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SPECIAL ISSUE

H. Förstl, Guest editor

Editorial:
Of mind and matter – or what really matters in Alzheimer's disease?
Neurobiological substrates of clinical deficits in Alzheimer's disease

Alzheimer felt that senile plaques were not the heart of the matter, not the true cause of dementia in the patients he had examined (1911). In this special issue, Haass reviews current research on amyloid and argues strongly in favour of the amyloid plaques' pivotal role in Alzheimer's disease. Hüll and co-workers demonstrate that inflammatory mechanisms are involved at an early stage of plaque formation. Gattaz et al. present their evidence for a role of phospholipase A_2 in Alzheimer's disease. There are clearly more things to consider in the pathogenesis of degenerative dementia than amyloid plaques and neurofibrillary tangles – even though these are still the top-ranking suspects since the early days of Alzheimer's research (1906).

Some of the early work indicated that there was an association of plaques or tangles not only with a diagnosis of Alzheimer's disease, but more specifically with the severity and type of clinical deficits. Fischer (1907; 1910) suggested that a certain type of dementia with severe memory impairment and preserved personality ("presbyophrenic dementia") was associated with severe cortical plaque pathology ("Sphärotrichia multiplex cerebri"). Simchowicz (1911) observed a lower cortical plaque count in the frontal as compared with the occipital cortex in presenile dementia, and a higher frontal than occipital plaque count in senile dementia ("senile index"), and he defined a critical limit of plaque density (10 plaques per visual field = 1.77 mm^2) between normal brain aging and senile dementia. Grünthal (1927) analysed 13 patients with senile dementia, all of whom had senile plaques; 11 had neurofibrillary tangles; the patients with mild dementia had low plaque numbers and tangles were restricted to the mediotemporal lobe. One patient with amnestic aphasia had tangles and gliosis in the left temporal lobe. One agitated patient had shrinkage and gliosis of the putamen. Another patient with autonomic disturbances showed plaques in the vicinity of the third ventricle. Then, Gellerstedt's (1933) extensive study on brain changes in clinically normal elderly discouraged exaggerated expectations. He demostrated variable plaque depositions in different parts of the brain and neurofibrillary tangles in the temporal allocortex in clinically normal elderly persons. This led to the counter-reactionist thesis that there was no relevant correlation between clinical dementia and brain pathology (Rothschild 1937).

The agnostical view of Rothschild and others was slowly overcome by modest attitude and conclusions (for example "... the ways in which organic deterioration manifests itself during life are more often than not reflected in the ultimate appearance of the brain"...; Corsellis 1962). It took some time until a positive scientific attitute was re-introduced into the systematic investigation of clinico-pathological correlations in psychiatric disorders. The Newcastle group (Blessed et al. 1968) used larger patient samples who were studied prospectively and in a structured way. The neuropathological work-up was carried out in a standardized and (semi-)quantitative manner. The correlations were examined with simple statistical methods. Several methodological criticisms did not outweigh the advantages of this approach, and most of the later clinico-pathological work on dementia was developed from this material.

Braak and Braak (1991) have pointed out the importance of the localization or extension of Alzheimer-related changes. This topographic aspect had been underestimated in previous studies. They described six stages of brain degeneration based on the distribution pattern of neurofibrillary tangles and neuropil threads. The tangles in Gellerstedt's cases were confined to the mediotemporal lobe, and this would be compatible with Braak and Braak's transentorhinal or limbic stages (I–IV), but not with the isocortical stages of Alzheimer's disease (V and VI). Using large representative, prospectively assessed study samples. Gertz et al. and Bancher et al. have now underscored the validity of the hierarchical stageing model, and demonstrated a relationship between severe

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cognitive impairment and isocortical neurofibrillary tangle pathology. Both elaborate the difficulties in disentangling the relative contribution of the extension and of the severity of histopathological features.

The clinical and the neuropathological parameters which may need to be considered in the mind-brain relationship of Alzheimer's disease appear virtually countless. A number of symptoms (e.g. "non-cognitive") and large parts of the brain (e.g. the stem) are usually neglected in this type of research (Förstl et al. 1994). It should not be forgotten that nondemented individuals tend to show a good deal of behavioural and probably also morphological variability which may even be increased by a heterogeneous disease like Alzheimer's. Significant statistical correlations between one clinical score and one histopathological feature do not prove causal relationship, but are often explained by the composition of the patient sample, the sensitivity of a staining method, the reliability of a counting procedure and by the statistical approach (Föstl and Fischer, 1994). We will have to wrestle with a large number of intricacies until we find out what really matters in Alzheimer's disease, and the struggle will lead beyond mindless biology and brainless psychology.

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