The cholinergic deficit in Alzheimer’s disease

Peter Davies

In the period immediately prior to publication of the first reports of cholinergic markers in the brains of patients with Alzheimer’s disease, there was very little hard science going on in this field. This was before the recognition that Alzheimer’s disease was the most common cause of dementia in the elderly, and it was generally thought to be a rather rare, pre-senile dementia. Having spent some time trying to do neurochemical analyses on the brains of schizophrenics, I became disillusioned by the subjectivity of the diagnostic criteria and looked around for a brain disease that was reasonably common and one in which objective, neuropathological diagnosis was possible. The late AJF Maloney convinced me that Alzheimer’s disease would be a relatively easy problem to tackle, and so my systematic biochemical studies were undertaken in 1975. I was not aware at that time that two other groups in Great Britain were doing almost exactly the same things as I was, and the discovery of the cholinergic deficit in Alzheimer’s disease was made independently and simultaneously by three groups: David Bowen and his colleagues in London (Bowen et al. 1976; White et al. 1977), Elaine and Robert Perry in Newcastle (Perry et al. 1977), and myself with AJF Maloney in Edinburgh (Davies and Maloney 1976). All three groups reported marked losses of choline acetyltransferase and acetyl cholinesterase activities in the brains of patients with histologically confirmed Alzheimer’s disease, observations that have been repeated many times.

My own work was very much influenced by the work of Oleh Hornykiewicz on the dopamine deficiency in Parkinson’s disease (Hornykiewicz 1970, 1971, 1973), and even in 1976, the therapeutic implications of the cholinergic deficiency were obvious. A psychiatrist I worked with went to an Edinburgh health food store and bought a supply of choline bitartrate with the intention of trying it in Alzheimer patients, even before the Lancet paper was published. Many similar attempts followed, with choline and later with lecithin (phosphatidyl choline), before cholinesterase inhibitors were tested and became the standard treatment. Without going into a review of the effectiveness of therapy using cholinesterase inhibitors, it is notable that we are still waiting for something better, 30 years after the initial reports on the cholinergic deficit.

The most dramatic effect of the early work on the cholinergic system was the vastly increased attention that Alzheimer’s disease received from the research (and funding) community. The thought that Alzheimer’s disease might be a specific degenerative disorder, akin to Parkinson’s disease, and that it might be possible to develop rational treatments spurred a huge increase in basic science and clinical investigation. My own

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1 Departments of Pathology and Neuroscience, Albert Einstein College of Medicine, 1300 Morris Park Ave, Bronx, New York 10461, USA