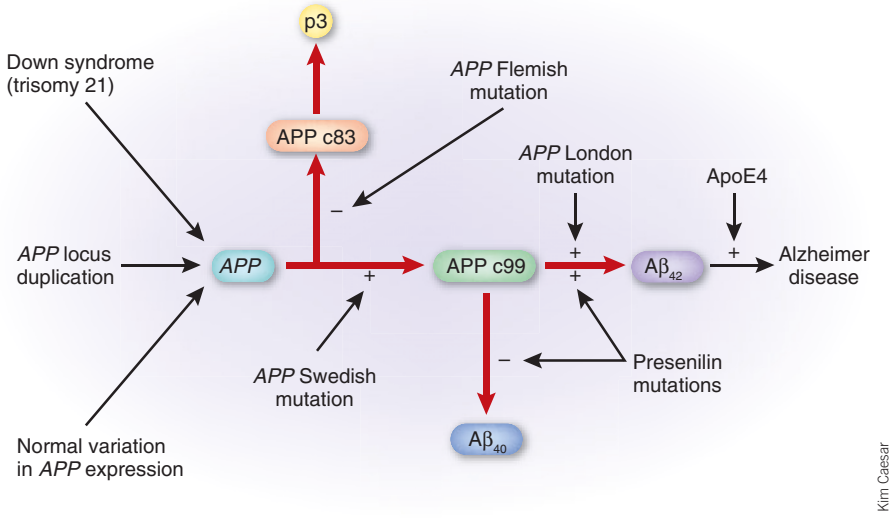

Figure 1 The pathway by which Alzheimer disease pathogenesis is initiated.

families with these duplications had not been identified before. Perhaps clinicians had not appreciated that family members with a stroke phenotype and related family members with a dementia phenotype had the same underlying lesion, particularly because evidence of a stroke is part of the exclusionary criteria for making the diagnosis of Alzheimer disease.

In general, the relationship between the vascular and parenchymal lesions in all the β-amyloidopathies deserves re-examination in light of this overlap between angiopathy and plaque and between hemorrhage and dementia. This reinvestigation is also important because it is likely that the T lymphocyte–mediated meningoencephalitis seen in the Aβ vaccination (AN-1792) trial for Alzheimer disease may have been caused by antibody-induced damage to the microvasculature[4]. Recent data have corroborated an old view of amyloid plaques: that at their center they have amyloid fibrils extruding from an angiopathic blood vessel[5–7]. In addition, there is clear evidence that amyloid plaques represent the sites of microhemorrhages in Alzheimer disease[8,9]. Ironically, this new view comes close to the long-discredited notion of Alzheimer disease as being caused by hardening of the arteries. Whatever the history of this idea, these findings all suggest that it is crucial we understand the vascular deposition of Aβ in Alzheimer disease. Such an understanding may be necessary not only to understand the initiation of the disease, but also to avoid potential side effects of treatment.

One hundred years after Alois Alzheimer's description of the plaques and tangles in the first reported case of Alzheimer disease, we have looked at the proteins that make up these deposits as pathologies and have not extensively investigated their physiologic roles. Perhaps we should consider the possibility that Aβ has a function that relates directly to its involvement in vascular pathology. We know, for example, that APP is involved in blood clotting[10] and that Aβ drains from the brain along the walls of the microvasculature[11]. Perhaps we should consider the possibility that Aβ has complementary damage-response roles: (i) as an emergency sealant of the vasculature during hemorrhage and (ii) as a neuronal depressant[12]. As a depressant, it would reduce the brain's oxygen requirement during an ischemic event and thus help control the extent of hypoxic damage in a hemorrhage. This physiologic view would fit with the observation of a continuum of Aβ pathology between the blood vessels and the plaques, which is especially seen in the individuals with *APP* duplications Research over the last 20 years has focused on Aβ pathology; perhaps we should now shift our focus to understanding Aβ physiology in order to garner further information as to the process which leads to dementia.

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[a]Number of citations as of 13 June 2006. Table includes all primary research articles that have the terms 'Alzheimer' or 'Alzheimer's' in their title, abstract or keywords, and that have been cited at least 50 times. Table does not include reviews. Data source: *Scopus*