

Blessed G, Tomlinson B E & Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects.

*Brit. J. Psychiat.* 114:797-811, 1968.

[MRC, Newcastle upon Tyne, and Dept. Psychol. Med., Univ. Newcastle upon Tyne, England]

We investigated the relationship between diagnosis and measures of dementia during life and the post-mortem quantitative assessment of the "Alzheimer" changes in cerebral grey matter of elderly persons. Results suggested that a close relationship existed between numbers of plaques and tangles and the causation of the Alzheimer form of cerebral degeneration and dementia. [The *SCI*® indicates that this paper has been cited in more than 900 publications.]

## Alzheimer's and Cortex Changes

Martin Roth

Department of Medicine, Level 5  
Addenbrooke's Hospital  
Cambridge CB2 2QQ  
England

Within two decades of A. Alzheimer's seminal paper,<sup>1</sup> the "senile plaques" (SP) and "neurofibrillary tangles" (NFT) he observed in the brain of his 51-year-old patient had also been described in normal aged persons, depressive and paranoid disorders, and "senile dementia." Alzheimer, however, considered his syndrome distinct. SP and NFT thus came increasingly to be regarded as nonspecific and unimportant.

Systematic studies of course and outcome in 1955 refuted the unitary concept of mental disorder in old age. Depressive or paranoid illnesses had a more favorable clinical outcome than the dementias, and a near-normal life expectation. But the survival rate of demented, as estimated in clinical and community samples, was only 25 percent of the norm. We tried to resolve the riddle of the apparent ubiquity of Alzheimer pathology. Elderly patients admitted with various psychiatric disorders, and control subjects aged 60 years and over, were diagnosed by the strict 1955 criteria. These measures formed the starting point of CAMDEX.<sup>2</sup>

There were five main findings included in this *Classic* and two other papers:<sup>3,4</sup> (1) SP and NFT were indeed widespread in the brains of the normal aged population, where they were not associated with variation in measurable cognitive impairment; (2) when SP and NFT occurred in large numbers, the person was invariably

demented. A "threshold effect" therefore governed the relationship between the aggregation of SP and NFT and the development of dementia; (3) the severity of Alzheimer pathology varied with lifetime diagnosis; (4) high correlations existed between the degree of cognitive and other impairments during life and the number of SP and NFT found postmortem; and, (5) the single feature that best distinguished demented from controls was the incidence of widespread tangles throughout the cortex.<sup>4</sup> But neuritic SP and NFT showed the same dense aggregate of paired helical filaments (PHF).

Alzheimer believed he had discovered a new but rare syndrome of precocious mental decline associated with a unique cerebral pathology. However, similar lesions were later found in "senile dementia"—prevalent in advanced age. These three papers established that Alzheimer's claims could be reconciled with the observations of those who considered SP and NFT to be normal and nonspecific.

Lingering doubts about the significance of SP and NFT and the relevance of neuronal loss in Alzheimer's disease (AD) were settled later. A highly significant outfall of large pyramidal cells from frontal and temporal cortex was demonstrated, while plaque and tangle counts were shown to correlate inversely with neuronal counts in the same cortical areas.<sup>5</sup> Association of the structural changes with the neurotransmitter deficits, first reported in 1977, proved similar. Thus SP and NFT could provide clear starting points for inquiries into the etiology of the most common dementing illness (and possibly into normal aging in the brain).

In 1985, following help from Aaron Klug of the Laboratory of Molecular Biology, we published a model of the structure of PHF—a double helical stack of transversely oriented subunits twisted into a left-handed helical ribbon.<sup>6</sup>

Very recently, we have shown that NFT within seemingly intact neurons are immunologically distinct from tangles left behind after neuronal death in extracellular space.<sup>7</sup> In the transition from one to the other type of tangle, we appeared to be observing successive stages in the process whereby neurons in Alzheimer's disease are destroyed by NFT.

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