G.W. Bruyn, Leyden). In Amsterdam, H. van Crevel (A.M.C.) has developed a standard neurological diagnostic procedure, aimed at recognizing treatable forms of dementia, while some research has been focused on normal pressure hydrocephalus. G.M.J. van Kempen (Oegstgeest) works on the correlation of various parameters during dementia in a longitudinal investigation. J.A.M. Frederiks (Eindhoven) analyses clinical data on dialysis dementia. One programme (J. Lindeboom et al., Free University, Amsterdam) is dealing with the screening of aged people for dementia. Research on specific behavioral characteristics of demented patients is performed by H.M.L. Miesen (Rotterdam). P. Gilson (Blaricum) is analyzing differential memory deficits in institutionalized patients and their implications for therapy and prognosis. In Utrecht, J. Jolles and W.M.A. Verhoeven (AZU) are developing neuropsychological tests for cognitive functions while, in collaboration with the Rudolf Magnus Institute (Utrecht), the effects of a number of neuropeptides on dementia will be
evaluated. The effect of Org 2766 is evaluated by Organon (M. v.d. Waart). Changes in peptidergic neurons in aging and dementia in the human brain are compared to changes in similar cells in the aging rat brain in the Netherlands Institute for Brain Research (D.F. Swaab and E. Fliers, Amsterdam). One group is planning to start working on the development of an animal experimental model for dementia (C.F. Hollander, Rijswijk). J.M.B.V. de Jong (AMC) works on the development of an animal experimental model for Parkinson's disease. Effects of chronic dietary administration of choline on memory and cholinergic neurotransmission in aged rats are investigated by W.C.M. Raaymakers (University of Nijmegen), with several rat strains being compared.

Chapter X

With respect to future research and education on dementia in The Netherlands, high priority should be given to the development of an animal experimental model. As discussed in the present report, more knowledge concerning the normal process of aging of the brain is essential for this purpose. Experimental brain research is a conditio sine qua non in order to achieve a breakthrough in understanding the changes described in the aging brain and the possible therapeutic effects of chemicals and the environment. Human behavioural research should be encouraged in the framework of dementia (improvement of neuropsychological tests), while the study of the role of environmental factors (causal as well as therapeutic) should receive more emphasis. Such non-pharmacological therapies deserve special attention from universities and research institutes, since the pharmaceutical industries are not likely to develop this line of investigation. Research on dementia, and the collection and availability of human brain material should be coordinated and centralized. Measures in the medical training, improving knowledge about dementia itself and about the limited possibilities and associated hazards of prescription of medicines to aged people are required. Recent developments in neurobiological research should be incorporated in clinical medicine (central PET scan facilities) and in neuropathology. The development of neurotrophic substances needs further investigation. Research on neuronal membrane alterations during aging and dementia might have good prospects in The Netherlands.
I. DEFINITION OF DEMENTIA

Many definitions of dementia have been proposed, all of which are purely descriptive and without etiological implications, not only in history (cf. Chapter II) but also at present (cf. Organic Mental Impairment in the Elderly, 1981). Since Kraepelin (1910), dementia has been considered to be an ACQUIRED IRREVERSIBLE GLOBAL DETERIORATION OF COGNITIVE FUNCTIONS (such that it interferes with daily life, i.e., with work and relationships). The deterioration is often PROGRESSIVE and due to ORGANIC BRAIN DAMAGE (Ringoir, 1981; Frederiks, 1980). More recent insights, however, cause various terms in the definition to be no longer tenable:

1. The term ACQUIRED has little scientific substructure. Although it may be true that no major symptoms existed before the development of dementia, data excluding the presence of early minor symptoms in individuals that will dement later do not exist.

2. Dementia is not always IRREVERSIBLE. Progress has been made as regards diagnostic and therapeutic possibilities in a number of conditions. An increasing number of causes of ‘reversible dementias’ (also known as ‘secondary dementias’, or ‘pseudo-dementias’) are distinguished and can be treated (cf. Chapter III). Although it is the least important group in terms of size (5-10%, Kiloh 1981), ‘reversible dementias’ have, in fact, become of great importance in clinical practice, because of their relatively favourable prognosis in case of an adequate therapy.


4. Although dementia may be PROGRESSIVE, it can also be stationary for a long time (Frederiks, 1980).

5. Some authors claim that dementia is always due to ORGANIC BRAIN DAMAGE. Frederiks (1980) even calls the term ‘organic dementia’ a pleonasm. On the other hand, the necessity of brain damage in the classical sense is negated for dementia by the existence of a number of reversible dementias, such as medicine-intoxication (VII-2). On theoretical grounds this makes the term ‘functional disturbance’ preferable to ‘organic brain damage’ (cf., Goedhard and Knoek, 1981), although this term is meaningless for making a distinction with other neuropsychiatric conditions.

As a result, the diagnosis of dementia is currently based on rather dubious terms, and the diagnosis of the most frequent form of dementia (viz. SDAT) is made per exclusionem. The diagnosis SDAT means in practice simply that the patient is older than 65 years, while no clearcut cause of dementia can be identified. Replacing the term dementia with ‘chronic brain syndrome’ or ‘brain failure’ (Ringoir, 1981; Frederiks, 1980) does not solve this problem. SDAT will remain difficult to define until either its specific etiology has been clarified or its character as an accelerated and advanced form of aging per se has been established beyond any reasonable doubt.
Although recent developments in clinical diagnostic tools (PET scan) and the findings of localized changes in SDAT brains (Rossor et al., 1982) still give some hope that the definition of SDAT may soon be extended by an insight into the specific brain area(s) involved in the functional changes of this condition, there is little reason to expect any signs that are qualitatively different from the normal aging process (vide infra).
II. HISTORICAL BACKGROUND

Pinel (1745-1826) was the first to use the term 'dementia' for mental deterioration and idiocy caused by lesions in the central nervous system. Esquirol (1772-1840) introduced a connection between dementia and the aging process: 'La démérence sénile est la suite de progrès de l'âge'. (cf. Ringoir, 1981). He described the condition of senile dementia as a weakening of the memory for recent experiences and mentioned the loss of drive and will power, the insidious onset, and referred to the emotional disturbances which may appear in its early phase. Furthermore, Esquirol described the differences between mental subnormality existing from development ('amentia'), and an acquired loss of mental faculties ('dementia'). In 1826, Caluviel introduced the term 'general paralysis of the insane' (paralyse générale des aliénes) and this condition was of interest to 19th-century physicians, because of its high incidence and unknown etiology. Its syphilitic origin ('dementia paralytica') had been suspected long before it was confirmed by Mogenchi in 1913. (cf. Ringoir, 1981).

