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D. Collerton

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Abbreviations

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COMMENTARY

CHOLINERGIC FUNCTION AND INTELLECTUAL DECLINE IN ALZHEIMER'S DISEASE

D. COLLERTON
Institute of Psychiatry, De Crespigny Park, London SE5 8AF, U.K.

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Medical and social institutions are coming under increasing pressure as the number of demented elderly rises.[26] The most common cause of this dementia is Alzheimer's disease (AD—here used to refer both to senile and presenile Alzheimer's disease); an illness which affects between 5 and 15% of the population over the age of 65.[16,107,198] Its characteristic feature of a relentlessly progressive decline in all intellectual abilities in the absence of marked changes in alertness or sensory or motor abilities,[44] the lack of an effective treatment, and its unknown aetiology[98,100] have combined to make AD a major health problem.

AD was first described by Alois Alzheimer in 1907.[3] At post-mortem, he identified the cortical senile plaques and neurofibrillary tangles which are its classical neuropathological hallmarks. In 1911, Simchowicz[174] drew attention to the common finding of granulovacuolar degeneration in the hippocampal region and more recently cerebrovascular amyloidosis and the presence of Hirano bodies have been recognized as common pathological findings.[85,185] The functional importance of these abnormalities was indicated in 1968 when Blessed *et al.*[17] reported that plaque counts in the cortex were correlated with scores upon a functional rating scale of dementia and a short information–memory–concentration test. From this, they suggest that the cortical abnormalities indexed by plaque counts were an important cause of the dementia of AD. Further major progress was made in the mid 1970s when three British groups reported that the brains of patients dying with AD had consistently low levels of markers of cholinergic function. In particular, the synthesizing enzyme choline acetyltransferase (ChAT) was markedly reduced.[23,49,155] These findings have been replicated and extended and together with evidence on the role of the cerebral cholinergic systems in behaviour taken from other lines of enquiry, have led to the development of the cholinergic hypothesis of dementia in AD:[150,177] the hypothesis which has been the single greatest impetus to research into AD.

Although there are numerous alternative versions, in its commonest form the cholinergic hypothesis relegates the classical pathological signs of AD to a subsidiary role and states that loss of cholinergic function causes or contributes to some of the intellectual impairments particularly the memory deficits of AD.[10,40,150,166,177] There are, however, two potential problems with the hypothesis in this form. First, as described later, although there is ample evidence to suggest that cholinergic function is involved in

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