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EDITORIAL

Stuck in the Mire

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Alzheimer's disease researchers are a pretty dispirited lot these days. In the first half of the 20th century research on this malady and an understanding of its impact on society were limited in scope and intensity. The dementia described by Alois Alzheimer was felt to refer to a relatively rare disease of middle age and different from senile dementia of the elderly, which was often attributed to cerebral atherosclerosis. It was not until the application of electron microscopy to the brain at the beginning of the second half of the 20th century that it became clear that the neurofibrillary degeneration seen in senile dementia was composed of the same, unique, paired helical filaments that were seen in Alzheimer's disease and that there was an identical deposition of congophilic senile plaques and of synaptic changes in both entities. This entity in the elderly was first called "Senile Dementia of the Alzheimer's type (SDAT)" and eventually both were grouped as Alzheimer's disease (AD). There was a lively debate at that time as to whether AD was or was not an amyloidosis that was eventually resolved in a rapid series of discoveries that followed on the purification and identification of the amyloid peptide (Aβ or beta amyloid) from the brain by the late George Glenner.

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The findings that mutations in the Amyloid Precursor Protein (APP), from which Aβ is processed, and the proteins presenilin 1 (PS1) and presenilin 2 (PS2) were associated with early onset AD helped established the "Amyloid Hypothesis" that, reduced to its simplest form, overproduction of Aβ (or reductions in its clearance) leads to the histopathological and behavioral changes that characterize AD. In this model, the widespread intracellular neurofibrillary tangles composed of *tau* protein are believed to be downstream of the generation of Aβ. These discoveries led to the generation of transgenic mice that over-expressed mutant human APP, developed amyloid plaques quite similar to those seen in human AD and showed age-related alterations in memory. None of these mice showed significant neuronal loss nor development of neurofibrillary tangles, though increased *tau* phosphorylation was seen.

These models have been the primary objects of biological study on AD over the past few years, and a large number of agents have shown the ability to reverse the electrophysiological and behavioral changes seen in them. These include a number of the classes of agents that are discussed in this volume. The development of clinical drugs has focused on the removal of Aβ and on blocking its production. These include active and passive immunization against Aβ and inhibition of the γ-secretase and β-secretases that cleave APP to produce Aβ. These approaches have been extremely successful in the rodent but clinical trials using them have all failed to improve established AD. This has led to the view that the mouse models reflect only the early stages of the disease and that latter stages of the disease—the stages with neurofibrillary tangles and neuronal loss—are irreversible and too late to treat. This question is being addressed by using these agents to treat patients who have dominant mutations in PS1 that will

lead to AD in 100% of persons carrying the mutation. Therefore, treatment can be started before symptoms appear and alterations in the normally rapid progression of the disease assessed. The introduction of PET scanning ligands for Aβ and for *tau* also will allow for treating patients who are developing Aβ pathology prior to the clinical manifestations of the disease.

Even if these approaches are successful, it is likely that more than one drug will be needed to treat the disease and arrest its progression. The articles in this volume focus on a number of systems that are affected in AD. They explore key topics such as energetics and mitochondria, the role of heavy metals, molecules to increase synaptic plasticity and approaches to the defects in protein sorting and in protein degradation. Given the limitations mentioned in current animal models, articles in this volume describe advances in the use of human stem cells and stem cell-derived neurons for the study of AD, as well as the application of the new areas of computational and systems biology to analyze data derived from post-mortem human brain to predict master regulators of AD progression.

The sum total of the articles provides a snapshot of where we are at this place and time, the model systems that might be appropriate and some glimpse of future research directions. We apologize to authors and areas that have been omitted from this volume because of limits of space and time. We hope that the papers presented here will assist those in the field, those contemplating entering AD research and to the professionals involved in the care of AD patients.

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