Gradually, the natural scientific approach gained momentum. In 1882 Huntington's Chorea was first described and in 1892 Pick published a contribution to the study of aphasia. He analyzed aphasic disturbances associated with temporal lobe atrophy, but he was not primarily concerned with demarcating a particular disease (Pick, 1892). It was left to other investigators to define the disease that was named after him, which manifests itself clinically by dysphasia and progressive intellectual and emotional deterioration, developing in middle or later life and based on frontal/temporal lobar atrophy. In 1898 Redlich found 'plaques' in the brains of two cases of senile cerebral atrophy, and in 1911 Simchowitz described granulovacuolar changes in neurons. When Alzheimer (1864-1915) described in 1907 the disease which now bears his name, he considered it an atypical form of senile dementia. He reported 'a peculiar disease of the cerebral cortex' affecting a woman of 51, who had become progressively more forgetful, disoriented and finally demented over a period of 4 years (Alzheimer, 1907). It was Kraepelin (1855-1926) who proposed the name 'Alzheimer's disease' for this condition, although he was by then already impressed by the neuropathological similarity between this disease and senile dementia (Kraepelin, 1910).

In later years, less and less value was attached to distinguishing and classifying various types of dementia as distinct diseases purely on clinical grounds. On the other hand, more emphasis has been put upon the various etiological and pathogenetic mechanisms which can lead to similar clinical conditions. This approach has proven to be of value both for preventive and for therapeutic measures, e.g. for the prevention of Kuru and the treatment of reversible dementias. The term dementia now refers to a SYNDROME of varied etiology. Kraepelin's doubts on the fundamental differences between Alzheimer's disease and senile dementia have been proven justified. Few arguments are left nowadays to distinguish between Alzheimer's disease (AD) and the commonest form of
senile dementia, viz., Senile Dementia of the Alzheimer Type (SDAT). More recently, this line of thinking has developed even further, since even some other neurological diseases are considered to have a common degenerative denominator (e.g., SDAT and Parkinson's disease, cf. Rossor, 1981 and Chapter VI, this report). Yet it remains to be seen whether this common denominator is in truth different from the normal aging process.
III. CLASSIFICATION

Dementia is not a disease, but rather a syndrome that has been classified: (1) according to the age at which it emerges (presenile vs. senile dementia); (2) according to its gravity—the WHO scientific Group Report includes senile dementia in the category Atrophic Senile Psychoses, subdivided into (a) mild psycho-organic syndrome, (b) moderate dementia and (c) severe dementia (Organic Mental Impairment in the Elderly, 1981)—and (3) according to the etiology and clinical manifestations. This last classification arbitrarily distinguishes i—the irreversible forms of dementia (or ‘dementia diseases’) and ii—reversible dementias [or ‘diseases associated with dementia’, ‘secondary dementias’, ‘pseudodementias’ and ‘confusional states’ (cf. Frederiks, 1980)]. The dementias included in this last group often turn out upon closer examination to be not reversible at all. The distinction, however, is certainly of practical importance in view of the fact that only the dementias in the second group may be treated successfully. Unfortunately, however, this group makes up only 5-10% of the diagnosed dementias (Goedhard and Knoor, 1981, Kiloh, 1981).

sub I. Irreversible forms of dementia (dementia diseases, primary dementias) are:
- SDAT – by far the most common form of the irreversible dementias (50%; cf. Plum, 1979);
- Alzheimer’s disease, at present considered to be the presenile form of SDAT, except for a genetic argument, still pointing to possible distinct entities (see VII,3);
- Pick’s disease and other neuronal storage diseases;
- multi-infarct dementia, the frequency of which, according to different sources, ranges between 8 - 20% of the irreversible dementias (cf. Cahn, 1981; Plum, 1979) and mostly emerges in presenility;
- Huntington’s chorea and other hereditary ataxias (5%, cf. Plum, 1979);
- Slow virus dementias (Creutzfeld-Jakob; Kuru);
- Dementia associated with advanced Parkinson’s disease or Down’s syndrome;

sub II. ‘Reversible’ dementias (diseases associated with dementia, secondary dementias) are found in a wide variety of conditions:
- brain tumors (primary or metastatic);
- traumata (e.g., ‘punch-drunk syndrome’, subdural haematoma);
- postepileptic states;
- normopressive hydrocephalus;
- depressions leading to confusional states (sometimes only considered to be a differential diagnostic problem);
- hypo/hyper-thyroidism (thyrotoxicosis, myxoedema, Cushing);
- metabolic disorders (hypoglycaemia, hypercalcemia);
- infections and their late complications (meningitis, encephalitis, septicemia, Kluver-Bucy syndrome, neurosyphilis);
- deficiency of Vit. B12, folic acid or thiamine (e.g., in
alcoholism, M. Wernicke);
- hypertension;
- intoxications, medicines (barbiturates, neuroleptics, vincristine, amphetamine), hard drugs (morphine, heroin), dialysis dementia;
- anoxia (anaemia, respiratory anoxia, carbon dioxide poisoning, cardiac insufficiency, dehydration);

Of course, more than one causal factor may exist at a single time. The enormous diversity of possible causes of diseases associated with dementia, and the fact that 5 to 10% of the patients with the diagnosis 'dementia' can be treated (Kiloh, 1981), makes a strong case for an extensive and careful physical examination of patients with dementia. The same can be applied to the observation that 5 to 20 % of the patients referred with diagnoses of dementia prove upon closer examination not to be demented at all. (Kiloh, 1981, J.Schouten, pers. comm.)
IV. DIAGNOSIS

"Das Schwierigste bei der Diagnose ist die Abgrenzung gegenüber dem 'normalen' Senium. Es ist willkürlich, wo man die Grenze ziehen will" (Bleuler, 1920)

Dementia is a syndrome leading to disturbances of various psychological functions. Methods for systematic and standardized behavioural observations are therefore an important aid in research on dementia. Psychology has contributed a great deal to the development of behavioural observation scales. In The Netherlands the 'Beoordelingsschaal voor Oudere Patienten' (BOP) has successfully been used for this purpose since 1971 (van der Kam et al., 1971). With respect to diagnostic procedures, however, the situation is less favourable: diagnostic procedures should ideally lead to a positive and early diagnosis of SDAT.

On historical grounds, there are two diagnostic approaches towards the demented patient, which unfortunately even in combination are insufficient to attain the above-mentioned goal, viz.,

(1) psychological/psychiatric, and
(2) neurological.

sub 1. According to the Royal College of Physicians (Organic Mental Impairment in the Elderly, 1981) psychological assessment is required to differentiate between dementia and functional psychiatric disorders, to measure changes in demented patients and make decisions in relation to management. In 1981, the progress report of the National Institute on Aging (Emr, 1981) stated: 'Physicians need a mental status test that is quick and simple, yet sensitive enough to detect brain disorders in the earliest stages and to track the rate and extent of any changes in a patient's condition'. Taking into account the difficulty in defining SDAT, also due to the lack of understanding of its etiology (cf. Chapter I), it is not surprising that the validity of clinical-diagnostic criteria has proven to be far from satisfactory (Jonker et al., 1981, Godderis, 1981). This situation has resulted in high frequencies of false positive diagnoses (e.g., Marsden and Harrison, 1972; Nott and Fleminger, 1975), the consequences of which can be most dramatic for the patient (e.g., Shaw and Caro, 1982). Although some recently developed psychometric test batteries are capable of discriminating between functional psychiatric disorders and organic disorders, and also have a high test-retest reliability, opening the possibility of follow-up studies (e.g., Lindeboom et al., 1979; Lindeboom and Jonker, 1980), they are incapable of positively diagnosing SDAT.

sub 2. Neurological diagnostic tools are only capable of excluding a relatively small number of pathological conditions leading to dementia (cf. Chapter III).

