

ALZHEIMER DISEASE NEUROPATHOLOGY IS PATHOGNOMONIC BUT NOT PATHOGENIC

Rudy J. Castellani¹, Hyoung-gon Lee², Xiongwei Zhu², Akihiko Nunomura³, George Perry^{2,4},
Mark A. Smith²

Department of Pathology, University of Maryland, Baltimore, Maryland, USA; ²*Department of Pathology, Case Western Reserve University, Cleveland, Ohio, USA;* ³*Department of Psychiatry and Neurology, Asahikawa Medical College, Asahikawa, Japan;*

⁴*UTSA Neurosciences Institute and Department of Biology, College of Sciences, University of Texas at San Antonio, San Antonio, Texas, USA*

mark.smith@case.edu

Neuropathological changes in subjects with dementia are, by definition, end-stage phenomena. While evaluation of changes allows for the characterization and classification of individual cases, as well as disease modeling, the lesions themselves are not etiological. Yet the medical and scientific literature suggests otherwise. The foundation for this line of thinking lies in the existence of rare kindreds with mutations in amyloid- β . Extrapolation of the inherited disease condition to sporadic cases has maintained that the view that amyloid plaques in Alzheimer disease are primary etiological, neurotoxic lesions, and removing them through immunotherapy may result in clinical improvement. We believe that this overall construct ignores early events that are critical to the onset and progression of sporadic disease. After studying subjects with sporadic Alzheimer disease, early onset familial Alzheimer disease, and Down's syndrome, we found that oxidative stress precedes amyloid deposits in all three conditions. Amyloid and neurofibrillary pathology in the Alzheimer brain show a decrease in oxidative stress relative to vulnerable but morphologically intact brain, suggesting that neurodegenerative lesions are compensatory phenomena, and thus manifestations of cellular adaptation during disease progression. The resulting pathology of neurodegenerative diseases should be viewed as the end-stage consequence of the disease processes, and not the cause, so that early disease processes that are amenable to intervention can be properly recognized and treated.