

This Week's Citation Classic[®]

Perry E K, Tomlinson B E, Blessed G, Bergmann K, Gibson P H & Perry R H.
Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. *Brit. Med. J.* 2:1457-9, 1978.
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A relationship exists between the extent of the cholinergic deficit (reduced choline acetyltransferase) and the severity of either cognitive impairment or neuropathological abnormality (senile plaque numbers) in Alzheimer's disease. This observation suggests that the transmitter acetylcholine may be involved in functional aspects of the brain, particularly memory, that are impaired by the disease process. [The *SCF*[®] indicates that this paper has been cited in over 340 publications.]

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In the mid-1970s Alzheimer's disease—the most common form of dementia in the elderly—was regarded by the majority of those working in the scientific world as a somewhat obscure subject, and surprisingly little was known about the involvement of neurotransmitters in the disease. In 1975 I was a biochemist when I joined the Newcastle Neuropathology Department, where structural aspects of Alzheimer's disease had been pursued by Bernard E. Tomlinson (assisted by Peter H. Gibson) for over a decade. Transmitters seemed a logical starting point for our neurochemical analysis in dementia.

In retrospect, several factors stimulated this research. One was an early report of a gamma-aminobutyric acid (GABA) deficit in Alzheimer autopsy tissue from David M. Bowen's group at Queen Square.¹ Another factor was the attraction of combining classical neuropathology with neurochemistry—neurochemical pathology—prompting Robert H. Perry to establish in the department a bank of neuropathologically assessed frozen human brain tissue.

It rapidly became apparent that there was a substantial and consistent deficit of one particular transmitter system—the cholinergic system—and three research groups in the UK published similar findings within a few months of each other.²⁻⁴ At that stage it was not immediately clear what relevance the cholinergic deficit had to the clinical features of the disease, although a link between memory and acetylcholine had been variously hinted at in the past literature. Within a short time, as recorded in our *British Medical Journal* paper, a robust relationship between impaired cognitive function in Alzheimer's disease and the cortical cholinergic deficit was apparent. Decreasing mental test scores, assessed by Garry Blessed and Klaus Bergmann within six months before death using the Blessed test of memory and information processing, were associated with progressive reductions in cortical choline acetyltransferase (the enzyme, measured post-mortem, that synthesizes acetylcholine).

Pharmacological and lesioning studies in experimental animals (triggered by this and other reports on the cholinergic system in Alzheimer's disease) have since substantiated the idea that basal forebrain cholinergic neurons projecting to the cortex are involved in memory function, and this probably accounts for the frequency with which the article has been cited. Regarding the specificity of the cholinergic deficit—still a controversial issue—several noncholinergic abnormalities have now been detected in Alzheimer's disease, although none has so far been as clearly linked with the memory or cognitive impairment as the cholinergic system itself.⁵

It is most encouraging to receive recognition for this work, since it was carried out during a period of employment within the National Health Service (NHS) in a position rather warily defined as "probationary basic grade nonmedical biochemist." The popularity of the paper should encourage the NHS to support more neurochemists—"on probation" if necessary!—to research these and other central nervous system disorders. Ultimately, however, one of the main reasons for investigating human brain neurochemical pathology is the prospect of developing rational and effective forms of treatment. The recent promising report⁶ of significant and in some instances dramatic effects of the drug tetrahydroaminoacridine, an anticholinesterase, in countering clinical symptoms of Alzheimer's disease provides considerable hope.

1. Bowen D M, White P, Flack R H A, Smith C B & Davison A N. Brain decarboxylase activities as indices of pathological changes in senile dementia. *Lancet* 1:1247-9, 1974. (Cited 60 times.)
2. Davies P & Maloney A J F. Letter to editor. (Selective loss of cholinergic neurons in Alzheimer's disease.) *Lancet* 2:1403, 1976. (Cited 540 times.)
3. Perry E K, Perry R H, Blessed G & Tomlinson B F. Letter to editor. (Necropsy evidence of central cholinergic deficits in senile dementia.) *Lancet* 1:189, 1977. (Cited 315 times.)
4. White P, Hiley C R, Goodhart M J, Carrasco L H, Keet J P, Williams I E I & Bowen D M. Neocortical cholinergic neurons in elderly people. *Lancet* 1:668-70, 1977. (Cited 270 times.)
5. Perry E K. The cholinergic hypothesis—ten years on. *Brit. Med. Bull.* 42:63-9, 1986.
6. Summers W K, Majovski L V, Marsh G M, Tachiki K & Kling A. Oral tetrahydroaminoacridine in long term treatment of senile dementia, Alzheimer type. *N. Engl. J. Med.* 315:1241-5, 1986.