The computerized tomography (CT) scan is very useful in detecting intracranial tumours, subdural haematomas and hydrocephalus. However, 'diffuse atrophy' as visualized by CT scanning occurs both in SDAT and in normal aging (Godderis, 1981), although the CT findings of Soininen et al. (1982) have
revealed significant differences between SDAT patients and age-matched controls in a number of atrophy indices. Small infarcts cannot be visualized by the CT scan (Goddersis, 1981), casting doubt upon the possibility of distinguishing multi-infarct dementia (M.I.D) from other irreversible forms of dementia. However, a higher frequency of local atrophies was reported to occur in M.I.D. in comparison with both SDAT and controls (Soininen et al., 1982).

The electro-encephalogram (EEG) has only a limited value in distinguishing among dementias. A normal EEG in an apparently demented subject may point to the possibility of pseudodementia (Organic Mental Impairment in the Elderly, 1981), but also in Pick's disease a normal EEG is found very frequently (Goddersis, 1981). SDAT cannot be diagnosed by the EEG, as an abnormal EEG is not found in all demented patients, while non-demented patients are very frequently found to have an abnormal EEG (Goddersis, 1981).

'Event-related potentials' (ERP) have been reported to be capable of distinguishing between demented and non-demented subjects (Goddersis, 1981). Harkins (1981) reported differences in the brainstem auditory evoked potential between demented patients and healthy volunteers. Also the visual evoked response seems to be promising in this respect (Visser et al., 1976). However, it remains questionable whether ERP studies can be used to detect dementia in an early phase. In addition, there is a lack of control values from non-demented age-matched controls (Goddersis, 1981, cf. Visser et al., 1976).

Regional cerebral blood flow (rCBF) studies, using inhalation of radioactive Xenon 133, have a potential value in discriminating between various types of dementia (Alzheimer, Pick, M.D.; cf. Risberg et al., 1982) and in differentiating dementia from functional disorders. However, at present there is no evidence for an early recognition of dementia, while a major drawback could be that the rCBF is only visualized in superficial regions of the hemispheres, and not, e.g., in the hippocampus, where major pathological changes are found in SDAT (cf. Goddersis, 1981).

Position emission tomography (PET scan) is a non-invasive technique, capable of mapping local glucose utilization differences in the brain. If dementia-induced cognitive changes indeed depend upon disturbances in metabolic activity in specific brain regions (Rossor et al., 1982), this technique has some potential for distinguishing SDAT from normal aging. It might be of value in confusional states, where metabolic changes are not accompanied by any anatomical abnormality (Organic Mental Impairment in the Elderly, 1981). However, the first reports on local glucose metabolism as measured by means of PET scanning are at variance. Reivich et al. (1981) were not able to demonstrate statistically significant differences in mean cortical metabolic rate for glucose between demented patients and age-matched controls. By contrast, De Leon et al. (1982) and Ferris et al. (1982) reported differences in PET metabolic measures between SDAT patients and age-matched controls.

Consequently, psychological assessment is still the most important diagnostic approach towards dementia at the present
time (Godderis, 1981), although even here an unequivocal diagnosis of SDAT is not possible. Some recently developed techniques (ERPs, CT scan, rCBF studies) may do no more than visualize, in a most sophisticated way, phenomena that are not specific for SDAT but which are also found in normal aging. Perhaps an exception must be made for the PET scan, which may be capable of revealing positive signs of SDAT. However, as long as the mechanisms involved in the development of SDAT are not clear, and as long as there is no insight into the fundamental differences between SDAT and normal aging, it will be next to impossible to ever obtain conclusive criteria for the diagnosis of SDAT.
V. NEUROPATHOLOGY

"As far as can be judged with the aid of existing techniques, the differences between the 'senile dement' and other subjects reflect a quantitative gradation of a pathological process common in old age, rather than qualitative differences" (Blessed et al., 1968)

Marked atrophy resulting in decreased brain weight has traditionally been considered to be one of the important characteristics of senile dementia. However, during normal aging, the brain loses weight as well. Ho et al. (1980) found a gradual decrease after the age of 25, followed by a more rapid decrease after 80 years. Also CT studies, ruling out any interference with secular trends, indicated a decrease in brain volume during normal aging (e.g., Yamaura et al., 1980). In addition, atrophy does not necessarily lead to dementia (e.g., Lewin, 1980).

According to Tomlinson et al. (1970) total brain weight in SDAT would not differ from age-matched controls. Others, however, reported an additional decrease of the hemispheres (Corsellis, 1976), of the temporal lobes (Bowen et al., 1976) and of the amygdala (Herzog and Kemper, 1980) in SDAT. In the presenile dementias marked regional accentuations of the atrophy are found, e.g., in the Caudate Nucleus and Putamen in Huntington's chorea, in addition to lower total brain weights (Bird and Iversen, 1974).

The neuropathological literature has reported both ventricular and sulcal widening to be associated with SDAT. Although De Leon et al. (1980) reported a correlation between the width of the third ventricle as measured by CT methods and the degree of cognitive impairment in a group with the presumptive diagnosis of SDAT, other investigations cast doubt on the value of ventricular measurements for the diagnosis of SDAT: cortical atrophy is associated with normal aging as well (Yamaura et al., 1980), while ventricles were reported to be of normal size for age in about 40% of all senile dementia patients (Hubbard and Anderson, 1981).

During normal aging an average loss of approximately 20% of all neurons has been reported (Ban, 1978). These losses vary regionally to a large extent: while losses may be pronounced e.g., in the frontal lobe of the cerebral cortex, the olivary inferior nucleus is not affected (Brody, 1973). Until recently nerve cell loss has not been considered to be more pronounced in SDAT than during normal aging (Tomlinson and Henderson, 1976). Essentially, these results implicate unaltered cell packing density in SDAT, leaving open the possibility of a decreased total neuron number because of decreased cortical surface area. Brun and Englund (1981) reported a marked difference in neuron number between mild and severe cases of SDAT in the superior and inferior parietal lobules and in the posterior cingular gyrus, whereas mild cases did not differ from controls. In the amygdala, neuron loss in dementia was reported to be more pronounced than in normal aging (Herzog and Kemper, 1980).
Consequently, local accentuations of cell loss in comparison with age-matched controls may exist. In addition, extreme cortical neuronal loss has been reported in presenile dementia (Colon, 1973, Tomlinson and Henderson, 1976).

