Chapter 27

Rationale for the Use of Therapeutic Agents in Affective Disorders (AD) and Senile Dementia of the Alzheimer Type (SDAT)

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Summary

Several studies have focused on the role of the metabolism of acetylcholine and the monoamines in the pathophysiology of AD/SDAT.

Different methods have been tried to activate the cholinergic system in the brain. By giving different forms of precursors the synthesis of ACh has been stimulated. Also by giving enzyme inhibitors, the breakdown of ACh has been inhibited, and by giving receptor agonists cholinergic functioning has been activated. The effect of this treatment has, however, been very marginal.

Treatment models in which one tries to substitute monoamines have also been adapted in the care of demented patients. The positive effect of levodopa treatment in parkinsonism is well known and as there is reduced activity of DA in the brains of patients with AD/SDAT, the same treatment has been offered to demented patients. Again, however, the effect of the treatment has been marginal or negative. DA agonists have also been used but the experience with this kind of drug is still very limited and convincing positive effects are as yet not shown.

Investigations have been made in which an attempt has been made to substitute in the 5-HT system. These investigations are of special interest as malabsorption of tryptophan has been suspected in some subgroups of senile dementia. Experience is, however, still limited and no conclusion can be drawn.

From a theoretical point of view it would be of interest to use drugs that down-regulate the activity in the NA system. Biochemical findings
indicate an increased speed of turnover in the locus ceruleus. Such investigations have not been made.

Alaproclate is a drug which selectively blocks the reuptake of 5-HT, and in preliminary investigations this drug has given positive results in the treatment of organic symptoms. In brains from patients with AD/SDAT there is an increased activity of MAO-B. Although the increase is not considered to be of biological importance the use of MAO inhibitors would be of interest in the treatment of dementia disorders. Such investigations are as yet not made.

Hydergine, a drug that has long been used in the treatment of organic brain syndromes, has gained new interest as its mode of action is reconsidered. The drug seems not only to influence cerebral blood flow, but also neurotransmitter function in the brain. A stimulating effect on DA and 5-HT functioning, and a blockade of NA activity is reported. This pattern of action is of great interest.

Some neuropeptides, such as somatostatin, ACTH analogues and vasopressin have attracted attention. Experience with these peptides in man is still limited. Although the effect on dementia syndromes does not seem to be dramatic, it is of great interest to further investigate the therapeutic value of these drugs. The nootropic agent piracetam has also created interest in the treatment of organic brain disorders. The drug has not been shown to be of value in severely demented patients, but in mild organic brain syndromes effects have been reported, although the findings are not consistent.

**Introduction and Diagnostic Aspects**

Old-age dementias can be divided into those due to disturbances in cerebral blood flow and those due to a primary degenerative process. Dementia caused by disturbed cerebral blood flow is called “multi-infarction dementia.” It was formally assumed that arteriosclerotic narrowing of the brain vessels was the primary pathology responsible for cerebral ischemia, which gave rise to the dementia syndrome. Today it is assumed that infarctions of the brain are the necessary pathology for dementia to appear. This may be an oversimplification.

The most important group of primary degenerative diseases of the brain is the one with onset at the age of 65 and above called senile dementia (Fig. 27-1). If the onset of the dementia process occurs earlier it is called presenile dementia. The latter group includes several forms of which Alzheimer’s disease (AD) is one. In the beginning of this century Alzheimer (1907) described the neuropathological lesions occurring in this disease. Later on the same lesions were also found in patients with senile dementia and therefore this group is called senile dementia of the Alzheimer type (SDAT). This group is often combined with AD to a group