Cerebral Amyloid Angiopathy in Alzheimer's Disease and Related Disorders

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Dedication

Dedicated to the late dr. George Glenner, dr. Henryk Wisniewski and dr. Thaddeus Mandybur, pioneers in research on amyloid in the nervous system, including its blood vessels.

Preface

Since at least the time of Scholz, students of Alzheimer's disease have been grappling with the role of microvascular pathology in the cause and mechanism of this complex and devastating disorder. A number of historical milestones in the elucidation of Alzheimer's disease have derived directly from scientists' desire to understand the whys and wherefores of the striking cerebrovascular amyloidosis that accompanies the disorder. Perhaps the most notable example of this connection is the original discovery by George Glenner of the amyloid beta protein. Glenner was understandably fascinated by the parallels between Alzheimer's disease and other human amyloidoses, and he purposely focused on the high prevalence of meningovascular amyloid deposition in approaching AD, both conceptually and experimentally. While neurobiologists were generally more interested in the neurofibrillary tangles and senile plaques that filled the cerebral cortex, Glenner correctly surmised that understanding the biochemical nature of meningovascular amyloid would provide a simpler and more tractable route to understanding Alzheimer's disease. Applying the methods that had been well-developed by pathologists and biochemists studying other human amyloidoses, Glenner and Wong successfully purified and partially sequenced the subunit of the meningovascular amyloid deposit of both Alzheimer's disease and Down's syndrome. What Glenner instinctively knew quickly became apparent to others: that deciphering the microvascular amyloid would be an excellent first step in unraveling the pathogenesis of Alzheimer's. We now know that his instincts were prescient.

It is both timely and compelling that Marcel Verbeek, Harry Vinters and Rob de Waal and their many talented co-authors have now decided to weave together the many threads of knowledge about cerebrovascular amyloidosis

in Alzheimer's disease and related disorders. As I have examined the brains of Alzheimer victims under the microscope over the years, I have been impressed by the striking relationship of beta-amyloidosis to the cerebral microvasculature. In a series of brains of patients dying with Alzheimer's disease, Cathy Joachim and I observed the invariant occurrence of at least some and often many meningeal and intracortical microvessels bearing amyloid β-protein deposits. Not infrequently, the immediately surrounding brain tissue showed a neuritic and gliotic response that closely resembled that found in senile plaques. Numerous investigators have pointed to the potential importance of vascular basement membrane constituents as a substrate for β-amyloidosis in the brain. While it has been exceedingly difficult to confirm unequivocally a seminal pathogenetic role for microvessel constituents, there can be no doubt that a full understanding of Alzheimer's disease will require a detailed knowledge of the contribution of altered vascular form and function. The comprehensive review of current information about many aspects of this subject provided by this volume will no doubt serve as a highly useful resource to investigators seeking to make further progress.

The attention devoted to the genetics and clinicopathology of hereditary cerebral hemorrhage with amyloidosis (HCHWA) of the Dutch type in this volume seems particularly appropriate. Those of us working in the field of Alzheimer pathogenesis sometimes forget that the first specific genetic abnormality that could be credibly linked to the Alzheimer phenotype was the missense mutation in the beta-amyloid precursor protein causing the "Dutch disease." This discovery made it highly likely that APP would turn out to be the site of missense mutations in conventional Alzheimer's disease, a prediction that was soon shown to be true. HCHWA-D epitomizes the intimate relationship between vascular and parenchymal β-amyloidosis in the human brain that has fascinated neuropathologists for so long.

The current volume cogently places the Dutch disorder into the broader context of "sporadic" cerebral amyloid angiopathy, a syndrome which we now know occurs more frequently and with more disastrous consequences than was once believed. Thus, the old and new information brought together in one place by dr. Verbeek, Vinters and de Waal and their colleagues is meaningful not just for those concerned about Alzheimer's disease but for basic and applied biologists interested in understanding how the cerebral microvasculature works. I commend the editors and authors for taking on this important task and believe that you, the reader, will find their efforts to be both highly informative and useful to your own work.

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