The extensive presence of three classical neuropathological characteristics has always been used as a decisive diagnostic criterion for SDAT:

1) the neurofibrillary tangle, consisting of a bundle of argentophilic fibers running through the cytoplasm of medium-sized and large neurons; EM work has revealed these fibers to be made up of paired helical filaments (Terry, 1980);

2) the senile plaque, consisting of a core of extracellular amyloid, surrounded by argentophilic fibers and granules; EM examinations have shown these argentophilic structures to be abnormal neurites, synaptic boutons, clusters of paired helical filaments and degenerating mitochondria and lysosomes (Terry, 1980); and

3) the granulovacuolar degeneration, which is confined to the pyramidal nerve cells of the hippocampus; the cytoplasm of affected cells contains vacuoles, surrounding a dense granule.

Plaques and tangles are found especially in the neocortex (Tomlinson, 1979). There have been reports on a positive correlation between the clinical severity of the dementia and the extent to which the lesions are present (Blessed et al., 1968). These classical histopathological lesions, however, are not pathognomonic for SDAT. Plaques and tangles have been found during normal aging as well, even in up to 25% of non-demented individuals at ‘presenile’ age (Ulrich, 1982). In addition, these lesions have been found to a large extent in patients with degenerative brain diseases other than SDAT, such as Parkinson’s disease (Boller et al., 1980) and Down’s syndrome (Burger and Vogel, 1973). Although as a group SDAT patients may have more of these histopathological lesions, it therefore does not seem possible to diagnose SDAT solely on the basis of such changes.

Golgi-stained material was reported to reveal a shortening of the dendrites and a loss of dendritic spines during normal aging (Feldman, 1977). In the rat, quantitative EM studies have revealed a decrease in the number of synapses with increasing age in the dentate gyrus (Bondareff, 1979). The loss of synapses did not depend on an antecedent loss of postsynaptic neurons or their dendrites. The primary lesion seems to be presynaptic, therefore, which is in agreement with biochemical data (cf. Chapter VI). Mehraein (1975) reported a reduced number of spines in the human gyrus cinguli and the hippocampus in SDAT. Buell and Coleman (1979) measured the size of dendritic trees in layer II pyramidal neurons of the human parahippocampal gyrus. They reported, in contrast with Scheibel and Scheibel’s (1977) qualitative descriptions, an increasing number and length of terminal segments during normal aging, while dendritic trees were less extensive in demented patients than in adult brains. These results were interpreted as a compensatory growth of dendrites during normal aging, which would ultimately fail in senile dementia. Also Connor et al. (1982) have reported an increase in the total number of dendritic branches in the somatosensory cortex of aged rats.
Although with modern neurobiological techniques 'dead cells do tell more and more tales' (free after Roth, 1963) it will be obvious from the data mentioned above that no specific neuropathological characteristics of SDAT have been found so far. The abnormalities found in SDAT are qualitatively similar to those seen during normal aging, but there are quantitative differences. Until now there seems to be no evidence contradicting the thesis that SDAT can best be regarded as an aggravation of the 'normal' aging process. On the contrary, many observations from various disciplines plead in favour of this concept.
VI. NEUROCHEMISTRY

Much attention has been paid to changes in the cholinergic system in SDAT (Bartus et al., 1982a). The drop in choline acetyltransferase (CAT) which is found in SDAT is more pronounced in all cortical areas than during normal aging, and relates both to the extent of histopathological changes and to the mental score of the patient (Organic Mental Impairment in the Elderly, 1981). The diminution of CAT is most pronounced in the temporal cortex (Davies and Maloney, 1976; Rossor et al., 1980). In cortical biopsies which were obtained by craniotomy (sic!) the ACh production was found to be 60-70% lower in dementia, a drop which correlates with changes in CAT levels (Sims et al., 1980). Recently the diminution in cortical ACh was suggested to be due to selective cell loss in the ascending cholinergic system, originating from the basal nucleus within the substantia innominata (Rossor et al., 1982), which would make SDAT comparable to the Parkinsonian degeneration of the substantia nigra. Neither cholinergic muscarine receptors (Perry et al., 1977) nor beta-adrenergic binding (Maggi et al., 1979) are affected in senile dementia and aging, suggesting the lesion to be primarily presynaptic, and only secondarily followed by postsynaptic degeneration of cortical spines, dendrites and cell bodies. Still, the concept of Davison (1979) that ‘dementia is a defect of the presynaptic cholinergic terminals’ might be an oversimplification. It is not known, for instance, whether the changes in the cholinergic system are the cause or the result of SDAT. Not only the cholinergic system is affected by SDAT: catecholamine and serotonin turnover in the cerebrospinal fluid (CSF) have been reported to be deficient (Meyer et al., 1976; Soininen et al., 1981; Organic Mental Impairment in the Elderly, 1981) while noradrenaline deficiency has also been reported in cortical and subcortical areas (Rossor, 1981). Extreme cell losses were recently observed in the site of origin of this innervation (viz., the nucleus locus coeruleus) in a group of SDAT patients who were characterized by high dementia scores and relatively young age at death (Bondareff et al., 1982). Other neurotransmitter changes in SDAT are an extra severe GAD loss in the temporal cortex (Bowen et al., 1976; Meyer et al., 1976), a drop of somatostatin in the cerebral cortex (Davies et al., 1980) and an increase in CCK and glucagon in the white and grey matter, respectively, of the cortex (Sanders et al., 1982). ACh and CAT are also diminished in Huntington’s chorea, but this time mainly in the neostriatum, but many other transmitters are affected in this structure (cf. Bruyn, 1982). Now that more biochemical data are becoming available that compare parameters in demented patients with normal life-span changes, it becomes apparent that (as with the morphological alterations; vide supra) no biochemical changes have so far been reported that are specific for dementia: changes in dementia seem to be more pronounced and to occur earlier than in normal aging.

As discussed above, presynaptic degeneration of cortical cholinergic and other nerve terminals is supposed to be one of the early features of SDAT. The diminished glucose utilization
(Smith et al., 1980), which appeared from PET scanning to be localized mainly frontally (Reivich et al., 1981), will probably be secondary to this loss of neurons and synapses. It has been proposed for changes observed in the aging rat (without any evidence for SDAT so far) that presynaptic degeneration might be secondary to axonal transport disturbances, resulting in a change in synaptic glycoproteins and, thus, in a loss of synapses (Bondareff, 1979). In this respect it is of interest that axonal flow inhibitors such as colchicine and vinblastine induce neurofibrillary changes in neurons (Dahl et al., 1980). A great deal of new information may be expected from future studies on contractile proteins in SDAT (cf. Iqbal et al., 1978, 1980, 1982; Dahl et al., 1982; Eng et al., 1980; Gambetti et al., 1980). It is not clear what mechanism might cause such disturbances in axonal flow, but many conditions affecting the neuron are of potential importance in this respect: free radicals (Koster, 1981), auto-antibodies (VII, 2; Sotelo et al., 1980), slow virus (VII, 4), anoxia, traumata, infections, etc. Changes in glial cells too can influence the function of the neuron. Vernadakis et al. (1982) have reported that cultured glial cells change their expression with age, and that their response to intrinsic substances such as hormones and nucleotides becomes altered with age. A recent line of investigation concerns research on membrane alterations during aging: neuronal membrane microviscosity increases with advancing age, resulting in a lower capacity for receptor modulation (Samuel et al., 1982). Future research, aimed at restoring membrane fluidity by the administration of active lipid fractions in order to maintain the adaptability of the aged organism to its environment, thus seems to be a promising possibility.

In general we can say that, at the present time, it is not clear whether the observed biochemical changes are causing dementia or resulting from it. This fundamental question can only be tackled if a good animal experimental model for dementia becomes available or, on the other hand, if it can be established beyond reasonable doubt that dementia is an accelerated form of the normal aging process. This point obviously also applies to the aspects dealt with in other chapters.
VII. THEORIES ON CAUSAL FACTORS OF DEMENTIA

"Die Ursachen des Altersblödsinns sind noch ganz dunkel, jedenfalls ist hereditäre Anlage dabei beteiligt" (Bleuler, 1920)

1. External factors

A number of toxic agents have been hypothesized to be causal factors in the development of SDAT. Thallium, for instance, has led to dementia in patients who had survived a coma (Bank, 1980). Methotrexate (a folic acid antagonist) administered intrathecally has been reported to be capable of inducing dementia (Sterman and Schaumburg, 1980). Nikaido et al. (1972) reported increased silicon contents in plaques, tangles and corpora amylacea in brains from patients with Alzheimer’s disease. In animal experiments a number of agents (e.g., maytansinoids, oncodazole, colchicine and vinca alkaloids) have been demonstrated to (1) have a specific affinity for tubulin; (2) induce a disruption of cytoplasmic microtubules; (3) block axoplasmic transport and (4) induce an accumulation of 10 nm filaments (Ghetti, 1980).

Since 1965, when investigators induced the development of neurofibrillary tangles in experimental animals by injecting aluminium salts, a great deal of research has been focused on aluminium (Emr, 1981). Elevation of the aluminium content of the brain has been suggested to be implicated in the pathogenesis of SDAT and dialysis encephalopathy (Crapper et al., 1976; for review see Crapper and De Boni, 1980). Perl and Brody (1980) reported that the site of aluminium accumulation in the hippocampus is the nuclear region of the neuron. They postulated that 90% of the neurons with neurofibrillary tangles contained aluminium in the nuclear regions. Markesbery et al. (1980) found a gradual increase in the concentrations of aluminium with age, but no difference was observed between SDAT patients and healthy individuals of the same age, which casts doubt on a causal relationship between aluminium and SDAT.

Also non-chemical environmental factors might be of importance in the development of SDAT. Bower (1967) advanced the hypothesis that some of the symptoms of senile dementia are the direct consequence of an associated chronic ‘sensory deprivation’. Indeed, layer IV of the neocortex seems to be the most markedly affected part of the neocortex during aging (Smith et al., 1980) and in presenile dementia (Colon, 1973), suggesting that a lack of input might be an important causal factor in these processes. This possibility has an important therapeutic potential that deserves to be explored in the near future (cf. VIII).
2. Immunology

Immunological processes have been related to the aging process for three reasons. First of all, immunocompetence declines with advancing age, making the organism more susceptible to infections. This age-related decline in immunological capacity presumably reflects mainly the primary response (Haayman et al., 1982). Another characteristic of the immune response during aging is the proliferation of single immunoglobulin producing clones, resulting in the appearance of benign monoclonal gammapathies (Haayman et al., 1982).

Secondly, antibodies from sera of aged mice and human beings are capable of producing a positive immunocytochemical reaction in neurons of young and old mice and of the human brain, respectively (Nandy, 1977; Ingram 1974). Immune system involvement in Creutzfeldt-Jakob disease and Kuru was demonstrated by Sotelo et al. (1980), who found immunoglobulin G (IgG) antibodies against normal filament proteins of cultured neurons in 60% of serum samples of patients with Creutzfeldt-Jakob disease, in 27% of patients with Kuru and, less frequently, in sera from patients with other neurological diseases or healthy subjects. However, the absence of these antibodies in the CSF of patients with positive sera as well as their presence in 10% of normal subjects (Sotelo et al., 1980) raise doubt on their role in the pathogenesis of Creutzfeldt-Jakob disease and Kuru.

A third reason for suspecting immunological involvement in dementia is the presence of antibodies in senile plaques in SDAT patients. Powers et al. (1981) demonstrated immunocytochemically the presence of IgG and its light chains, other immunoglobulins (e.g., IgA) and several plasma proteins in the amyloid core of senile plaques of patients with SDAT. Stam and Eikelenboom (1981) observed IgG and IgGFC in the coronae of the plaques, but not in their amyloid core. These discrepancies in localization may be due to differences in fixation (formaldehyde vs. aceton). Furthermore, Stam reported immunocytochemical evidence for complement activation in the plaque. On the basis of the localization of IgG and the presence of other plasma proteins, Powers et al. (1981) suggested that the immunoglobulins in the plaques are not of primary pathogenetic significance but rather reflect local increases in vascular permeability. This was confirmed by Mann et al. (1982), who reported that staining of immunoglobulins and other serum proteins occurred only in relation to areas of cerebral infarctions or in the vicinity of small vessels displaying arteriosclerotic changes. The absence of cellular infiltration, altered lymphocyte function or changes in humoral immunity in SDAT (Organic Mental Impairment in the Elderly, 1981) also diminishes the likelihood of a primary immunological mechanism.

In conclusion, a pathogenetic role for circulating auto-antibodies against CNS components in the development of SDAT is far from being established. Circulating antibodies against CNS structures occur both in SDAT and normal aging, as well as in a number of other pathological conditions that are
not related to dementia. Under normal conditions, IgG concentrations in the brain and in CSF are negligible as a consequence of the effectiveness of the blood-brain barrier (Rapoport, 1977). Whether in SDAT the blood-brain barrier is less effective is not known and should be subject of future research. The question of whether the presence of complement factors and immunoglobulins in the senile plaque reflects a primary pathogenetic mechanism or a secondary immunological response clearly calls for an animal experimental model.

3. Genetics

Genes have been implicated in the etiology of Huntington’s chorea. This disease is transmitted as an autosomal dominant trait, the difference between carriers and non-carriers usually not becoming manifest before the third or fourth decade of life. Although the disease can be diagnosed in its preclinical phase by pharmacological provocation with L-DOPA (see Bruijn, 1982), it is generally accepted that one should not inform the patient about this fatal disease decades before it manifests itself. A more promising approach would be genetic counseling on the basis of prenatal diagnosis, but markers for the identification of the causative gene have not yet been found. Attempts to produce an animal model for the disease on the basis of a genetic defect have so far been unsuccessful (Martin, 1982). Numerous familial examples have been described also for Pick’s disease (e.g. Schenk, 1959), which is more frequent in families in which Parkinson’s disease or Huntington’s chorea are present (De Groot, 1981). Its exact mode of inheritance is not clear.

Heston et al. (1981) investigated the relatives of 125 probands with SDAT, as ‘confirmed’ by autopsy. These relatives exhibited an excess of SDAT, a finding which is consistent with genetic transmission of the disease. The risk was correlated positively with the severity of the proband’s affliction. The risk to siblings of probands who had become demented before the age of 70 and who had an affected parent approached 50%, which is within the range of an autosomal dominant trait. In contrast, the risk to siblings of probands whose illness began after the age of 70 was barely different from that in the control population. At present time this seems to be the only argument to distinguish between SDAT and (presenile) Alzheimer’s disease. The relatives of the probands with SDAT suffered, in addition, more frequently from Down’s syndrome, lymphoma and immune diatheses than did a control group.

4. Virology

Viruses (i.e., slow viruses) have proven to be implicated in some cases of dementia. The first evidence came from Kuru, a rare form of dementia, which was common among the Fore tribe in New Guinea, and appeared several years after the consumption of human brains during cannibalistic ceremonies. Kuru disappeared after cannibalism had been banned. Kuru is one of a quartet of
neurological disorders, the spongiform encephalopathies, the others being scrapie in sheep and goats, transmittable mink encephalopathy and Creutzfeldt-Jakob disease (CJD). They have an inexorable course to death and are caused by slow viruses (for review see Gajdusek, 1977). Of the four slow-virus encephalopathies mentioned above, Creutzfeldt-Jakob disease (first reported in 1920 by Creutzfeldt) is the only one with any clinical importance, since Kuru has become extinct and the other two are not believed to infect man.

Renewed interest in Creutzfeldt-Jakob disease followed its transmission to chimpanzees. In the first of such cases reported (Gibbs et al., 1968), homogenized frozen brain from cortical biopsies of CJD patients was inoculated into the brains of chimpanzees, which developed symptoms comparable to Creutzfeldt-Jakob disease some 13 months later. Histopathological changes similar to those of Creutzfeldt-Jakob disease were also demonstrated. Transmission has also been reported to New-World and Old-World monkeys, domestic cats, guinea pigs and laboratory rodents (see Gajdusek, 1977). The subject has also become of considerable practical importance in neurosurgery and ophthalmia, as there is a well authenticated case of transmission to the recipient by a corneal graft of a donor who had died of the disease (Duffy et al., 1974) as well as an account on record of transmission by stereotactically implanted electro-encephalographic electrodes (Bernoulli et al., 1977). Moreover, Cathala et al. (1982) have recently reported a correlation in France between lamb consumption and mortality from Creutzfeldt-Jakob Disease.

Numerous attempts to reproduce Gajdusek's findings of the late 1960s, when material from patients with SDAT was reported to produce degenerative brain disease in chimpanzees, have been without success (Emr, 1981). Nevertheless, a role for reactivated herpes virus in the etiology of SDAT was hypothesized on theoretical grounds by Ball (1982) in a recent paper.
VIII. Therapeutic possibilities

"Die Dementia senilis ist eine unheilbare Krankheit und wird es wohl auch immer bleiben" (Jelgersma, 1931)

The therapies for the reversible dementias (pseudodementias) follow logically from a correct, well-founded diagnosis (cf. IV; Frederiks, 1980) and need no further discussion in this context. It goes without saying that for the dementia diseases with unknown etiology (e.g., SDAT), for which no accepted animal experimental model is present, a rational therapy can hardly be expected. It is not surprising, therefore, that the many therapies that have been applied in demented patients have yielded disheartening results. A complicating factor in the evaluation of therapeutical studies is the lack of a reliable psychological test to measure and distinguish between the various aspects of memory (Jolles and Verhoeven, 1981).

I. Pharmacological therapies

The pharmacas used in dementia can, rather arbitrarily, be subdivided into four groups.

I. Pharmacas that were not primarily developed for dementia or gerontology comprise the following two classes:

(A) The classical psychopharmacas (anxiolytics, neuroleptics, antidepressants, hypnotics). These are frequently used as symptomatic agents in psycho-geriatric patients and are not effective against dementia as such. This holds good for both major and minor tranquillizers (Wittenborn, 1981). In fact, overtreatment with these compounds is often a causal factor in pseudodementia and may cause many other serious side-effects (De Beer and Simons, 1977; Meier-Ruge, 1981). Alcohol is still the best anxiolytic irrespective of whether it is given in a clinic or pub (Epstein, 1978), yet in the long run it may have so many drawbacks for gnostic functions (Freund and Butters, 1982; Freund, 1982) that it cannot be recommended as a preferable alternative therapy.

(B) Anti-coagulantia were used to prevent the formation of emboli, which seems to be a causal factor in a small percentage of dementias. The results were not convincing, while the risk of overdosage - and consequently of bleeding - is considerable.

II. Geronto-psychiatric medicines, which are claimed to specifically affect the symptoms of aging via their actions on blood vessels or brain metabolism, may be divided into four groups.

(A) Cerebrovascular dilatators (e.g., papaverine, isoxuprine) were developed as a result of the misconception that SDAT primarily results from vascular insufficiency. In addition, these drugs were developed on questionable acute animal model systems, and the results obtained with such compounds in dementia have been disappointing. Vasodilatators may have adverse effects and even cause severe signs of cerebral insufficiency (Frederiks, 1980). Also codergocrine mesylate (Hydergin[R]) was originally developed as a vasodilatator (as which it is not effective), later being claimed to act by the
cyclic AMP metabolism, or to affect brain metabolism in general (Meier-Ruge, 1981) and now to affect receptor binding of aminergic neurotransmitters. Nandy and Schneider (1978) reported that codergocrine mesylate causes a drop in the lipofuscin content of cultured cells. Although its way of action is obscure, yet it seems to have at least some beneficial effect in dementia, although this might be only on the basis of an antidepressant effect (Fliers, 1982; Loew and Weil, 1982). Animal experiments revealed no effect on learning tasks in old rats (De Koning-Verest, 1981), although other rat models suggest positive central effects of this drug (Loew, 1980). However, at present there is no animal experimental model with any predictive value for dementia.

(B) Procain, originally proposed to be a ‘rejuvenating agent’ (Aslan, 1956) seems to have only a mild antidepressive effect (Branconnier and Cole, 1977) probably by its action as a MAO inhibitor (Zung et al., 1974).

(C) Magnesium pemoline (Cylert[R]), claimed to be a ‘specific memory drug’ by stimulating the RNA synthesis in the brain, does not seem to have any such effect (Wittenborn, 1981).

(D) For many other compounds used in geriatric practice, e.g. piracetam (Nootropil (R), see Ban 1978; Diesfeldt et al. 1978), hyperbaric oxygen (Wittenborn, 1981) or alpha-tocopherol (vit. E), which would lower lipofuscin concentrations in the mouse brain (Kruk and Enesco, 1981), no convincing clinical trials are present.

III. Motivated by the reported deficiency of ACh in SDAT, and in analogy with Parkinsonism, various transmitter substitutions have been tried in dementia, but all with rather disappointing results so far.

(A) Choline itself (Barbeau, 1978) or its source in food lecithin were not effective (Etienne et al., 1981; Petrie and Bann, 1981, Meier-Ruge, 1981; Thal et al., 1981; Bartus et al., 1982a). L-Dopa also gave negative results (Smith and Swash, 1980). On the basis of the effects of peptides in animal experimental paradigms for memory (De Wied et al., 1976), and since Legros et al. (1978) found an improvement of memory in 50-60 year old men by administration of vasopressin (see also Bartus et al., 1982b) a number of studies have tried to restore memory deficits in dementia by administration of this neuropeptide. Results in dementia were not consistent, however (Jolles and Verhoeven, 1981), while Collins et al. (1981) even reported paranoid psychosis after DDAVP treatment for Alzheimer’s disease.

(B) Agonists such as arecoline and bromocryptine were not effective (Loew, 1980).

(C) Inhibitors of ACh breakdown (Loew, 1980), such as physostigmine (Meier-Ruge, 1981) appear to be equally useless. However, Summers et al. (1981) claimed significant improvements following treatment with 1,2,3,4 tetra-hydro-5- aminoacridine (THA), an anticholinesterase drug.

Various pharmacological explanations have been offered for the failure of the substitution therapies (e.g., Corkin, 1981; Wurtman, 1982). One should bear in mind, however, that a large number of transmitters have been reported to change in SDAT,
while an even larger number of neurotransmitters is probably not even known at the present time. In addition, the concept of substitution disregards the essence of a neuron: substitution for dying neurons by their neurotransmitter will not replace their integrative properties. Therapeutic developments within the framework of this concept therefore seem to have little future.

IV. Perhaps the use of peptides (and possibly of other transmitters) that may act not only as neurotransmitters but also as trophic substances (cf. Swaab and Martin, 1981) is more promising in this respect. If so, long-acting preparations such as 'Accurel' (e.g., Kruisbrink and Boer, 1982) might be more effective than the short-term preparations tried hitherto. ACTH[4-9] is reported to impede aging-related changes in the rat hippocampus (Landfield et al., 1981), to enhance activation and attention in healthy volunteers (Jolles and Verhoeven, 1981) and to act as an anxiolyticum in aging people. Whether oxytocin, which has life span-increasing actions in the rat (Bodanszky and Engel, 1966), acts in a similar trophic way is unknown. The observation that it induces memory impairment in aged monkeys (Bartus et al., 1982b) and in humans (Ferrier et al., 1980) points to the possibility that life span-increasing effects are not necessarily concomitant with an improvement in the quality of life.

In conclusion, it is clear that the therapeutic possibilities for the irreversible dementias are very limited, a problem for which a breakthrough can only be hoped for on the basis of a program of sound, systematic neurobiological research.

II. Non-pharmacological therapies

Recently food restriction was proven to enhance longevity, and also to prevent the loss of dopamine receptors in the rat (Levin et al., 1981). This, along with the alterations in transmitter metabolism caused by diet changes (Wurtman, 1982), may open a new field in the research on therapeutic or preventive measures in dementia although no remarkable therapeutic success in man has been obtained as yet.

There are encouraging indications that it might be possible to ameliorate the effects of dementia by adapting the environment to the needs of the patient ('prosthetic environment') and thus to improve the quality of life. Although the ability of the demented patients to learn and adapt remains reduced, worthwhile changes have been obtained. Some previous studies showed that social interactions could be improved by simple alterations in the pattern of ward activities or by introducing community activities. Bower (1967), who implemented the idea that some symptoms of dementia were due to 'sensory deprivation', subjected the patients to 'structured stimulation'. His findings were confirmed by Brody, who reported an improvement in a number of behavioural functions. Various later studies gave similar results (for review and references on this topic see Miller, 1977). The beneficial
effects of some general measures (exercises, reactivation, adequate sleep and rest, occupational therapy etc., cf. Frederiks, 1980) may be interpreted in the same spirit. A promising 'environmental' approach is the reality orientation therapy (ROT): Zepelin et al. (1981) claimed that ROT over a one-year period prevented further mental deterioration in institutionalized psycho-geriatric patients.

The reverse proposition seems also to be true: institutionalization (i.e., 'sensory restriction') appears to be associated with intellectual and cognitive decline (Lieberman et al., 1968; Panek and Rush, 1979), particularly in the first six months following institutionalization (Lieberman et al., 1968). Although the possible beneficial response of demented patients to environmental measures seems clear, no systematic work has been done on the question what procedures might be particularly effective. Experimental variation of conditions should lead to a more individually differentiated therapy. In fact, similar questions and possibly similar mechanisms may be encountered in developmental disturbances, where an 'enriched environment' has been found to produce favourable effects in rats (Uylings et al., 1978). It is well known that an 'enriched environment' stimulates brain development and limits the deficits resulting from developmental disturbances (for review see Greenough et al., 1976). Even in adulthood such an environment can stimulate the formation of new dendritic branches (Uylings et al., 1978). The results of Connor (1982), who reported a dichotomous response by two populations of layer V pyramidal neurons in the old adult rat visual cortex to differential housing conditions, point in the same direction. Buell and Coleman (1979) claimed that a compensatory dendritic growth pattern takes place in the parahippocampal gyrus during normal aging, while this mechanism is absent in dementia. Here too, however, an animal experimental model with enough relevance for dementia to enable detailed testing of the effects of the 'enriched' environments either does not exist or is not yet recognized as such.

In conclusion, the potentially beneficial effects of environmental measures on the demented patient are certainly as promising as pharmacological therapies. This possibility deserves more systematic attention, both in patient care and experimental research.
## IX. INVENTORY OF RESEARCH ON DEMENTIA IN THE NETHERLANDS

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<tr>
<th>NAME/ADDRESS</th>
<th>DISCIPLINE/FUNCTION</th>
<th>CURRENT RESEARCH ON DEMENTIA</th>
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physiological, biochemical, genetic and morphological parameters in a longitudinal investigation (SDAT, Huntington, Creutzfeldt-Jakob)

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training for aged people

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screening of aged people for dementia

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research on specific behavioural characteristics of demented patients. Implications for intervention/management

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effects of chronic dietary administration of choline on memory and cholinergic neurotransmission in aged rats. Comparison of several rat strains

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X. OPPORTUNITIES FOR FURTHER EDUCATION AND RESEARCH IN THE NETHERLANDS

1. Dementia, like all major neuroscience problems, can best be studied in an integrated multidisciplinary way, combining data obtained in man with that from animal experimental research. This means that (apart from coordination) some form of centralization of dementia research is inevitable, especially since the number of active research workers in this field is small and the animal costs are very high. Such a form of centralized research on dementia does not yet exist in The Netherlands. In spite of the fact that the level of dementia research in The Netherlands is comparatively low, there exist some established groups working either on aging (but not the brain) or in brain research (but not primarily focused on aging). Combination of research programmes between such groups, and redirection of their combined efforts towards specific problems concerning dementia, will be of great benefit for the stimulation of research in this area in The Netherlands. The systematic collection and storage of human brain material of demented patients and matched controls to be made available to qualified research workers, should be organized and made more acceptable to the public. Contacts should be established between the research institutions and universities on the one hand, and institutions for psycho-geriatric patients on the other hand.

2. Establishment of a satisfactory animal experimental model for dementia should have high priority. One could then either study animals which are 'demented' deviations within the normal population, look for strains having age-dependent memory deficits or, taking as a starting point the thesis that dementia is in essence an accelerated form of aging, study the normal process of aging. Essential in all cases, however, is a detailed comparison between changes in structures or processes in such animals and changes in the corresponding systems in aged and demented human beings. For fruitful research on dementia aimed at achieving a breakthrough in therapeutic measures, highly developed research in gerontology and neurosciences is essential. The high price of aged animals (Dfl. 2,000 – 5,000 per aged rat) calls for a number of measures which are currently being discussed in the ‘ZWO Dwarsverbandcommissie Gerontologie’.

3. Epidemiological research might help both in answering the question of whether dementia is a disease entity or rather should be looked upon as an exaggerated form of aging, and in determining the precipitating or predisposing factors.

4. The study of viruses as causal factors in dementia can only be successful in The Netherlands if a group of molecular biologists were to become interested in the problem. In view of the fact that there is no evidence at present for a viral etiology in SDAT, it does not seem advisable to stimulate large-scale research along these lines in The Netherlands.
5. In the study of the effect of cholinergic drugs on dementia, many foreign groups abroad are far ahead of any Dutch groups. The Netherlands will therefore have little to contribute in this field for at least the next few years. In addition, the entire approach seems less promising than is often claimed because one cannot replace the integrating properties of a lost neuron by merely making its transmitter available. A search for long-term (trophic) peptide effects seems more promising, and would be based upon a strong Dutch tradition in basic clinical and pharmaceutical research. One interesting question is whether presynaptic degeneration can be delayed or stopped by such compounds. Animal experimental observations which parallel studies on the human brain, clinical observations in combination with PET scanning, and research on the influence of long-acting peptide preparations on the aging animal brain thus seem to be the most promising strategies.

6. Behavioural research should be encouraged within the framework of dementia. In particular, longitudinal studies and the development of psychological tests that can be used for the (differential) diagnosis, follow-up and evaluation of therapeutical effects in demented patients should receive a high priority. The results of such tests should be related to data obtained by EEG (quantification), CT-scan and PET-scan, and be followed by neuropathological observations. Good psychological tests form the basis for any clinically orientated type of research and these tests should therefore be improved on short notice. Animal experimental research should include the question of the role of environmental stimulation and of challenging learning tasks in possibly retarding the process of aging.

7. High priority should be given to the stimulation of clinical research on the effects of non-pharmacological factors on aging and dementia. Here lies a special task for universities, research institutes and institutions for psycho-geriatric patients, since the pharmaceutical industries are not very likely to develop this important line of investigation. Furthermore, social research in The Netherlands might be able to contribute considerably to revealing the importance of environmental factors in dementia. Before this can be achieved, however, the social sciences in The Netherlands will need to improve their infrastructure.

8. Programmes on aging and dementia should be combined, and should make use of the existing infrastructure and procedures of ZWO and its foundations for the purpose of scientific evaluation and integration, and should continue to stimulate interest in this field among researchers in related fields. In general, there are many parallels between the problems encountered in the study of brain development and aging. Since research on brain development has strong roots in The Netherlands (see FUNGO programmes) it might be useful to try and interest more of these groups in incorporating aging and dementia in their programmes. There is also a strong need for internationally orientated
training programmes in the field of aging and dementia. The ETP-BBR programme of the ESF is at present the only European organization that could contribute in a useful way in this respect. Although the value of this organization has been fully recognized, no special attention has so far been paid to the problem of aging and dementia.

9. Several measures should be taken in medical training: (a) physicians should give high priority to a detailed physical of psycho-geriatric patients, in order to detect reversible forms of dementia; (b) interest deserves to be raised for all medical aspects (including research) of aging and dementia. (c) practitioners should become more aware of the limited possibilities and considerable hazards of medicines commonly used in aging and dementia. Moreover, most drugs have not been tested for their possibly adverse effects on the process of aging. An easily accessible system for informing physicians about the drugs that are used by older patients (medication form) could be an important measure to restrict to a minimum the administration of medicines to the elderly.

10. At present, the diagnosis SDAT implies that the patient is older than 65 years, while no clearcut cause of the dementia can be identified. Emphasis should be put upon research that could lead to a positive sign of SDAT, although there is some reason to doubt the possibility of discovering any such signs. This type of information may nevertheless emerge from the study of identified neurons in brain material taken from aged and demented patients, and by the application and improvement of PET scan techniques.

11. In relation to the high prevalence of dementia, neuropathology in The Netherlands is currently paying too little attention to this problem. Measures should be taken to increase the effort, among other things by introducing the most recent technical advances in neurobiology into neuropathology (e.g., immunocytochemistry, microchemical techniques, and quantification and statistical treatment of data).

12. PET scan facilities should be introduced into one of the centrally located university hospitals in The Netherlands, so as to facilitate the evaluation of pharmacological and non-pharmacological therapies. Such extremely expensive equipment should also be made available to selected investigators from other universities and research institutes.

13. Research on membrane alterations in aging and dementia is a relatively new and promising topic which has good prospects in The Netherlands. Stimulation of neurochemistry in The Netherlands, and integration of biochemical, biophysical and neurobiological aspects of membrane research deserve serious consideration.
XI. KEY REFERENCES


X11 REFERENCES

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APPENDIX

Zeer Geachte Colleega,

In opdracht van het Nederlands Instituut voor Gerontologie zijn wij een 'review' studie op het terrein van dementie aan het samenstellen, waarin opgenomen een nadere verkenning van mogelijkheden voor Nederlands onderzoek.

Wij zouden daarom enkele Nederlandse experts op dit gebied de volgende punten willen voorleggen.

1. Voor zover U klinisch betrokken bent bij deze onderzoekingen zouden wij gaarne van U vernemen wat naar Uw mening momenteel de kernproblemen van de diagnostiek en behandeling van demente patienten zijn, in welke richting naar Uw mening hiervoor een oplossing gezocht dient te worden en welke voorzieningen cq. technieken hiervoor tot stand zouden moeten komen of ontwikkeld moeten worden.

2. Tevens willen wij gaarne van U vernemen of U momenteel onderzoek verricht op het terrein van de dementie, welke kernproblemen naar Uw mening het dementie-onderzoek in Nederland op het ogenblik in de weg staan, welke onderzoekstechnieken gebruikt worden op dit gebied en welke terreinen er naar Uw mening in Nederland gestimuleerd zouden moeten worden.

3. Ook zouden wij gaarne ter completering van ons adressenbestand de namen van andere Nederlandse onderzoekers die momenteel op het gebied van de dementie werkzaam zijn van U vernemen.

Wij zouden verheugd zijn met Uw suggesties.

Hoogachtend,

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